Doctoral Dissertation of

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CHEMISTRY
MATERIALS
AND
CHEMICAL ENGINEERING
"Giulio Natta"

"VALORISATION OF GLYCEROL FROM BIO-DIESEL WASTE TO HIGH VALUE CHEMICALS"

XXV Cycle

2010 - 2012

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Tutore: Prof. Dr. Stefano SERVI

Coordinatore: Prof. Dr. Tiziano FARAVELLI

Dedicated to my beloved parents

and specialy to my wife Tejswini,

who have been my inspiration throughout.

And to all who have been with me, beside me,

all through my life.

DECLARATION

I hereby declare that the work presented in the thesis entitled **"VALORISATION OF GLYCEROL FROM BIO-DIESEL WASTE TO HIGH VALUE CHEMICALS"** submitted for the award of degree of **Doctor of Philosophy** to the Politecnico Di Milano, Milan, under the supervision of **Prof. Attilio Citterio.** The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University. This work was carried out by me at the department of **Chemistry Materials and Chemical Engineering "Giulio Natta" Politecnico Di Milano, Milan, Italy.**

Date: February 2013

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"VALORISATION OF GLYCEROL FROM BIO-DIESEL WASTE TO HIGH VALUE CHEMICALS"** which is being submitted to the **Politecnico Di Milano**, **Milan,** for the award of **Doctor of Philosophy** by **Suresh Udhavrao Shisodia** was carried out by him under my supervision at **Politecnico Di Milano**, **Milan.** This work is original and has not been submitted in part or full, for any degree or diploma to this or any other University.

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Acknowledgement

It may sound formal, but as convention demands, I pay homage to my teacher and guide ***Prof. Attilio Citterio****, for his expert and encouraging guidance throughout the work. His personal care and affection knew no bounds when and where needed. It gives me immense pleasure to express my deep sense of gratitude and indebtedness to* ***Prof. Stefano Servi****, my tutor and* ***Prof. Roberto Sebastiano, Prof. Sergio Auricchio****,* ***Dr.ssa Ada Truscello, Dr. Cristian Gambarotti,*** *whose personnel care and indomitable spirit has resulted in this successful endeavour. I also express my sincere gratitude to* ***Prof. Renato Rota*** *the director of the institute and Prof. Pier Giorgio Righetti, Dr. Maurizio Galimberti, Dr. Carlo Punta.*

I feel myself very fortunate to be associated with all my co-workers because of there co-operation has led to the fulfilment of a part of this work, to name a few- Dr.ssa Gabriella Leonardi and Lauria Mirvana, Antonio Marion, Giovanna Calatozzolo, Nunzia Contiello, Dafne Cozzi, Pamela Martino, Laura Tiné, Dr. Lucio Melone, Dr.ssa Elisa Fasoli, Dr.ssa Monica Guenzi, Dr.ssa Julia Peli. Their efforts towards creating a pleasant atmosphere inside and outside the lab were tremendous. The support of all the spectroscopic divisions is thankfully acknowledged.

I pay respect to my mentor and teacher, ***Dr. R. P. Pawar****, who had always been a true guide, whose inspiring thoughts and direction, has made it possible for a generation to conquer great heights. I will cherish dearly the valuable time I have spent with him for many more years to reach this position. I express my sincere thanks to* ***Prof. B. V. Sangvikar****, (Professor, Dept. of Management Studies, university of Pune – India),* ***Dr. Hanumant Borate*** *(Scientist, National Chemical laboratory (CSIR), Pune-India).* ***Dr. Vasant Chabukswar*** (*Nowrosjee Wadia College, India).*

The single largest contribution in shaping my present comes from the faith, hope, encouragement and affection of my beloved parents mother Suman & father Udhavrao and wife Tejswini. The debt of gratitude I owe them is beyond literal expression hence I make no effort. I express my heartfelt thanks to my brother and all family members for their support and encouragement throughout my studies.

Last, but not the least, I thank ***Prof. Dr. Tiziano Faravelli****, Co-ordinator, School of Doctoral Studies in Industrial Chemistry and Chemical Engineering and* ***Sig.ra. Myriam Oggioni****,* ***Sig.ra. Daniela Rignanese*** *Secratery, School of Doctoral Studies in Industrial Chemistry and Chemical Engineering*

List of Publications:

1) "One-pot synthesis of aryloxypropandiols from glycerol: towards valuable chemicals from renewable sources" Ada M. Truscello, Cristian Gambarotti, Mirvana Lauria, Sergio Auricchio, Gabriella Leonardi, Suresh U. Shisodia and Attilio Citterio. Accepted in *Green Chemistry* 2013. DOI: 10.1039/c2gc36793a.

2) "Micron Particles of AlN/Al: Efficient, Novel and Reusable Heterogeneous Catalyst for the Synthesis of Bis(indolyl)methanes" Sunil U. Tekale, Suresh U. Shisodia, Sushma S. Kauthale, Vivekanand Jadhav, Nilesh S. Kanhe, Savita V. Bhoraskar and Rajendra P. Pawar. Accepted in *Synthetic Communications* 2012.

3) "Selective Monoetherification of 1,4-Hydroquinone promoted by $NaNO_2$" Cristian Gambarotti, Lucio Melone, Carlo Punta, Suresh U. Shisodia Accepted in *Current Organic Chemistry* 2012.

4) "Easy Solvent Free Synthesis of Novel 1-Ferrocenylmethylglycerols with Antifungal Activity" Shisodia Suresh Udhavrao, Roberto Sebastiano, Sergio Auricchio, Attilio Citterio, *Green Chemistry* 2013 – submitted.

5) "Preparation and Reactivity of Diglycerol Dicarbonate Diastereoisomers: an Approach to the Valorisation of Glycerol". Shisodia Suresh Udhavrao, Gabriella Leonardi, Ada Truscello, Sergio Auricchio, Attilio Citterio. *Manuscript under preparation.*

6) "H_2O_2/Ethyl lactate: A New Eco-Friendly Per acids-like System for the Selective Oxidation of Organic Sulfides and phosphines" Shisodia Suresh Udhavrao, Cristian Gambarotti, Attilio Citterio, *Manuscript under preparation.*

7) "Selective Baeyer-Villiger reaction by using H_2O_2/Ethyl lactate: A New Eco-Friendly Per acids-like System" Shisodia Suresh Udhavrao, Cristian Gambarotti, Attilio Citterio, *Manuscript under preparation*

List of posters presented at conferences:

Poster-I:- ICOS-18th International Conference on Organic Synthesis Bergen, Norway August 1- 6, 2010 www.icos-18.no "H_2O_2/Ethyl lactate: A New Eco-Friendly Per acids-like System for the Selective Oxidation of Organic Sulfides" Cristian Gambarotti, Suresh U. Shisodia, Attilio Citterio.

Poster-II:- COFEM 2010 Roma, Italy, 2 – 4 September, "A New Eco-Friendly Per acids-like System for the Selective Oxidation of Organic Sulfides and Phosphines" Attilio Citterio, Suresh U. Shisodia, Cristian Gambarotti.

Poster-III:- Poster presentation on PhD day 23, March 2012, Politecnico Di Milano, Milano, Italy. "Glycerol Derivatives As Renewable Materials" Piazza L. Da Vinci 32, 20133 Milano, Italy. Suresh U. Shisoida, Citterio Attilio, Stefano Servi.

Poster-IV:- "XVIII National Congress of Industrial Chemistry Division of Italian Chemical Society", The challenges in Industrial Chemistry for sustainable Innovation, Florence, Italy, 11-14 June 2012. Poster presented "New Monomer for Diverse Molecular Architectures From C-3 Natural Precursors" Suresh U. Shisoida, Citterio Attilio, Roberto Sebastiano, Galimberti Maurizio, Ada Truscello, Gabriella Leonardi and Terraneo Giancarlo. * First price winner for best poster.

Poster-V:- BOSS XIII - 13th Belgian Organic Synthesis Symposium, Leuven, Belgium, 15-20 July 2012. "Synthesis, Solvent and Catalyst Free, Of Novel 1-Ferrocenylmethyl Glycerols with Antifungal Activity" Suresh U. Shisodia, Citterio Attilio, Sergio Auricchio, Roberto Sebastiano.

Poster-VI:- "MACROGIOVANI 2013, Giornata di discussione su progetti di ricerca macromolecolare" Politecnico Di Milano, Milano, Italy, 11 February 2013, "Conducting Polyindole-ZnO nanospher: Ecofriendly preparation, Formation mechanism, biological activity" Suresh U. Shisodia, Attilio Citterio, Vasant V. Chabukswar.

ABRIVATIONS:-

SEM - Scanning Electron Microscope	PTSA - para toluenesulfonic acid
XRD - X-Ray Diffraction	MeOH - Methanol
TGA - Thermo Gravimetric Analysis	EtOH - Ethanol
Tg - Glass Transition Temperature	DCM - Dichloromethane
DSC - Differential Scanning Calorimetry	THF - Tetrahydrofuran
FT-IR - Fourier Transform Infrared Spectroscopy	TFA - Trifluoroacetic acid
IR - Infrared Spectroscopy	MSA - Methylsulfonic acid
NMR - Nuclear Magnetic Resonance	AcOH - Acetic acid
GC-MS - Gas Mass Spectroscopy	AcOEt - Ethyl acetate
MS - Mass Spectroscopy	PAA - Peracetic acid
ESIMS - Electrospray Ionization Mass Spectrometry	Ph - Phenyl
HPLC - High-Performance Liquid Chromatography	R - Alkyl
CE - Capillary Electrophoresis	P - Phosphorus
TLC - Thin Layer Chromatography	K - potassium
DG - Diglycerol	C - Carbon
DGDC - Diglycerol dicarbonate	O - Oxygen
GC - Glycerol carbonate	N - Nitrogen
DMC - Dimethyl carbonate	N_2 - Nitrogen Gas
DEC - Diethyl carbonate	Cl - Chlorine
Fc-CH_2-OH - Ferrocenemethanol	mp - Melting point
BV - Baeyer-Villiger	BP - Boiling point
TMS - Tetramethylsilane	µL - Microliters
$CDCl_3$ - Deutarated chloroform	mL - Milliliters
D_2O - Deutarated water	mmol - Millimoles
CD_3-OD - Deutarated Methanol	°C - Degree Celsius
DMSO-d_6 - Deutarated Dimethyl Sulfoxide	Å - Angstroms
H_2O_2 - Hydrogen Peroxide	Min - Minutes

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ABSTRACT

State of art:

In the 21st century some major issues are the generation of energy, sustainable chemicals and materials for industry, by lower consumption of energy and to reduce pollution by using renewable biological materials (biomass) instead of fossil fuels. The concept of agro-refinery from biomasses has been developed mainly in the context of bioenergy, i.e. biofuels bioethanol and biodiesel, but increasing efforts has been devised also in the vision of non-energetic valorization of vegetable and animal by-products to produce useful molecular fractions. Saccharides, oils & fats, terpenes, etc. were evaluated, converted and utilized as platform[1] to produce value added products such as biomaterials (films, resins, panels …), bio-based health products, unconventional food and feeds, etc.

In this context, a remarkable attention has been devoted to C-3 platforms, mainly represented by lactic acid[2] and glycerol[3]. Both compounds are easily available in large amount in well established processes, but their conversion into high-value chemicals is in infancy. In particular, glycerol has emerged as relevant renewable resource, spurred by the growing of the biodiesel production.[4] Actually, the European and American annual production of this commodity from biodiesel is about 950000 [t/y] (10 kg/100 kg of biodiesel), with an annual increase of 3%,[5] moreover, glycerol can also be obtained from the fermentation of glucose[6]. Glycerol is used in pharmaceutics, cosmetics, food and polymers industry with more than 3000 different actual uses. Derivatisation of glycerol is possible both at carbon and at oxygen atoms but, owing to problem of chemo- and regio- and stereo-selectivity, its chemistry was mainly restricted to simple substitutions,[7] and only recently more complex oxidation, reduction and substitution reactions were investigated with some attempts to translate them into industrial processes.

The production of lactic acid[8] has drawn a lot of attention because of its various uses such as food industry (as food additive and preservative), pharmaceutical industry, cosmetic industry, and its market is expected to expand as it is an essential feedstock for biodegradable polymers resulting from the worldwide concern about the environment. Since the 1960s, in fact, biodegradable synthetic polymers, such as poly(L-lactic acid) (PLA), have been increasingly used in specialized applications, such as drug delivery, where long-term stability is not required, or plastic materials (films, fibers, bottles, woven, etc.). Lactic acid production is carried out by both bacteria and animal cells in an anaerobic respiration method, but production does not have much economic impact due to difficult downstream separation processes and end-product inhibition. However, ethyl lactate (obtained by esterification in-situ or ex-situ of lactic acid with ethanol) has emerged in recent years as important chemical commodity as environmentally benign solvent and reagent, which has renewed the interest for lactic acid.

For these reasons, the present thesis will focus on the use and potentiality of glycerol and ethyl lactate as C-3 chemical platforms obtained from biomass, to generate new green products, materials and bioactive compounds.

Objectives and Methods:

The objective of this research work is to develop new strategies to synthesize well-defined molecules or materials from glycerol (even crude) and ethyl lactate under as much as possible green conditions. The last substrate was investigated mainly as green solvent for oxidations with hydrogen peroxide of sulphides, phosphines and carbonyl compounds, identifying the eco-friendly peracids-like nature of this system. On the contrary, glycerol studies were addressed to control the chemo- and regio-selectivity of nucleophilic substitutions to C-O bonds through activation of carbonate substituents, or electrophilic substitution to O-H bonds.

In particular, in the first direction the aim was to investigate the factors affecting the unexplored area of regio-selective poly-condensation of glycerol derivatives by O and N nucleophiles and the possibility of using cascade reactions, without solvents, or by green methods, to produce stereo-ordered oligomers, polyglycerol ethers or urethanes and other functional products. In this area a further target was to identify the role of homogeneous and heterogeneous catalysis in the substitution. In the field of electrophilic substitution the research was centered on alkylation reaction by stabilized cations (i.e. ferrocenylmethyl and hydroxyalkyl) with the objective to prepare biologically active products. The aim was to devise simple derivatisation procedures to incorporate ferrocenyl or indolyl units in order to test the antifungal activity of the resulting products. By this approach we design to overcome the limits of active biocides and anticancer agents developed in the last few decades and based on a ferrocene substituent attached to complex biological molecules.[9]

The specific topics investigated can be summarized as follows (based on the thesis chapters):

Chapter 1. Glycerol and Glycerol Carbonate in the Context of Green Chemistry. This chapter is devoted to the introduction to Glycerol, its production, availability, and approaches to glycerol valorization, also methods to prepare glycerol carbonate is described in detail.

Chapter 2. Synthesis, purification and reactivity of diglycerol dicarbonate and conversion to stereoselective oligomers and polymers. In this context the following aspects were studied and explored: a) Green synthesis of diglycerol dicarbonate from impure diglycerol using carbonatation reaction by thermal or by microwave irradiation; b) Purification of *d,l*- and *meso*-diglycerol dicarbonate by crystallization; c) Hydrolysis of pure *d,l*- and *meso*-diglycerol dicarbonate to stereoordered α-diglycerols ; d) Selective nucleophilic substitution reactions at terminal C-O bond of pure *d,l*- and *meso*-diglycerol dicarbonate by N and O centred nucleophiles, e) Conversion of *d,l*- and *meso*-diglycerol dicarbonate to new stereo-ordered monomers and polymers. In all these cases the progress of reactions were controlled by using TLC, HPLC, GC-mass or capillary electrophoresis and the purified products were obtained by silica gel column chromatography and crystallization, and then characterized via ^{1}H-/^{13}C-NMR, IR, and LCMS. X-ray crystallographic study and SEM analysis were made where ever necessary. For the characterization of polymers, differential scanning calorimetry (DSC) and thermo gravimetric analysis (TGA) were applied. The same analytical techniques were applied also in the following explored areas.

Chapter 3. Cascade or one pot tree component solvent free synthesis of α-glycerolcarbamates. Methods to prepare carbamates and polyurethanes are of special interest for the biological activities of

the molecules containing this functional group and the versatility of these polymeric materials. In recent years special attention has been devoted to the substitution of dangerous and toxic reagents (isocyanate, phosgene, nitro derivatives, etc.) commonly used for the synthesis of these important compounds with more safe and benign equivalents. Alkyl and aryl carbonates were proposed as possible substitutes, but the drastic conditions generally used with these reagents prevented any selective transformations on polysubstituted derivatives. We approach the problem using glycerol as substrate, starting from the reactivity of glycerol carbonate (GC) and identifying conditions of significant selectivity. 5-Membered cyclic carbonates are generally slightly more reactive than simple dialkyl carbonates, but we found that GC shows much higher reactivity. From this starting point we devise a simple, direct approach to the synthesis of α-glycerolcarbamates by using one-pot three components system consisting of amines, organic carbonates and glycerol. The key point was a careful selection of the alkyl substituent of the alkyl carbonate in order to control the kinetics of complex interplay of parallel and consecutive nucleophilic substitution reactions.

Chapter 4. Easy Solvent Free Synthesis of Novel 1-Ferrocenylmethylglycerols and its derivatives as antifungal agents. For the synthesis of ferrocenylglycerol derivatives (in principle useful as bioactive compounds) a direct, green method was studied consisting in condensing ferrocenylalkanols with glycerol or its derivatives under mild conditions (20-90°C) without or in the presence of co-solvent and/or catalyst. Homogeneous Brönsted acid catalysis was mainly investigated but some work was carried out, in collaboration with the Pune University (India), with the novel heterogeneous Lewis catalyst aluminum nitride (AlN/Al). The role of carbon dioxide as promoter in these reactions was investigated and proved effective, but not general, with 1,2-diol substrates. The new water soluble, mono-substituted functional ferrocenylglycerol derivatives were tested in vitro for their antifungal activity towards 3 different plant fungi, *Fusarium spp*., *Botrytis cinerea*, *Penicillium spp*. The experiments were performed by surface and inclusion treatment of the cultural growth mediums, and shown significant antifungal activity, in general better expressed in the surface treatment method. The heterogeneous AlN/Al Lewis acid catalyst was mainly investigated in the condensation of carbonyl compounds with indoles to afford the corresponding bis(indolyl)methanes, compounds known to be biologically active agents. The catalyst, characterized by SEM, Raman and particle size analysis, was found recyclable and worked without any significant change in its catalytic activity for 10 cycles, this work related to bis(indolyl)methanes has been not included in the thesis but the publication[11] of this work is available in appendices.

Chapter 5. Hydrogen peroxide/Ethyl lactate: A New Eco-Friendly Peracids-like System for the Oxidation of Organic Compounds. The easily available and green solvent ethyl lactate was explored in the context of oxidation reactions. The presence of two reactive groups (OH and COOR) makes the compound in principle not such as an ideal solvent for oxidations. The research was mainly focused on the combination of this reagent with hydrogen peroxide. The system was characterized by a fast decay of the peroxide, but oxidations were observed in the presence of selected organic derivatives (organic sulfides, phospines, and carbonyl compounds to the corresponding sulfoxides, phosphine-oxides and esters through Bayer-Villiger reaction). The previous unknown perlactic acid was hypothesized as intermediate produced by *in situ* solvolysis of ethyl lactate by H_2O_2 and its fast decay explains the unsuccessful use of the system in the epoxidation of alkenes.

Results and discussion:

Chapter 2. The core of the research described in Chapter 1 was the preparation of *d,l*- and *meso*-diastereoisomers of diglycerol dicarbonate (DGDC) and the study of its reactivity towards base catalyzed nucleophilic substitution of C-O bond by N-, and O-centered nucleophiles. Factors controlling reactivity at terminal and internal carbon atom were identified and conditions were designed to reduce the outcome at C-2. The following results were specifically obtained:

A) Synthesis of diglycerol dicarbonate. A procedure to synthetize diglycerol dicarbonate (DGDC) by carbonatation reaction of commercially available impure αα'-diglycerol using diethyl carbonate (DEC) or dimethyl carbonate (DMC) under basic catalysis was developed, with high yields and without solvent by (1) thermal and (2) under microwave irradiations. Optimum conditions under basic catalysis were identified in comparative studies. Related data for *d,l*- and *meso*-GDGC diastereoisomers are summarized in Figure 1.

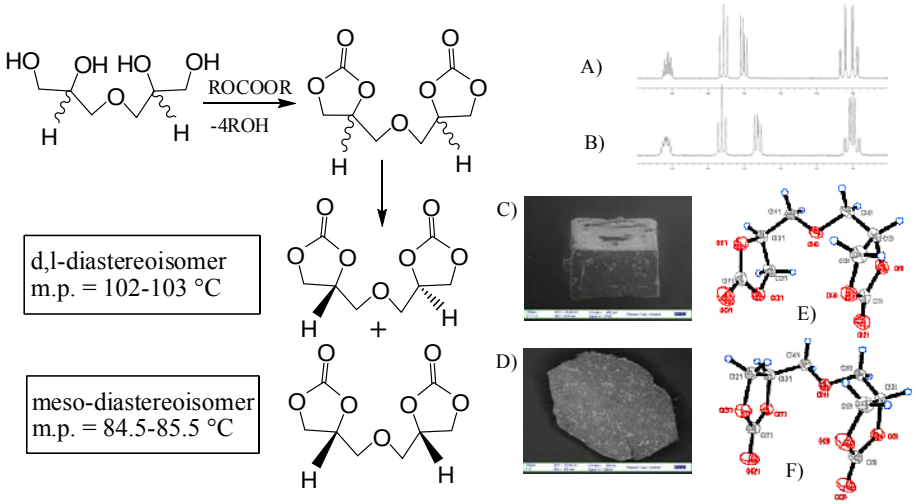


Figure-1 ^{1}H-NMR of DGDC A) *d,l*-DGDC, B) *meso*-DGDC, SEM micrographs of single crystals of C) *d,l*-DGDC and D) *meso*-DGDC, Structural characterization by X-rays of the two diastereoisomers; E) *d,l*, F) *meso*.

B) Purification of *d,l*- and *meso*-diglycerol dicarbonate by crystallization. A procedure has been developed to isolate pure forms of *d,l*- and *meso*-DGDC starting from the mixture of the diastereoisomers by crystallization. To improve the process productivity, a crystallization study in different solvents was carried out. The two diastereoisomeric forms of DGDC were characterized via ^{1}H-NMR, X-Ray crystallographic studies and SEM analysis; they shows different crystal structure and physical properties, as summarized in Figure 1.

C) Hydrolysis of pure *d,l*- and *meso*-diglycerol dicarbonate.

To our knowledge, no analytical or physical methods for separation nor a synthetic route to access to *d,l*- and *meso*-diglycerol (DG) diastereoisomers has been yet reported in literature. These compounds were selectively obtained from pure *d,l*- and *meso*- αα'-DGDC diastereoisomers in excellent yield by

hydrolysis under different acidic or basic catalysis and optimized reaction conditions. The stereo centers were preserved. In Figure 2 are reported the ^{1}H-NMR spectra of the pure diastereoisomers and the corresponding 1:1 mixture.

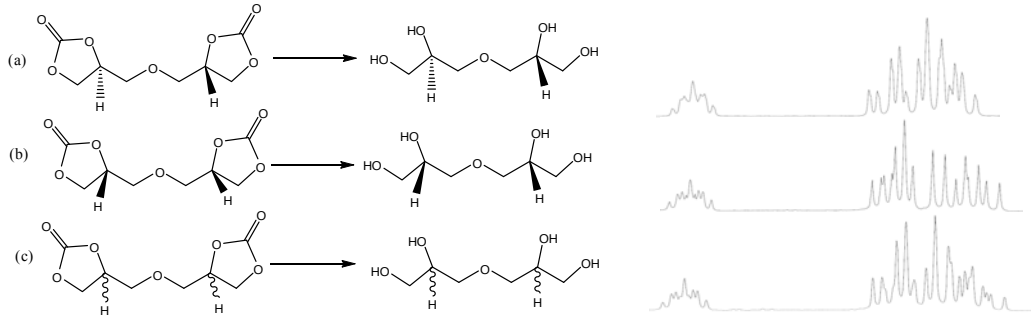


Figure 2. Hydrolysis of a) *d,l*- b) *meso*- c) mixture -DGDC ^{1}H-NMR *d,l*-; /*meso*-/1:1 mixture of α,α'-diglycerol

D) N and O centred selective nucleophilic substitutions reaction, on terminal C-O bond of *d,l*- and *meso*- DGDC.

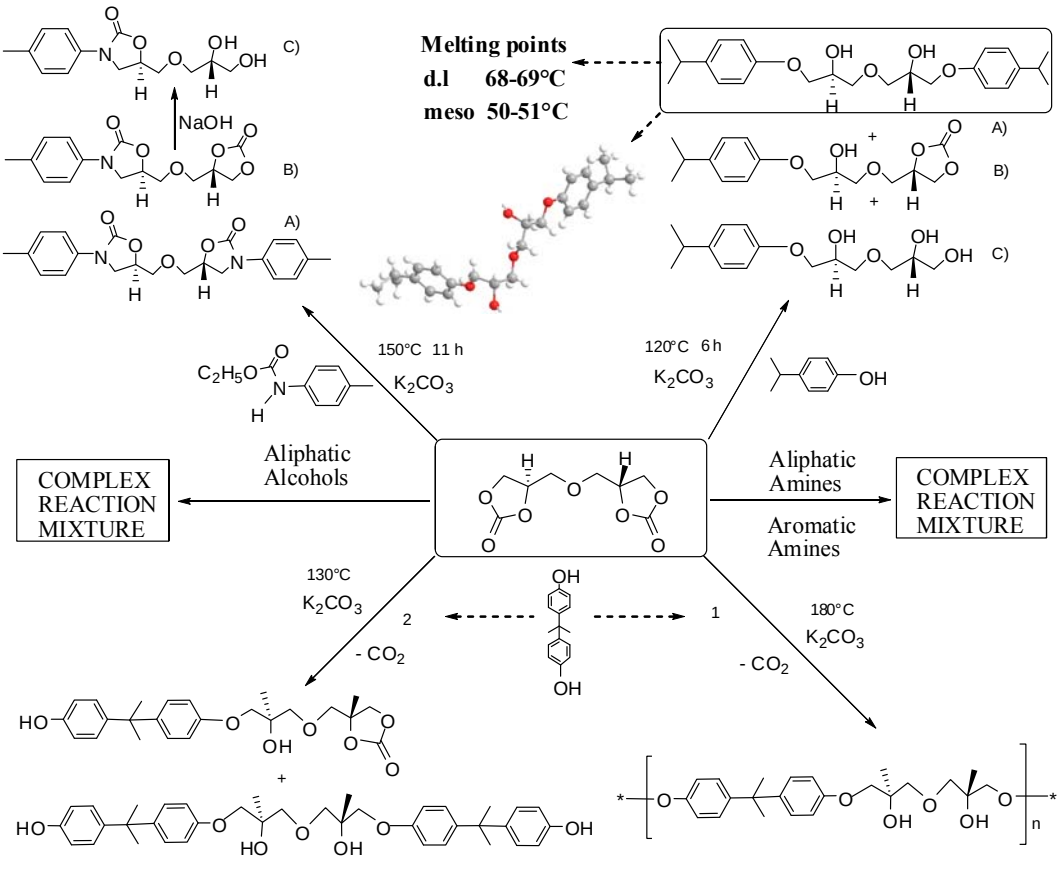


Figure-3 Stereoselective O and N nucleophilic substitution reactions on *d,l* diastereoisomer of DGDC.

Methods have been developed for the N and O centred nucleophilic substitutions at terminal C-O bond of pure *d,l*- and *meso*-DGDC diastereoisomers by using soft nucleophiles, such as carbamates and

phenols under basic catalysis.[10] On the contrary, hard oxygen and nitrogen centered nucleophiles fail to give clean substitutions. The obtained mono- and di-substituted compounds were found to retain the stereochemistry as deduced from ^{1}H-NMR, ^{13}C-NMR and X-Ray crystallographic studies. A pictorial summary of the reaction carried out and reaction conditions used under the best conditions are summarized in Figure 3.

E) Selective synthesis of stereo-ordered monomer and polymers from pure *d,l*- and *meso*-DGDC diastereoisomers.

Extension of the approach, outlined in the previous paragraph, to difuctional nucleophiles (i.e. diphenols and diamines) allows developing a method for the regioselective polycondensation of diglycerol derivatives. Distributions in molecular weight, chemical composition, chain architecture, and functionality were analyzed providing evidence that under basic catalysis the polymerization occurs without any crosslinking, suggesting that the internal OH groups in the polymer are unreactive towards further substitution. An experimental design, based on a multivariate sequential method and HPLC and CE analyses, was used to optimize yield and selectivity toward linear polyglycerols. With the aid of kinetic analyses, "one-pot" reactions were also assembled, in case starting from unprotected glycerol, under microwave irradiation. Preliminary exploration of possible uses of these polymers in environmental, analytical, and industrial sectors (cosmetic, pharmaceutical) was carried out. Oligomers and polymers obtained contain one OH group for glycerol residue which allows for further derivatisation to tune the mechanical properties and polarity of the polymer or to obtain co-polymers or improve crosslinking.

In conclusion: Stereo-ordered α,α'-diglycerol dicarbonate and α,α'-diglycerol are easily prepared and versatile intermediates, which can be successfully converted to a variety of interesting intermediates and stereo-ordered oligomers and polymers.

Chapter 3. Polyhydroxyurethanes are compounds of great interest having a wide range of applications in pharmacology, agriculture, and chemical industry, their conventional synthesis is based on the use of toxic reagents like isocyanates, phosgene, nitro derivatives, etc. It is important to substitute these reagents with green reagents like CO_2 or organic carbonates, but the drastic conditions generally used with these reagents prevented any selective transformations on poly-substituted derivatives. In order to solve the problem we have developed a new efficient synthetic route for the preparation of difunctional and polyfunctional molecules from C-3 inherent natural polyol monomer that is glycerol and green alkyl carbonate. α-glycerolcarbamates were selectively synthesized by single-step three components system (glycerol, dialkyl carbonates, and aliphatic amines or polyamines). Factors affecting the selectivity at terminal to internal carbamate isomers were investigated and the key role of the intermediate in-situ formed linear carbonate ester of glycerol for selective substitution at the terminal position was ascertained. Inhibition of further substitution by the carbamate product was also observed, facilitating the selective mono-functionalization of substrate. By this approach polyurethanes can be obtained under mild conditions and good productivity by using di- or poly-amines. In Figure 4 are collected some comparative results for the one step or two step procedures developed in this study.

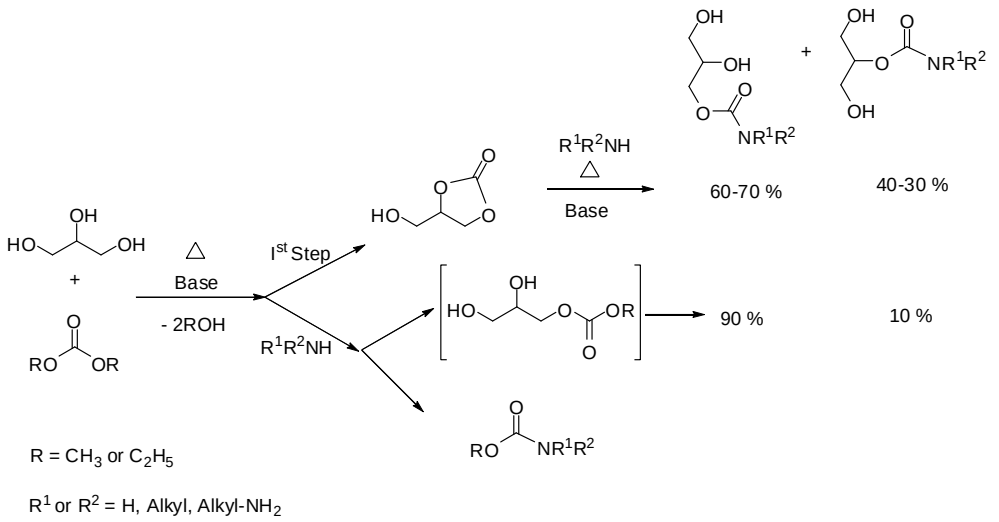


Figure 4. Selective one-pot synthesis of glycerol carbamates from glycerol (through *in-situ* formed linear glycerol carbonate), compared with the corresponding two steps reaction (through cyclic glycerol carbonate)

In conclusion:- A new single step method for the synthesis of α-glycerol carbamates in high yield and good selectivity is developed starting from glycerol, amine and diethyl carbonate involving a three components system, without solvent. The method can be applied to obtain polyurethane.

Chapter 4. The synthesis of target ferrocenylalkylglycerol ethers and bis(indolyl)methanes was approached through easy and green electrophilic condensation reactions and the obtained products were investigated for their biological activity. The synthetic approaches were different for the two classes of derivatives:

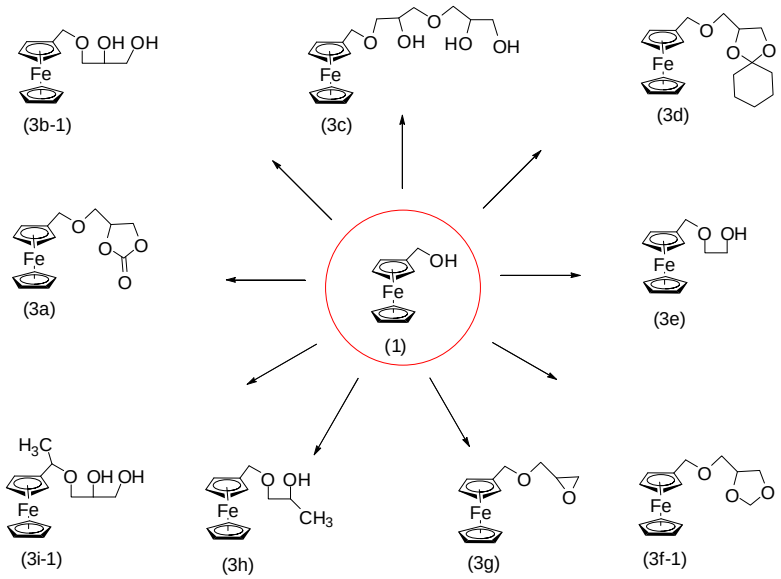
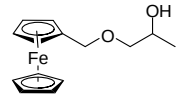
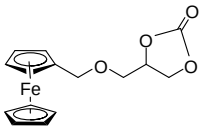
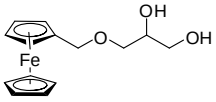
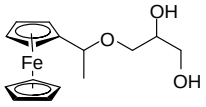


Figure 5. Synthesis of ferrocenylalkylglycerol ethers by etherification of ferrocenealkanols with glycerol and its derivatives without solvent and catalyst.

A) Synthesis of 1-Ferrocenylalkylglycerol ethers. The direct high yield synthesis of novel 1-ferrocenylmethylglycerol ether and its derivatives, without solvent and acid catalyst under mild conditions (20-90°C), was carried out by ferrocenylalkanol solvolysis in glycerol, glycerol carbonate, glycerol formal, cyclohexanone glycerol ketal, glycidol, diglycerol, and 1,2-dihydroxy propane (Figure 5). The role of carbon dioxide as acid promoter for the reaction was also investigated and proved effective with 1,2-diol substrate. Kinetics of representative reactions were also determined in the presence or absence of different acid catalysts and at different substrate concentrations and temperature. Mechanistic details (as intramolecular catalysis by H-bonds) and the S_N1 nature of these processes was ascertained.

Table 1 - Antifungal activity of selected ferocenylalkylethers against 3 different fungi

Sample		Fungal Growth Inhibition (FGI %)					
		Penicillium spp.		*Fusarium spp.*		*Botrytis Cinerea ssp.*	
		Surface	Inclusion	Surface	Inclusion	Surface	Inclusion
3h		77.0 (100) 46.2 (100) 74.6 (1)	84.2 (100) 58.2 (100) 46.8 (1)	23.4 (100) 7.4 (100) 817.8 (1)	2.0 (7) 0.6 (6) 12437 (22)	68.1 (100) 35.3 (100) 117.1 (1)	62.0 (100) 30.1 (100) 153.0 (1)
3i		72.2 (93.8) 40.2 (87) 96.1 (1.3)	72.6 (86) 40.2 (69) 96.9 (2.1)	22.0 (94) 6.8 (92) 884.5 (1.1)	0.4 (1) 0.2 (2) 62437 (109)	44.1 (65) 17.2 (49) 316 (2.7)	39.0 (63) 14.0 (47) 390 (2.6)
3b (1+2)		53.9 (70) 23.2 (50) 213.8 (2.9)	56.0 (66) 24.6 (42) 196.4 (4.2)	15.8 (67) 4.5 (61) 1332 (1.6)	12.06 (40) 4.0 (43) 1734 (3)	59.1 (87) 27.2 (77) 173 (1.5)	57.6 (93) 25.7 (85) 184 (1.2)
3i (1+2)		50.6 (65) 21.0 (45) 244.1 (3.3)	59.6 (71) 27.3 (47) 169.5 (3.6)	11.2 (48) 3.2 (43) 1982 (2.4)	19.8 (66) 6.2 (68) 1012 (1.8)	66.5 (98) 33.8 (96) 125 (1.1)	38.2 (62) 14.7 (49) 404 (1.1)

For any experiment are reported three data: FGI% at [sample] = 250 mg/mL, FGI% at [sample] = 62.5 mg/mL; and IC_{50} (mg/mL). The numbers in brackets are the corresponding normalized values, respect to the best values in the column.

The synthetized derivatives were tested for their antifungal activity in vitro on 3 different plant fungi, *Fusarium spp*., *Botrytis cinerea*, *Penicillium spp*. The experiments were performed by surface and inclusion treatment of the cultural growth mediums. The results summarized in table 1 clearly

indicate that all compounds show good to moderate activity, in general better expressed in the surface treatment method.

B) Synthesis of Bis(indolyl)methanes. During my PhD, for foreign period (3 month), I worked in collaboration with Dr. Rajendra P. Pawar, Head Department of Chemistry, Deogiri College, Aurangabad and Pune university, (MS), India, on "Micron Particles of AlN/Al: Efficient, Novel and Reusable Heterogeneous Catalyst for the Synthesis of Bis(indolyl)methanes". We have developed a simple, rapid and efficient method for the synthesis of bis(indolyl)methanes as biologically interesting compounds via electrophilic condensation of indoles with carbonyl compounds using micron particulate aluminium nitride as a novel Lewis acid catalyst in excellent yield. The striking features of this new protocol are cleaner reaction profiles, simple experimental and work-up procedures, high conversions, shorter reaction times to afford the bis-addition products in excellent yield, hence believed to be superior over many existing catalysts.[11]

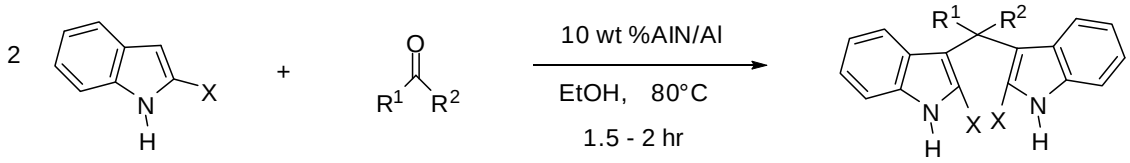


Figure 6. Synthesis of bis-indolylmethanes by electrophilic condensation of ketones and indoles catalyzed by heterogeneous AlN/Al micron catalyst.

In conclusion:

Two simple, cheap and easy approaches were developed for the synthesis of a series of biologically active compounds by not catalyzed or acid catalyzed electrophilic condensation. Ferrocenylalkanols easily solvolyse in polyol solvents to the corresponding ethers under general Bronsted acid catalysis: with glycerol derivatives no catalyst is necessary, whereas with less acidic alcohols acid catalysis is essential. In the synthesis of bis(indolyl)methanes a new heterogeneous micron particulate catalyst (AlN/Al) was developed and found efficient in electrophilic substitution of indoles by carbonyl compounds. Both series of synthetized compounds have shown good to moderate antifungal activity in biological tests.

Chapter 5. Oxidation of organic substrates by using H_2O_2 is a widely explored area, frequently applied on industrial scale. However H_2O_2 is relatively unreactive molecule and strong efforts have been devoted for selection and use of catalysts to accelerate or control the processes. Inorganic and metal catalysts were deeply investigated where as the use of organic catalyst was more scantly analyzed and applied (except for formation of alkyl or arylalkyl peroxides and peracids). However, for a "green oxidation" point of view the ideal system is the one which use environmentally-friendly

oxidants together with recyclable catalysts in a nontoxic solvent. Thus, the use of organic solvents able to dissolve a wide variety of substrates and to activate H_2O_2 was explored as oxidant system, focusing on natural esters of α-hydroxy carboxylic acids. We found that ethyl lactate, an easily available, green and safe solvent, has the peculiarity to react rapidly with H_2O_2 to give an intermediate able to oxidize organic sulfides RSR', reduced organophosphorous substrates of general structure [$PR_x(OR)_{3-x}$ with x = 0-2], to the corresponding oxygen addition products sulfoxides, phosphine oxides, phosphates, phosphinates and phosphonates, where as carbonyl compounds were converted to the ester in a Bayer-Villiger oxygen insertion reaction. The oxygenation of aryl methyl sulfides, follows an overall second-order kinetics, first order in H_2O_2 and sulfide and involve general acid catalysis. In *p*-substituted phenyl methyl sulfides the negative r value obtained in the correlation analysis of rate constants with s constants indicate that positive charge is generated on sulfur atom and the electrophilic oxygen of "perlactic acid" is responsible for the acceleration by electron withdrawing substituents. The fast decay of the peroxidic intermediate prevents the possibility to apply the system to less reactive substrates, i.e. olefins and electron withdrawing substituted aromatics. Figure 7 summarizes the oxidation reactions investigated with this system.

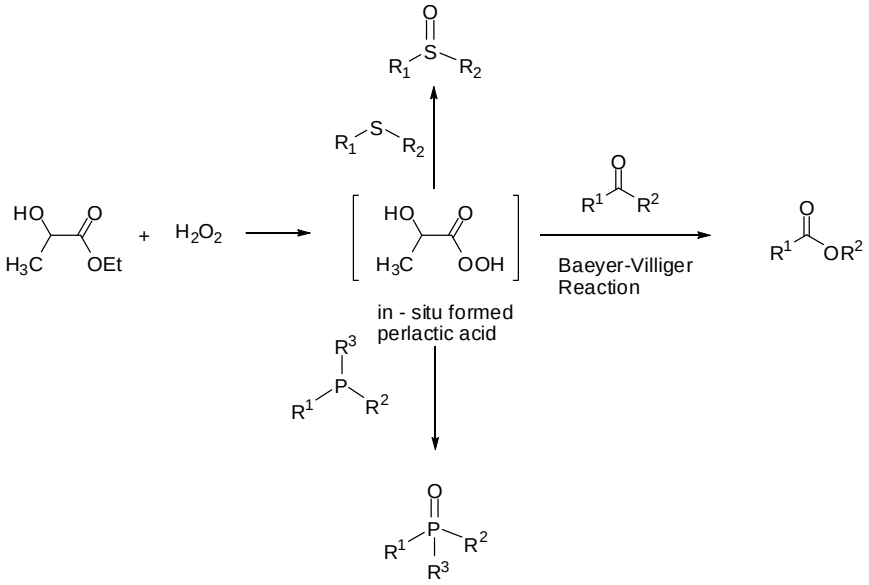


Figure 7. Organic oxidation reactions tested for the system H_2O_2/ethyl lactate.

In conclusion: A new eco-friendly green oxidation system was identified consisting in the mixture of H_2O_2/ethyl lactate. From preliminary screening experiments this oxidizing agent is effective for the selective conversion of sulfides to sulfoxide, phosphine to phosphine-oxides, of carbonyl compounds to esters through a Baeyer-Villiger reaction. The high solvation power of ethyl lactate towards a large variety of organic compounds and the mild reaction conditions makes this system of great potentiality in organic oxidations and open expectations for industrial synthesis of fine and specialty products and materials.

Overall conclusions:-

The present investigations have shown that Green Chemistry approaches by using both bio C-3 starting materials and mild conditions can be successful to perform organic catalytic reactions in different areas of industrial synthesis.

Particularly promising are the reactions of glycerol with nucleophilic species after activation ex-situ or in situ by carbonate esters. This will allows to carry out several new in situ cascade reactions on this substrate, as proved by the one identified by us of synthesis of glycerolcarbamate. Also the explored areas of stereo-ordered polyglycerols appear to be quite promising for the versatility of the possible further transformations and the peculiarity of the polymers which can be obtained.

The successful synthesis of antifungal agents novel ferrocenylalkylglycerol ethers and bis-indolylmethanes clearly indicates the potentiality of green methodologies, based on electrophilic reactivity, in the contest of the screening for biological active molecules. The approach can be easily applied in a general context for the construction of selected libraries and for the related biological screening.

An interesting side result of this thesis was the identification of novel heterogeneous catalysts (AlN/Al) for electrophilic substitution. Developed in collaboration with the University of Pune and Aurangabad, this catalyst proved to be very successful for acid condensation of substituted indoles with carbonyl compounds and depending on the catalyst loading reaction times in a batch reaction could be in order of minutes.

The ethyl lactate/hydrogen peroxide system developed in this thesis is also quite promising, even if some limitations are apparent due to the relatively fast decomposition of the intermediate. A detailed kinetic study should be carried out to better define the decomposition fate of the perlactic acid intermediate and the related safety conditions of use.

Additionally, to achieve full Green Chemistry processes for the reactions investigated, more optimization experiments are necessary and physico-chemical data must be accumulated. Ultimately, the development of a pilot plant scale for the more promising reactions, one-step synthesis of 1-glycerolcarbamates and oxidations by H_2O_2/ethyl lactate system, operating in continuous mode would allow for evaluating practically the real relevance of these processes for industrial applications.

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Chapter – 1

Glycerol and Glycerol Carbonate in the Context of Green Chemistry.

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Glycerol and Glycerol Carbonate in the Context of Green Chemistry.

1.1 Introduction

In recent years a remarkable attention has been devoted to the conversion of glycerol into high-value chemicals, spurred by the emergence of glycerol as an abundant renewable resource, mainly related to the growing of the biodiesel production but also from the fermentation of glucose. Glycerol valorisation plays in fact a relevant role in the general context of environmental impact and cost reduction of biodiesel production processes and, more broadly, of oleo-chemistry. The reason of the selection of glycerol and its derivatives as substrate to prepare value added products by the trasesterification and carbamoylation reactions is due to the recent growing interest for biofuels and, more in general, for the so-called "green chemistry", that is a specific attention to the sustainability of chemical sources and development of safe, efficient, fast and quality oriented processes.

Transesterification is a well-known reaction whose importance has grown in connection with the recent interest to produce biodiesel by trans-esterification of vegetable oils (Figure 1) as a simple and economical acceptable method to access biofuels, owing to the low costs of reactants and catalysts and the relatively simple technology. Plants with high oil content (i.e. palm- rapeseed-, sunflower- or jatropha oil) are in the focus of the renewable feedstock research. The oils extracted from these plants are used for the production of bio-diesel. The combustion of this diesel fuel, where the carbon atoms are originated from renewable bio-resources, is considered to be environmentally benign, since the process does not emit new carbon atoms to the atmosphere, but only the ones which the plants absorbed during photosynthesis.

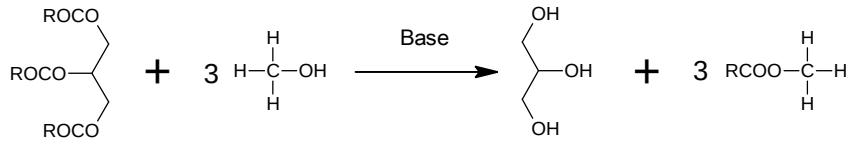


Figure 1– General scheme for the transesterification reaction of glycerides by methanol to produce FAME. Glycerol is the co-product of the process.

The first step of the biodiesel process is the refining of the oils to eliminate impurities and byproducts (i.e sterols, phospholipids, carboxylic acids, etc.) in order to limit the catalyst consumption and undesired byproducts. Conversion to biodiesel from appropriately refined oils is currently realized by methanol transesterification catalyzed by homogeneous or heterogeneous bases (NaOH, $Ba(OH)_2$, NaOMe,

$ZnAl_2O_4$, etc.) (Figure 1). The final methyl esters of carboxylic acids (FAME) have quite stringent quality requirements to be sell in the fuel market (i.e. must contain at least 96.5% of esters, less than 200 ppm of glycerol, less than 10 ppm of phosphorous, etc.). The demand for vegetable oils has increased rapidly in the past decade, catapulted by a combination of factors, including: i) increasing demand sparked off by higher consumption for edible oils, ii) the development of the biodiesel industry around the world, particularly in the EU, USA, Brazil, Argentina, China and India, iii) price increases which have been due to varying factors, changing weather patterns which can have major geographical impacts, iv) change in agriculture practices.

Wherever the raw materials come, the main issue regarding the process economics of biodiesel is the growing quantities of glycerol obtained as inevitable co-product: 10 kg of glycerol every 100 kg of biodiesel synthesized.[1] Actually the European and American annual production of this commodity is about 950000 [t/y] with an annual increase of 3%.[2]

Glycerol (1,2,3-Propanetriol or glycerin), a C-3 triol with formula $C_3H_8O_3$, is a well-known commodity used for decades in the industry as such or by conversion to a number of derivatives. It is a non-toxic, sweet tasting (about 75% as sweet as sucrose), colorless and viscous liquid, very polar in nature, therefore freely soluble in water and polar solvents, less soluble in organic solvents, such as ethers, and insoluble in hydrocarbons. Glycerol is widely produced from natural oils and fats as the side product of the saponification process and more recently of the transesterification to biodiesel. Two alternative chemical processes for the production of glycerol from petrol are also known: a) hydrolysis of epichlorohydrin, in turn obtained by radical chlorination of propylene and reaction of the intermediate allyl chloride with hypochlorous acid followed by calcium hydroxide, and b) hydrolysis of glycidol obtained by epoxydation of allyl alcohol catalyzed by tungstic acid salts ($NaHWO_4$). The product obtained from petrol is mainly used in industrial sectors, whereas glycerol from natural sources and from vegetable oil in particular, is used in pharmaceutics, cosmetics, food and polymers industry. More than 3000 different actual uses are known for this chemical. Some typical applications of glycerol are:

- Monomer for the production of polymers (alkyl resin, polyols, polyethers, polyurethanes, etc.);
- Solvent for food flavorings and colorings (also cosmetics);
- Emulsifier, humectant, lubricant, smooting and moistening agent;
- Tobacco production;
- Low temperature preserving agent and heat transfer mediums for frozen foods

Between the thousands of glycerol's derivatives some are very popular, i.e:

- Nitroglycerine;
- Acetin, from esterification of glycerol with acetic acid;
- Glycerides, mono, di-esters and tri-esters, used as emulsifier in the food and cleaning industry;
- Polyglycerols, used as lubricant, plasticizer, moisture agents, etc..

The many fields of use of glycerol are summarized in Figure 2, as summarized by a recent review on this compound.[3]

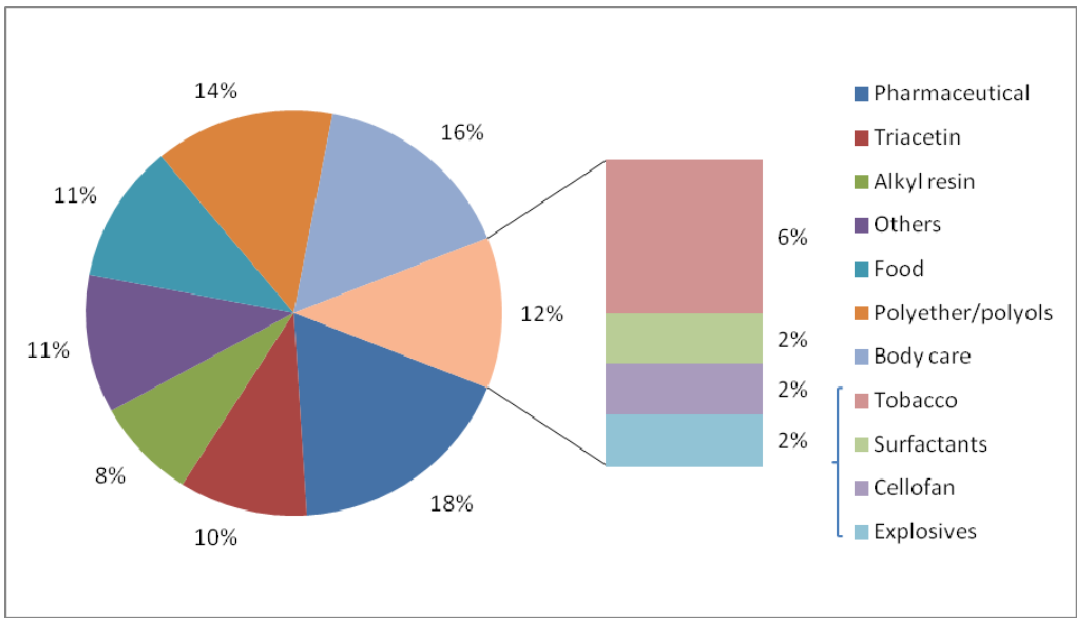


Figure 2 - The current fields of use for glycerol.

As previously indicated, food, pharma and cosmetic industry demands only very pure USP grade glycerol and the development of glycerol in these traditional fields depends mainly on final users and is quite uncertain. Moreover, the glycerol produced from biodiesel process is polluted with oils, salts (5-7 %) and additionally it is diluted with water (typically its purity is less than 85%) and costly procedures for purification must be applied. Accordingly, the price of crude glycerol decreased from about $0.55 per kg to $0.11 per kg. Therefore development of sustainable processes for utilizing this organic raw material is imperative and crude glycerol valorization plays a relevant role in the general context of environmental impact and cost reduction of biodiesel production processes and, more broadly, of oleo-chemistry. It is of concern of researchers the identification of new applications of crude glycerin.[4] Actually, the world market of glycerol is saturated and the main use of crude 80-85% glycerol is as food supplement for animals.

1.2 Approaches to glycerol valorization

The roadmap for glycerol valorization will proceed essentially through derivatization of the molecule both at carbon and at oxygen atoms. Until now the chemistry of this compound proved difficult to dominate, owing to its highly functionalized structure, and industrial processes were mainly restricted to simple substitutions.[5] In nature these limitations are less severe and a wide range of enzymatic reactions are known involving this key C-3 metabolite. Therefore, bioprocesses are expected to offer relevant opportunities for this compound, as recently demonstrated by Dow Chemicals in the production of 1,3-propandiol. Improvements in conventional homogeneous and heterogeneous catalysis have also provided good examples of complex functionalization of glycerol, including oxidative, reductive and substitution pathways, with high selectivity. The present efforts aim to define the potentiality of glycerol as C-3 chemical platform for future bio-refineries, in alternative to lactic acid.[6]

In Figure 3 are reported the main chemicals expected to be produced in future from glycerol. The more relevant appears 1,3-propandiol, epichlorohydrine, acrolein, allyl alcohol, dihydroxyacetone, glyceraldehyde, acetol, pyruvic acid, glyceric acid, 1,2-propandiol, etc. Same of the compounds are expected to be produced in single step from glycerol, some other from further elaboration of primary intermediates. Typical is for example the recently developed Epicerol process developed by Solvay and Dow to produce epichlorohydrine from glycerol.[7]

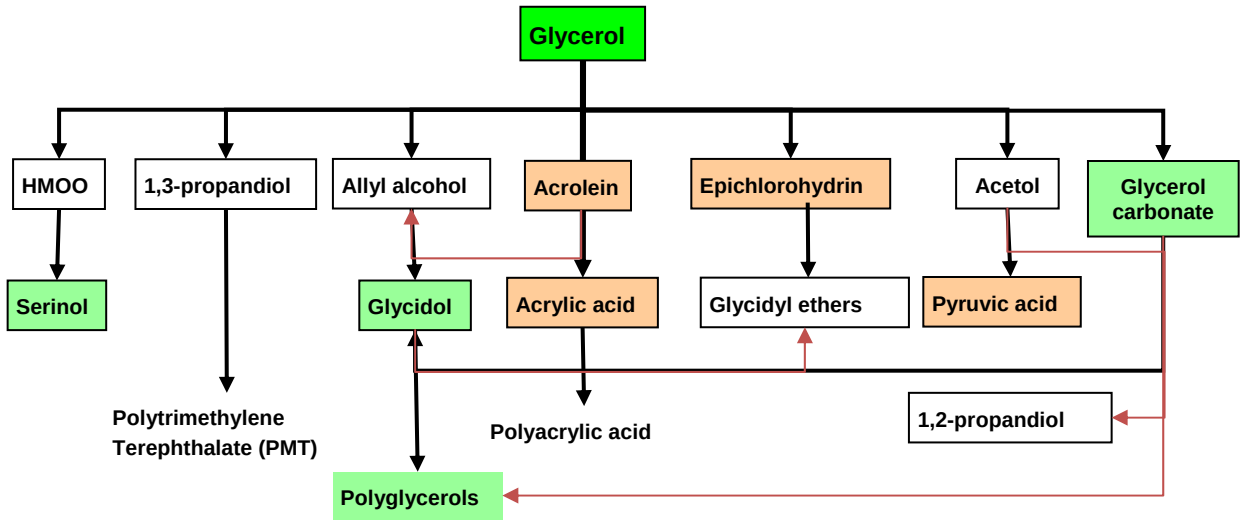
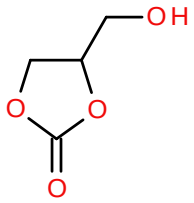


Figure 3 – Glycerol as C-3 chemical platform – The main derivatives.

Between the derivatives of glycerol, a special role is expected to be played by glycerol carbonate (4-hydroxymethyl-[1,3]dioxolan-2-one, **1**), a non-toxic, tasteless, colorless and non-viscous liquid, very polar, protic and good solvent, with remarkable stability but significant reactivity.[8]



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Glycerol carbonate is an ecological substitute for important petroleum-derivative compounds (e.g. ethylene carbonate or propylene carbonate).[9] Glycerol carbonate has value both as solvent and as chemical intermediate. As a solvent, it is used for produce polymers and resins (e.g. cellulose, acetate, polyamides, nitrocellulose and polyacrylonitrile). As chemical, it reacts with phenols, alcohols and carboxylic acids upon heating to form the corresponding glycerol ethers or esters. One of the most valuable uses of glycerol carbonate is as source of glycidol by thermally controlled decomposition at 130-200 °C. Because glycerol carbonate is non toxic whereas glycidol is toxic and relatively unstable, the carbonate represents a safe and readily accessible source of glycidol[10] which is a relevant precursor for the synthesis of polymers containing the soft glyceric units.[11] Also some derivatives of glycerol carbonate have useful properties, i.e. fatty esters can be used as surfactants and lubricating oils. Due to its low toxicity, low evaporation rate, low flammability, and moisturizing ability, GC is used as wetting agent for cosmetics and carrier solvent for medical preparations. On the other hand, the presence of a cyclic carbonate group along with a primary hydroxyl methyl group allows the molecule to react with anhydrides[12] to form ester linkages or with isocyanates to form urethane linkages.[13] These materials are used for the production of polyurethane protecting coatings for wood and metal substrates.

1.3 Methods for the synthesis of glycerol carbonate (1)

Several syntheses have been proposed for glycerol carbonate **1**. Recently there are nice reviews published on synthesis and reactivity of glycerol carbonate.[14] The more important processes use glycerol as starting material (1-5), but recently some attention has been addressed also to carbonatation of glycidol (6). The different approaches are summarized in Figure 4.

1) Carbonylation of glycerol by phosgene
2) Transcarbonatation of glycerol by organic carbonates
3) Carbonylation of glycerol by urea
4) Carbonatation of glycerol by carbon dioxide
5) Oxycarbonylation of glycerol
6) Catalyzed carbonylation of glycidol by carbon dioxide

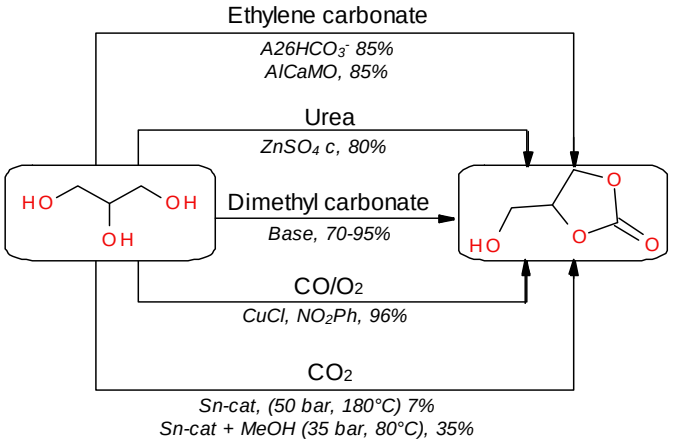


Figure 4 – Summary of reagents and conditions used to convert glycerol into glycerol carbonate.

1) Carbonylation of glycerol by phosgene

Cyclic carbonates have been synthesized from the corresponding 1,2-diols and the highly toxic gas, phosgene.[15] So, glycerol carbonate can be prepared by this approach in good yield (Figure 5), but the process is characterized by a low atom economy and is now recognized as unsafe and highly polluting, so alternative routes such as transesterification reaction of dialkyl or alkylene carbonates were applied.

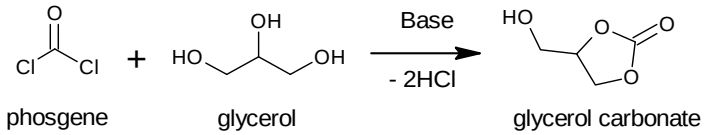


Figure 5 - Synthesis of glycerol carbonate from glycerol and phosgene

2) Transcarbonatation of glycerol by organic carbonates

A more practical method to produce glycerol carbonate is the transesterification of glycerol by dimethyl carbonate,[16] and more generally by dialkyl carbonates (figure 6).

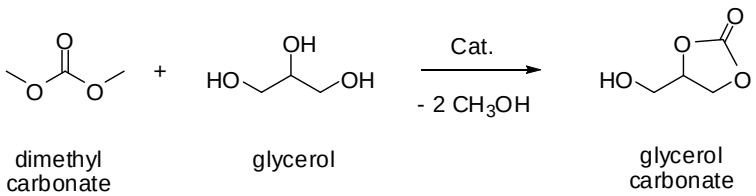


Figure 6 - Synthesis of glycerol carbonate from glycerol and dimethyl carbonate.

Dimethyl carbonate can be manufactured by environmental safe industrial methods and potentially from CO_2 and renewable sources. Many of the properties of dimethyl carbonate make it a genuinely green reagent, particularly if compared to conventional alkylating agents (e.g. methyl halides, dimethyl sulfate or phosgene used as a methoxycarbonylating agent).[17] Dimethyl carbonate is not toxic.[18] It can be produced by catalytic oxidative carbonylation of methanol with oxygen through a process developed by Enichem.[19] The only dangerous characteristic of dimethyl carbonate is that it is a flammable substance, but it does not exhibit irritating or mutagenic effects. Finally, dimethyl carbonate has a broad chemical reactivity.

In literature two different mechanisms for the transesterification reaction of glycerol by dimethyl carbonate were suggested.

1) When mild base catalyst is used, the transesterification reaction of glycerol and dimethyl carbonate involve a neutral intermediate that undergoes intramolecular cyclization, losing 2 moles of methanol as a by-product (Figure 7).[20]

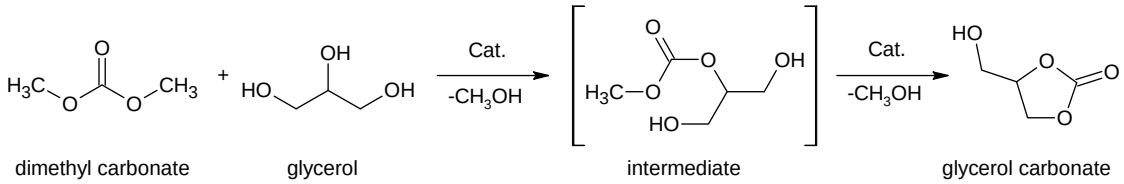


Figure 7 - Intermediate unsymmetrical carbonate in the formation of glycerol carbonate from glycerol and dimethyl carbonate under mild base catalysis.

2) In a second mechanism the base-catalyzed transesterification proceeds through a more basic alkoxide anion.[21] The first step in this case is a proton exchange reaction between the basic catalyst and the weak acid OH of primary hydroxyl groups of glycerol. This step leads to the corresponding glyceroxide anion and the conjugated acid of the base. Owing to the low acidity of the hydroxyl group, a strong base is needed. In the second step nucleophilic addition of glycerolate anion to the carbonyl group of dimethyl carbonate affords a mixed methyl glyceryl carbonate intermediate and a methoxide anion. In the third step, the methoxide anion reacts with a proton leading to the formation of methanol and regeneration of the base. In the fourth and last step, the carbonyl carbon of the intermediate undergoes a nucleophilic attack from the oxygen of the secondary hydroxyl group with cyclization to dioxolanone and another molecule of methanol (figure **8**)

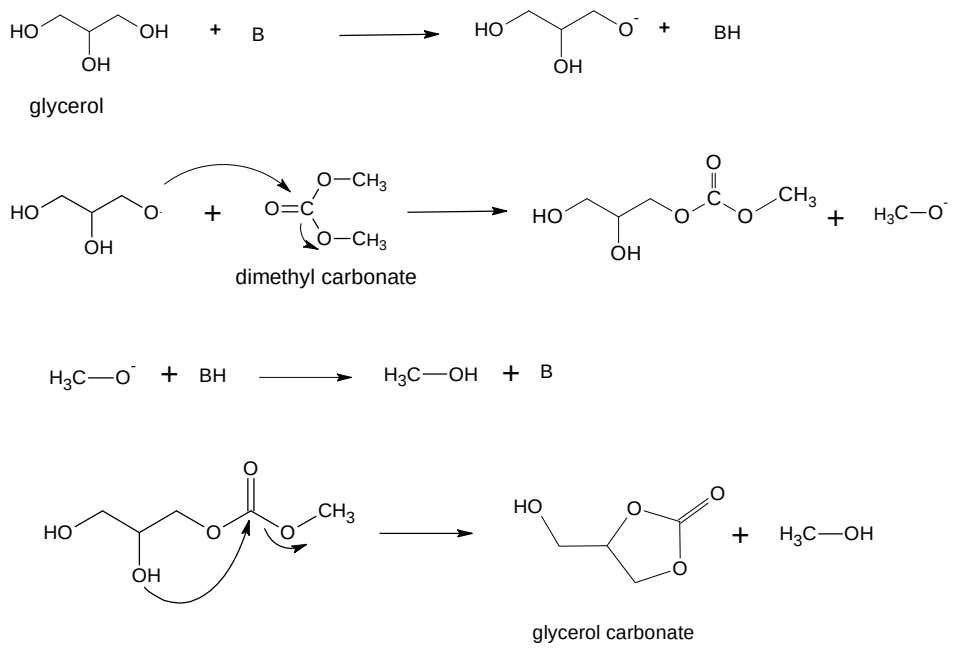


Figure 8 - Mechanism proposed for the formation of glycerol carbonate from glycerol and dimethyl carbonate under strong base catalysis.

Some other dialkyl carbonates undergoes similar reactions, but dimethyl carbonate is preferred for economic and ecological reasons. The main significant alternative uses cyclic carbonates, i.e. 1,3-dioxolanone, to transfer the carbonate group with formation of glycols as by-products. These last compounds can be recycled by conversion into the corresponding oxirane (ethylene oxide), a compound easily involved in a carbonation reaction with carbon dioxide under appropriate catalysis (Figure 9).[22]

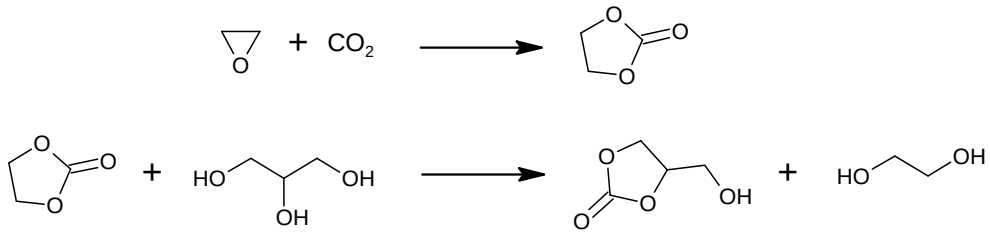
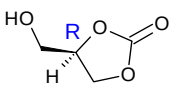
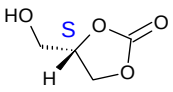


Figure 9 - Synthesis of glycerol carbonate from glycerol and 1,2-dioxolan-2-one

The transesterification reaction can be catalyzed also by enzymes and several Lipases were successfully used in the synthesis of glycerol carbonate from glycerol and dimethyl carbonate in THF. This approach provides also access to chiral (R) and (S) enantiomers of glycerol carbonate because this molecule contains a chiral center (C-4).



(R) glycerol carbonate



(S) glycerol carbonate

Although this material can be obtained in optically pure form[23] both by enzymatic hydrolysis or acylation procedures, the chiral recognition (expressed as the enantiomeric ratio E) is only moderate (E = 5-15), resulting in low product recovery. The value of this material is, however, beyond doubt and future applications are expected. Selecting the lipase, almost quantitative yield of racemic glycerol carbonate can be obtained under mild reaction conditions (mol ratio DMC/gly = 1, T = 60 °C, time = 30 hours). The main drawbacks reported are the high reaction time, the limited productivity, and the isolation problems.[24]

3) Carbonylation of glycerol by urea

Catalytic conversion of glycerol to glycerol carbonate by urea can be obtained in moderate to good yield (Figure 10). The reaction was studied mainly by different groups. Heterogeneous zinc and gold based catalysts were found particularly effective. At temperature between 140-150°C and very low pressure (around 50 mbar) equimolar amounts of glycerol and urea react to glycerol carbonate, reaching yields of glycerol carbonate higher than 80% in a relative short reaction time of about 1 hour.[25]

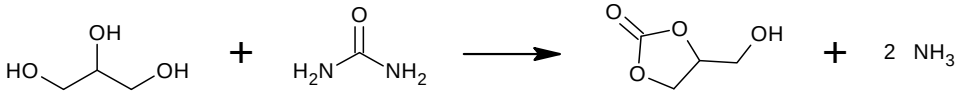


Figure 10 - Synthesis of glycerol carbonate from glycerol and urea

4) Carbonatation of glycerol by carbon dioxide

Several attempts were addressed to the direct synthesis of glycerol carbonate by condensation of glycerol with carbon dioxide (Figure 11).[26]

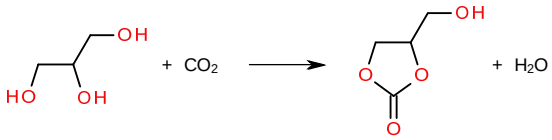


Figure 11 - Synthesis of glycerol carbonate by direct condensation of glycerol with Carbon dioxide.

Until now, only very low yields (7%) were obtained with tin catalyst, with recent improvement to 35% in less drastic conditions (35 bar of CO_2, 80°C, 4h) using dibutyltin oxide.[27] The reaction is extensively investigated worldwide.

5) Oxocarbonylation of glycerol by carbon monoxide/oxygen mixture

In this context the best yield was obtained using CuCl as catalyst in the presence of a gas mixture of of CO-O_2 in a ratio of 95:5. The reaction takes place at 130 °C in nitrobenzene and affords the glycerol carbonate in a 95% yield.[28]

6) Catalyzed carbonatation of glycidol by carbon dioxide

Another industrial approach to the synthesis of glycerol carbonate is the catalyzed addition of carbon dioxide to glycidol (oxiranylmethanol), an epoxide derived from allyl alcohol (Figure 12).

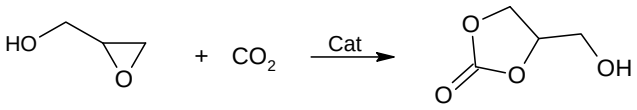


Figure 12 - Synthesis of glycerol carbonate by catalyzed carboxylation of glycidol with carbon dioxide.

Many catalysts has been proposed for this process, from alkali metal salts,[29] to MgO or Al/MgO catalysts,[30] to heavy metal catalysts,[31] ionic liquids,[32] and onium halides[33]. Some of them have problems, such as harsh reaction conditions (a high temperature and pressure) and the use of organic solvent or a Lewis base co-catalyst. Recently, solvent-free and metal-free catalysts as well as halogen-free catalysts are becoming more and more important[34] Reusability of catalysts, has also been investigated with organic–inorganic hybrid catalysts,[35] ion-exchange resins,[36] PEG-supported or polyfluoroalkyl-substituted phosphonium salts.[37] A typical carbon dioxide pressure value in industrial synthesis is between 5 and 150 bar. The highest yields for this reaction are obtained at high pressure at 80-120°C, whereas the yield is very low at atmospheric pressure.[38]

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Chapter – 2

Synthesis and reactivity of diglycerol dicarbonate.

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Synthesis and reactivity of diglycerol dicarbonate.

2.1 Introduction.

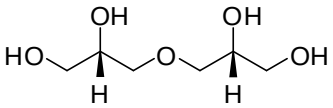
Glycerol has been used for decades in the industry, but its chemistry was mainly restricted to simple substitution processes, mainly due to the difficulty to convert selectively into useful chemical products, being a highly functionalized compound. The improvements have only marginally transferred glycerol to polyglycerols i.e. the condensation products of glycerol. Polyglycerols are increasingly used in the personal care industries for their multifunctionality, mildness and biodegradability. Generally they are polyols consisting of glycerol units linked by an ether linkage. Selective syntheses of these compounds are costly and conventional methods for polymerizing glycerol require drastic process conditions, including high temperature and caustic content. Therefore, this class of compounds is always produced as mixture of isomers and oligomers. Moreover, until now only limited attempts to control the stereochemistry at C-2 position in these condensation reactions have been made. In this part of the thesis we will focus on this specific aspect, starting from the lower oligomer of this family, that is the α,α'-diglycerol (bis-(2,3-dihydroxypropylether)).

2.1.1 - Diglycerol introduction.

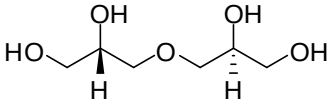
The high purity diglycerol is a clear colorless, odorless, water soluble liquid, less volatile and more viscous than glycerol. Diglycerol is a mixture of bis-(dihydroxypropyl)ethers, basically two molecules of glycerol linked by an ether bond; Diglycerol is the shortest oligomer in the polyglycerol family. Being non toxic, it is widely used in mixtures directly in personal care industry mainly because of its mild moisturizing property or as humectant[1]. It is also used as plasticizers in biodegradable compositions,[2] in the production of diglycerol esters,[3] diglycerol ethers,[4] polyurethanes[5] and polyesters.[6] Diglycerol, characterized by sweet, bitter and sour tastes,[7] is used in oral care compositions[8] such as toothpaste, gels, chewing gums[9] as humectants and emollient[10] and it is claimed to have long lasting flavor and cooling effect, due to which it is used as flavoring agents. In addition it provides odor masking qualities and shows a high refractive index.[11] Diglycerol or blends of polyglycerols and diglycerol, having a lower hydroxyl number has a lower affinity with water and in some cases is preferred as humectant in many personal care compositions to glycerol and sorbitol.[12] Linear diglycerol and linear oligomer of glycerol are used to prevent or delay ice nucleation for deicing solutions.[13] Diglycerol esters are used in rheology and stability of protein-stabilized emulsions.[14] Diglycerol derivatives and esters in particular are also products of great interest as they are used as emulsifying agents, surfactants and some industrial applications such as antifogging agents in polyolefin and PVC films, and so on.

Diglycerol presents three isomeric forms linear diglycerols, branched diglycerols, cyclic diglycerols. Linear diglycerols are α,α'-diglycerols (two diastereoisomers **1a** and **1a'**). Branched diglycerols are α,β-diglycerols (two diastereoisomers **1b** and **1b'**) and β,β'-diglycerol (**1c**). Cyclic diglycerols are (*trans*-(5-hydroxymethyl-(1,4)dioxane-2-yl)-methanol, *cis*-(6-hydroxymethyl-(1,4)dioxane-2-yl)-methanol, [1,5]-dioxocane-3,7-diol). Moreover, for the presence of the two asymmetric center at carbons 2 and 2' in compound **1a**, **1b** and **1c** increases the number of isomers to two further enantiomers for *d,l*-**1a** and *d,l*-**1c** and to four chiral isomers of unsymmetrical **1b**. Other higher oligomers obviously consist of a greater number of isomers.

Linear diglycerols:

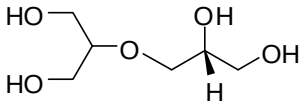


α,α'-diglycerol (**1a)**

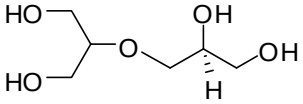


α,α'-diglycerol (**1a')**

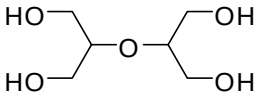
Branched diglycerols:



α,β-diglycerol (**1b**)

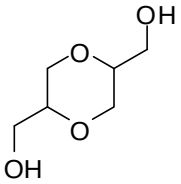


α,β-diglycerol (**1b'**)

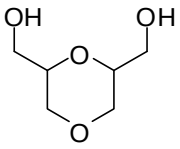


β,β'-diglycerol (**1c**)

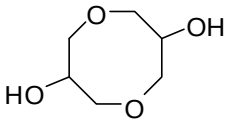
Cyclic diglycerols:



trans-(5-hydroxymethyl-(1,4)dioxane-2-yl)-methanol



cis-(6-hydroxymethyl-(1,4)dioxane-2-yl)-methanol



[1,5]dioxocane-3,7-diol

Diglycerol is synthesized on industrial level from glycerol oligomerization.[15] Diglycerol differs in composition depending upon its production process. Together with cyclic diglycerol, linear and branched diglycerol molecules are formed from glycerol or from other starting materials, although in different ratios. Reactions leading exclusively to the mixture of linear diglycerol have been reported in literature.[15]

To the best of our knowledge physical or chemical separation methods able to obtain pure stereo diglycerol from the mixture of the two stereoisomers are not reported in literature. The two isomeric α,α'-diglycerol were separated by analytical liquid chromatography but the structure of the two isomers was not assigned to the two peaks.[16]

It appears clear that diglycerol composition influences its performances in the final application as it can be thought for instance for binding properties or physical properties. It is already known for instance

that fatty acid esters of linear polyglycerols (LPG) have high valuable properties, resisting to hydrolysis by digestive enzymes and being poorly absorbed in animal feeding tests. In many other properties, LPG esters are similar to natural glycerides.

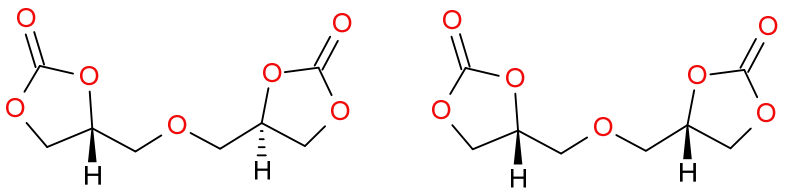
Therefore, the search of methods to obtain pure forms of diglycerols are increasingly recognized as important because these compounds could lead to products with highly specific performances and can be the staring materials to obtain other stereo ordered oligomers of glycerol.

On these basis, we developed a simple method to prepare the two isomeric α,α'-diglycerol through the preparation of the diastereoisomeric dicarbonate derivatives and subsequent stereoisomer's separation. The two form of α,α'-diglycerol (*d,l*- and *meso*-) were obtained from hydrolysis of the corresponding diastereoisomeric α,α'-diglycerol dicarbonate. Mixtures of diglycerol dicarbonate were recently used both as reagent in the preparation of carbamates (used as biodegradable thickeners in many applications)[17] and as spacer in polymer chemistry.[18]

2.2 - Synthesis of 4,4'-[oxybis(methylene)]bis(1,3-dioxolan-2-one) (diglycerol dicarbonate, DGDC)

While studying the thermal decomposition of glycerol carbonate to glycidol by distillation, it was found that a viscous compound was present in the residue in little quantity when bases were absent whereas it growth in abundance when the distillation time was high and in the presence of even trace of bases. Working with a series of alcoholic solvents (in particular, isopropanol) it was possible to crystallize the compound which was identified as a mixture of two diastereoisomers of the 4,4'-[oxybis(methylene)]bis(1,3-dioxolan-2-one) (hereafter indicated as diglycerol dicarbonate (DGDC)). Further purification by repeated fractional crystallizations from isopropanol afforded a single stereoisomer. With a program of experiment, using several solvents and fractional crystallization conditions, we identify dimethoxyethane as appropriate solvent for the separation of the two different white crystalline isomers, one of which was identical to the compound crystallized from isopropanol.

By IR, NMR, MS analysis and retention times in normal phase TLC and reverse phase TLC with various eluents, it was deduced that the two compounds were structurally related and corresponds to the two diastereoisomers *d,l*- (**2a**) and *meso*- (**2b**) of the α,α'-diglycerol dicarbonate reported in Figure 2.1.



2a **2b**

Figure 2.1 - *d,l*-DGDC (**2a**) and *meso*-DGDC (**2b**) of the α,α'-diglycerol dicarbonate.

While analyzing the melting point of mixture of *d,l*- and *meso*-diastereoisomers, we found that *meso*- isomer melts at lower temperature whereas the *d,l*-isomer melts at higher temperature. The mixture of the two compounds was described in the literature in a single scientific paper and was claimed in only one patent but had never been separated in to corresponding diastereoisomers. It was therefore decided to study the formation, separation and reactions of these products. According to best of our knowledge, so far in the literature only the following references were found which describe the synthesis of this compound:

1. Etherification of glycerol carbonate - by Prof. A. Citterio *et al.*[19]

2. Direct carbonation of 3-glycidyloxy-1, 2-propylene carbonate – by Prof. Rockiki *et al.*[20]

3. Carbonation of α,α'- diglycerol in autoclave – by Prof. A. Citterio *et al.*[21]

which will be briefly analyzed.

2.2.1 - Preparation of DGDC from etherification of glycerol carbonates by distillation.

The two compounds *d,l*- and *meso*-DGDC can be considered the products of etherification of glycerol carbonate (**3**) by water loss (figure 2.2), a reaction not obvious in the absence of catalyst, but comfortable with reports of neat etherification reactions by alkyl carbonates. Moreover, it is known in scientific and patent literature that preparation of glycerol carbonate under basic conditions generates not well defined oligomeric glycerol carbonate products.

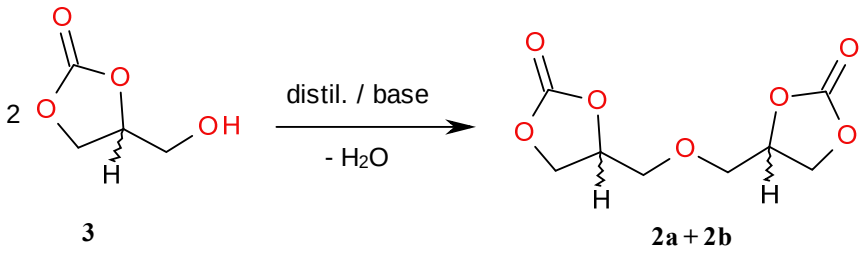


Figure 2.2 - Eterification reaction of glycerol carbonate by dehydration.

The amount of the diastereoisomeric *d,l*- and *meso*-DGDC residue was sensitive to the conditions of dehydration or distillation, and was found to be directly related to the increase of glycidol (**4**) in the system and to the distillation time. As it is well known that the carbon dioxide extrusion from glycerol carbonate to glycidol is a reversible process in the presence of carbon dioxide and appropriate catalyst, optimum conditions for the preparation of these compounds were investigated. By changing the variables temperature, reaction time, vacuum applied, pressure of CO_2 and type of catalyst, the results of Table 2.1 were obtained.

As can be seen from Table 2.1, in the absence of any catalyst, glycerol carbonate distills without decomposition. Significant results were obtained when zinc acetate was used as catalyst. In particular,

using light pressure of CO_2 for two hours and then a vacuum of 4 x 10^{-3} atm pressure for 6 hours at 160°C, an overall yield of 41% in diastereoisomeric mixture was obtained. The highest yield (52 %) was obtained with zinc acetate as catalyst extending the contact time to 10 hours.

Table 2.1 - Synthesis of *d,l-* and *meso-DGDC* from glycerol carbonate under various conditions.

Run	1 (mmol)	T (°C)	Time (h)	Pressure (atm)	Catalyst (mmol)	Yield % 3	2a-2b	4
1	500	140	2	4×10^{-3}	-	91	-	2
2	1000	160	10	4×10^{-3}	$NaHCO_3$ (5)	8	6	71
3	1000	160	5-6	4×10^{-3}	$NaHCO_3$ (5)	15	8	60
4	1020	160	2/6	$0.05^{*}/4 \times 10^{-3}$	$NaHCO_3$ (5)	5	30	10
5	1010	160	2/6	$0.05^{*}/4 \times 10^{-3}$	$Zn(OAc)_2$ (5)	3	41	16
6	1010	160	10	4×10^{-3}	$Zn(OAc)_2$ (5)	-	52	3

* from 0.05 atm to 4 atm in 1 hour.

In the absence of kinetic studies, a speculative mechanism for the formation of these dimers can be proposed in which glycerol carbonate (**3**) decomposes to glycidol (**4**) and then the alcoholic group of **4** adds (under catalysis of inorganic salts) to the carbonate group of **3,** followed by a trans-carbonation by another molecule of glycerol carbonate, as summarized in Figure 2.3.

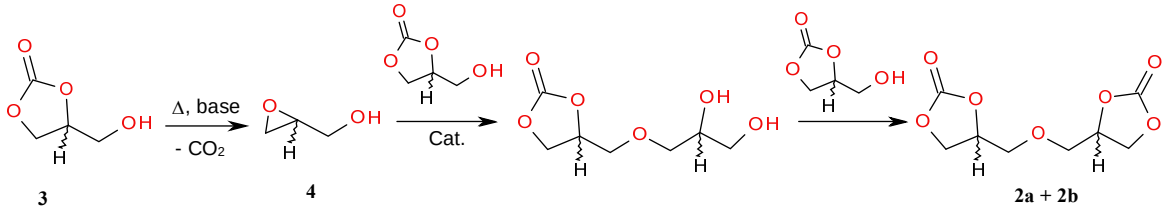


Figure 2.3 - Proposed mechanism for the formation of *d,l* and *meso DGDC* by catalyzed thermolysis of glycerol carbonate.

This mechanistic hypothesis is supported by the fact that glycerol carbonate never gives DGDC below 150°C or in the absence of a basic catalyst, i.e. in conditions which prevent the formation of glycidol.

2.2.2 Preparation of DGDC (2a, 2b) from epichlorohydrine

For the synthesis of DGDC by alternative approaches only one route was found in literature[19] by condensation of epichloridrin with potassium carbonate and subsequent carbon dioxide addition to 3-glycidyloxypropylene carbonate. For the synthesis of DGDC epichlorohydrin (1-chloro-2,3-epoxypropane) was condense in a controlled manner with potassium carbonate to give 3-glycidyloxypropylene carbonate and subsequent carbonatation with CO_2 (Scheme 2.4). The 3-glycidyloxypropylene carbonate was then carbonated in 93% yield with carbon dioxide in an autoclave at 30 atm pressure of CO_2 at 120°C for 12 h. The catalytic system used was based on KI and 18-crown-6 ether.

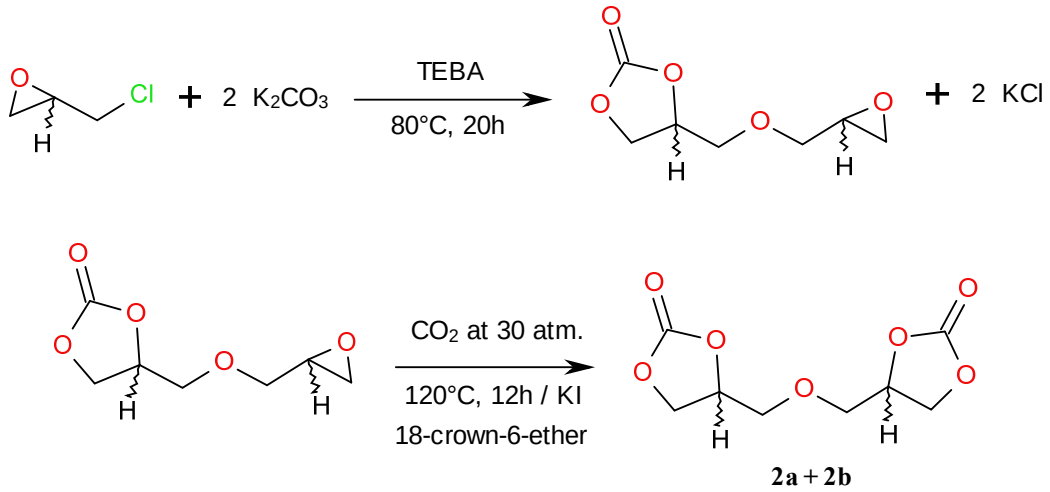


Figure 2.4 - Preparation of DGDC (**2a** + **2b**) from epichlorohydrine.

2.2.3 - Preparation of DGDC by direct trans-carbonatation of diglycerol.

An old Japanese patent claims the preparation of DGDC from pure diglycerol and diethyl carbonate in the presence of potassium carbonate in 45% isolated yield (Scheme 2.5), but no details were reported on diastereoisomers and their separation.

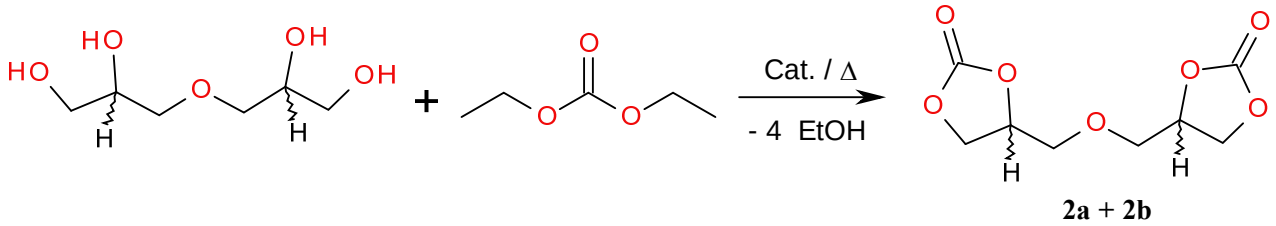


Figure 2.5 - Preparation of the mixture *d,l*- and *meso*-DGDC by trans-carbonation of α,α'-diglycerol

2.2.3.1 – Trans-carbonatation reaction of α,α'-diglycerol in autoclave.

Starting from a commercial α,α'-diglycerol diastereoisomer mixture and diethyl carbonate, by using a similar procedure, we have prepared DGDC in good yields. The reaction was carried out in autoclave above 120°C by changing variables such as the temperature, time, amount and the type of reagents and catalyst used in a design of experiments. The most significant results obtained are summarized in Table 2.2. The reported yields of DGDC refer on crude reaction mixture or after crystallization from ethylene glycol dimethyl ether, based on impure starting α,α'-diglycerol (Solvay, 85% purity).

Table 2.2 – Thermal synthesis of DGDC (*d,l*-, *meso*-) by trans-carbonatation of α,α'-diglycerol with diethyl carbonate

Run	Catalyst %	T (°C)	Time (h)	Pressure (atm)	Diethyl carbonate / Diglycerol	yield (%)
7	$NaHCO_3$ (3)	120	90	1	2:1	0
8	$NaHCO_3$ (3)	180	8	12.3		20
9	$NaHCO_3$ (5)	150	6.6	9.0	10:1	54
10	$NaHCO_3$ (5)	150**	4	8.9	10.5:1	60
11	DBTO (4.3)	120	90	1	9.3:1	40
12	SnO (10)	150	8	9.0	10:1	21

** The temperature has stabilized at about 150°C after 2.5 and was maintained for further 1.5 h.

A maximum yield of 60 % in DGDC was obtained at 150°C when a ratio of diethyl carbonate to crude α,α'-diglycerol of 10.5 was used and the reaction was run for 4 hours. The sodium bicarbonate catalyst was completely ineffective at the reflux temperature of diethyl carbonate (120°C) but becomes active at higher temperature (150-180°C). It must be emphasized that increasing the temperature above 160°C reduces the yield of DGDC owing to two competitive processes, 1) intramolecular cyclization of diglycerols to a mixture of substituted dioxane isomers, and 2) intermolecular etherification to polyglycerols favored by carbon dioxide extrusion.

Tin based catalysts, dibutyltin oxide and tin(II) oxide, show some activity but only the first was compatible with atmospheric pressure, affording DGDC in 40% yield after 90 hours. SnO was active at 150 °C affording a moderate yield (21 %). However, this oxide is interesting because it does not dissolve in the medium and can be easily recycled by filtration, improving the recovery of DGDC by simple recrystallization from solvents such as methanol, isopropanol and even water. This simple approach cannot be used with sodium bicarbonate since this catalyzes also the hydrolysis and trans-esterification.

In order to improve the yields and to evaluate milder and greener conditions, two synthetic alternative were investigated, both starting from commercial α,α'-diglycerol.

2.2.3.2 - Thermal carbonatation reaction of α,α'-diglycerol at atmospheric pressure.

The results with sodium bicarbonate working in autoclave were unexpected because previous work on the synthesis of glycerol carbonate by carbonatation with diethyl carbonate were successful, unless in moderate yield, at 120 °C under reflux at atmospheric pressure. When the reaction of linear α,α'-diglycerol was conducted by heating at atmospheric pressure with catalyst (sodium bicarbonate 0.04 % mol), than used in the reaction in autoclave (sodium bicarbonate 3-5 % mol). Thermal reaction has several advantages, the reaction was completed in 2 h, instead of 8 h in autoclave, and the yield of crystallized product was higher 79-80 % than in autoclave (54-60 %). The driving force of the reaction carried out by heating at atmospheric pressure was the distillation of ethanol which drift favorably the trans-esterification equilibrium to DGDC. Moreover, also elimination of diethyl carbonate by distillation at reduced pressure, make easy to separate relatively more pure form of the mixture of two diastereoisomers of 4,4'-[oxybis(methylene)]bis(1,3-dioxolan-2-one), from which pure *d,l-* and *meso-DGDC* were easily obtained by crystallization from dichloromethane.

2.2.3.3 Microwave promoted carbonatation of α,α'-diglycerol with diethyl carbonate.

Figure 2.6 - ETHOS 1600 Microwave Reactor from Milestone (Bg) used in the synthesis of DGDC. (35 x 35 x 35 cm); max power 1000 Watt - 2 industrial magnetron (800 W power) cooled by high flow fans MW supplied in a mixing chamber and distributed by a metallic Diffuser located on back wall.

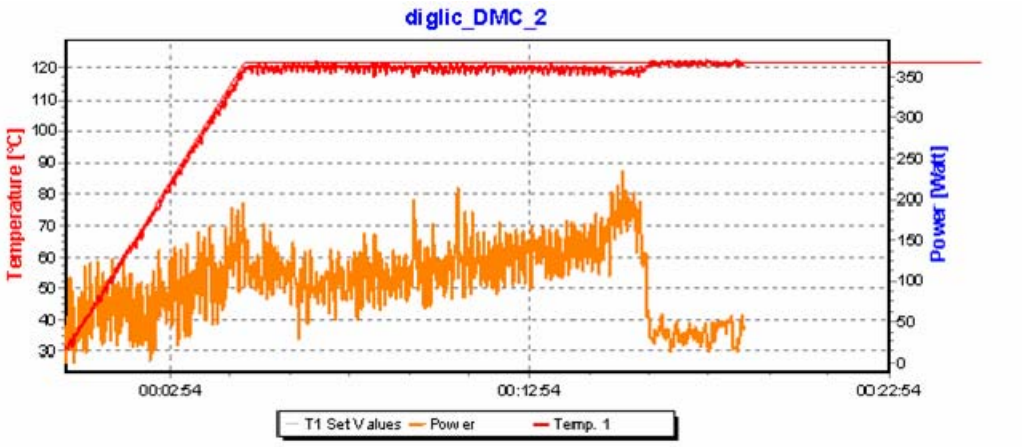


Figure 2.7 - On timely control of power and temperature in MW experiments

The practical feasibility of microwave accelerated solvent-free organic reactions protocols have been demonstrated in the past in useful transformations involving protection/deprotection, condensation, oxidation, reduction, rearrangement reactions and in the synthesis of various organic reactions. We decide to apply this technology to the synthesis of DGDC using a multimodal microwave equipment ETOS 1600 of Milestones. A typical arrangement of glass apparatus is reported in Figure 2.6. All reactions were performed in round-bottom flasks, equipped for distillation of ethanol and diethyl carbonate, at atmospheric pressure using neat reactants under solvent free conditions. It is noteworthy that MW irradiation using much milder conditions allows giving better yields than thermal reactions. This is probably related to a better control of temperature, based on timely measurements of power supplied to the oven (Figure 2.7) and to an appropriate slowdown of the reaction in connection with the fall in the power supply.

For comparative purposes, the carbonatation reactions of linear α,α'-diglycerol were firstly carried out at the same catalyst concentrations and temperature as in thermal reaction, then optimization experiments were performed. From this study (Table 2.3) the reaction was terminated in 30-40 minutes, instead of 2 hours by thermal way, and the reaction mixture was less colored and more easy to purify.

Table 2.3 – Microwave assisted synthesis of DGDC (*d,l*-, *meso*-) by trans-carbonatation of α,α'-diglycerol by ethyl carbonate

Run	Catalyst %	T (°C)	Time (min.)	Power (Watt)	DEC/Diglycerol	Yield (%)	Yield* (%)
13	$NaHCO_3$ (3)	120	40	400	2:1	80	75
14	$NaHCO_3$ (5)	120	30	300	3:1	90	84
15	$NaHCO_3$ (5)	120	40	300	4:1	92	88
16	$PNHCO_3$ (3)	120	55	400	5:1	74	70
17	DBTO (4.3)	120	65	400	3.5:1	82	75
18	SnO (10)	120	20	400	5:1	21	nd

*Purified mixture of *d,l*- and *meso*-DGDC.

As concerns the catalyst, there is an optimum amount of $NaHCO_3$ between 2-5 %. Larger or lower amount produces a decrease of DGDC yield. Tin compounds (i.e. dibutyltin oxide) was also effective but with somewhat higher time and with a less easy separation of the diastereoisomers. Sn(II) oxide was comparatively inefficient. The microwave assisted reaction is characterized by the absence (or the presence in trace amounts) of the intramolecular and intermolecular etherification products of diglycerol and the absence of higher polyglycerols. Moreover, the clean reaction mixture make easier the purification of the two diastereoisomers, an aspect which was investigated more deeply in the next section to make available large amount of the two pure products for further work.

2.3 - *d,l*- and *meso*-DGDC Separation & Characterization.

A study was undertaken to isolate pure *d,l*- and *meso*-DGDC by fractional crystallization form different solvents. The main difficulty to solve was the presence of isomers of α,α'-diglycerol in the starting mixture of commercial diglycerol and to the frequently not complete conversion to DGDC. The investigation was crucial for development of preparative studies involving the two diastereoisomers. In the following are collected the main results of this purification study.

2.3.1 - Crystallization of *d,l*- & *meso*-DGDC.

Different solvent, such as 1,2-dimethoxyethane, chloroform, ethanol, isopropanol, water, etc., were investigated for crystallization of crude DGDS. To some extent all affords the separation of stereoisomers but with moderate material recovery. Effective crystallization was obtained by using dichloromethane (DCM) (for developed procedure see experimental part). The results are collected in table 2.4 and evidence the phase behavior of the system and purity of isolated diastereoisomers from their melting point.

Changing the initial composition of the DGDC isomers, it was verified that, almost in DCM, the prevalent isomer can be crystallized first and the other isomer can be obtained after from the residue, i.e. if the reaction mixture contains more *d,l*-DGDC (> 45 %), the *d,l* got crystallized and if the reaction mixture contain more *meso*-DGDC (> 65 %), the *meso* got crystallized (Table 2.5). The same conclusion was proved on the neat reaction mixture after elimination of DCM reagent. DCM dissolves at 5 °C the DGDC crude mixture when the relative ratio DGDC/DCM is higher than 2.5.

Table 2.4 Crystallization and separation of *d,l*- and *meso*-DGDC (45:55) by using different solvent.

Solvent	Required solvent (ml)*	Solvent Phase (80°C)	m.p. *d,l-DGDC*	m.p. *meso-DGDC*	Crystallized product
H_2O	10	single	103 – 104 C	86 – 87 °C	*d,l* first; *meso*
DCM	5	single	102 - 103 °C	82 – 83 °C	*d,l* first; *meso*
CH_3OH	3	single	104.5- 105.5 °C	84-85 °C	*d,l* first; *meso*
$(CH_3O\text{-}H_2)_2$	3	two	102 -103 °C	84.5 - 85.5 °C	*meso* first; *d,l*
$(CH_3)_2CHOH$	4	two	102-103 °C	-	*d,l first; meso*
$CHCl_3$	5	single	-	84-85 °C	*meso*
Dioxane	2	single	-	-	-
n-Bu_2O	2	two	-	-	-
DMC	2	two	-	-	-

*for 1 gram

Table 2.5 – Fractional crystallization of mixtures of DGDC (20 g) from DCM (100 ml)

Composition *d,l-*: *meso-*	T (°C)	Time (h)	Ratio S/DGDC	Yield% *d,l*-DGDC	Yield% *meso-*	m.p. first isomer
45:55	5	5	5	30*	22**	103-4
45:55	0	12	5	32*	27**	102-3
45:55	2	2	0	33*	18**	103-4
67:33	5	8	7	45*	18**	104-5
35:65	0	12	5	20**	25*	84-5

*First precipitate, further recrystallized, ** Precipitate from the mother liquor after seeding and recrystallization

Faster crystallization of *meso*-DGDC can be obtained from an enriched reaction mixture after seeding with pure diastereoisomer at 5-8°C. In all cases the distribution of *d,l*- and *meso*-DGDC present in the crystallized product was determined by ^{1}H-NMR in $CDCl_3$.

2.3.2 Analytical characterization of *d,l*- and *meso*-DGDC.

In literature, no route was described for the synthesis and separation of the two diastereoisomers of DGDC. Only a patent indicates that DGDC has a melting point of 62-63°C. However, in our hand experimental melting points ranged from 50 to 102°C, depending on condition and solvent used for crystallization, and, frequently, on the heating time. In these solids *d,l*-isomer generally prevails over *meso*- and, when pure diastereoisomers were isolated by repeating recrystallization, *d,l*-DGDC has a melting point of 103-104°C whereas the *meso* 83- 84°C.

The pure isomers were analyzed by FTIR and mass spectroscopy and they showed practically identical spectra. On the contrary, ^{1}H-NMR analysis in $CDCl_3$ can easily distinguish between the two isomers whereas other solvent (i.e. Acetone-d_6) was unsuitable, and DMSO-d_6 showed less pronounced difference in chemical shifts. The major differences were observed for the (-CH-) methylene hydrogen of the ring. For the *d,l*-isomer this hydrogen resonates in $CDCl_3$ as a doublet of doublet at higher field (4.40 δ), whereas the analogous hydrogen in the *meso*-isomer occurs at lower field (4.32 δ). In DMSO the reverse was found, with the quartet of *d,l*-isomer occurring at lower field (4.22 δ) whereas the quartet of *meso*-isomer at higher field (4.25 δ). The ^{1}H-NMR spectrum of 1:1 mixture of diastereoisomers of DGDC in $CDCl_3$ is shown in Figure 2.4, while the ^{1}H-NMR spectra of the two purified *d,l*- and *meso*-diastereoisomers in the same solvent are shown in Figure 2.6. In Table 2.6 are reported the chemical shifts and coupling constant of the two diastereoisomers in these three solvents ($CDCl_3$, Acetone-d_6, DMSO-d_6).

Table 2.6 - Chemical shift (in δ) and coupling constant (in Hz) of *d,l*- and *meso*-DGDC in different deuterated solvents ($CDCl_3$, Acetone-d_6, DMSO-d_6).

solvent	***d,l-isomer***			***meso-isomer***		
	t, 1H, CH_2 Ring	**q, 1H,** CH_2 Ring	**dd, 2H,** α-CH_2 of ether	**t, 1H,** CH_2 Ring	**q, 1H,** CH_2 Ring	**dd, 2H,** α-CH_2 of ether
$CDCl_3$*	4.51	**4.40**	**3.85, 3.78**	4.52	**4.32**	**3.82, 3.77**
	J 8.2	*J* 5.7, 8.5	*J* 3.4, 11.4	*J* 8.4	*J* 5.8, 8.8	*J* 4.0, 11.0
Acetone-d_6*	4.62	4.38	3.89, 3.82	4.60	4.38	3.90, 3.82
	J 8.3	*J* 6.2, 8.3	*J* 3.1, 11.4	*J* 8.3	*J* 5.8, 8.6	*J* 2.7, 11.4
DMSO-d_6**	4.52	**4.22**	3.76, 3.68	4.52	**4.25**	3.76, 3.68
	J 8.4	*J* 6.4, 7.9	*J* 2.4, 11.3	*J* 8.4	*J* 6.0, 8.3	*J* 2.6, 11.5

*400 MHz **250 MHz

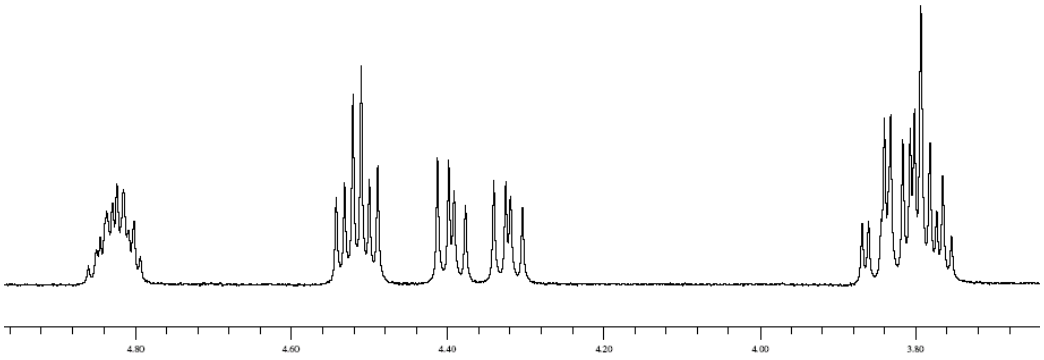


Figure 2.8 - ^{1}H-NMR spectrum of 1:1 mixture of *d,l* and *meso* diastereoisomers of DGDC in $CDCl_3$.

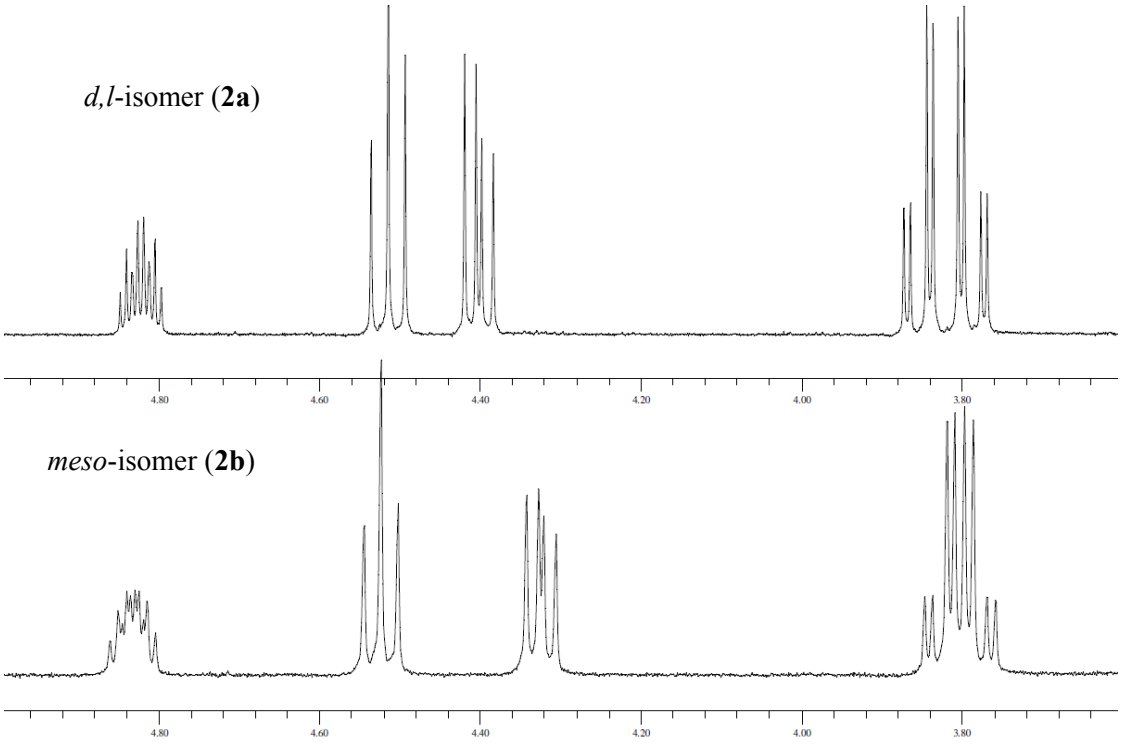
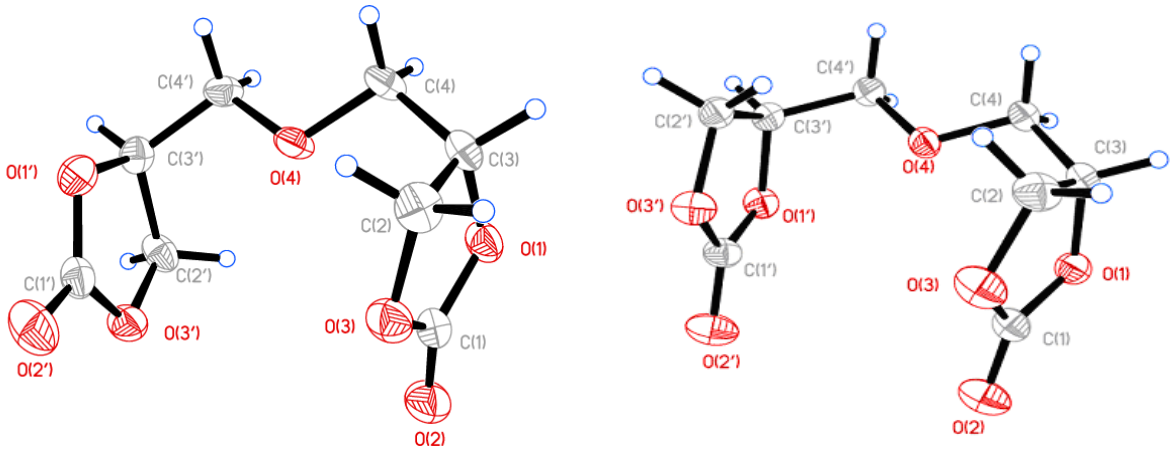


Figure 2.9 - ^{1}H-NMR spectrum of *d,l*- (a) and *meso*-DGDC (b) diastereoisomers in $CDCl_3$.

For conclusive structural elucidation, single crystals **X**-ray analysis of both diastereoisomers was performed. This technique allows to attribute the *d,l*-isomer (**2a**) to the compound with higher melting point (103-104°C), while the *meso*-isomer (**2b**) corresponds to the lower melting point (83-84°C). In Figure 2.10 are reported the Thermal Ellipsoid Plot (ORTEP) of two diastereoisomers deduced from this analysis.



2a **2b**

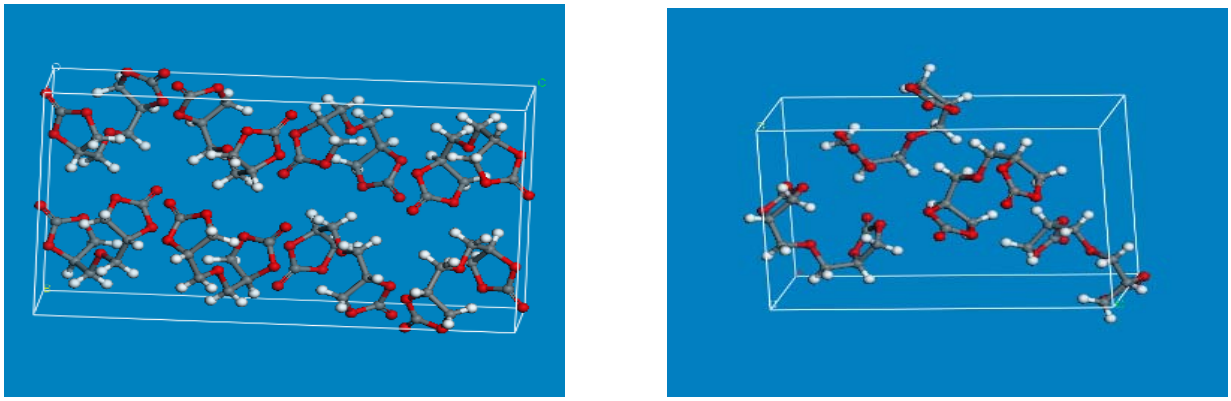
Figure 2.10 - Structural characterization via X-rays of the two diastereoisomers.

From the structural data it is clear the tendency of the two strong carbonyl dipoles to orient in a staggered mode to reduce the electrostatic repulsion. The relative positions of the two heterocyclic nuclei, however, show a tendency to organize in cage, with the electronegative oxygen atoms facing inward. This could be related to a more favorable packing in the crystal, but it could also be an indication of a tendency to favor hydrogen bonds since the crystals were grown from an alcohol solvent (isopropanol). However, in the two dioxolane-2-ones rings no distortion is evident, showing interatomic distances and angles very close to those of the parent nucleus.

X-Ray single crystals data.

***d,l*-Diglycerol dicarbonate (2a).** $C_8H_{10}O_7$, M_r = 218.16, orthorhombic, space group P_{bca} (no. 61), a = 7.8110(10), b = 11.998(2), c = 20.600(3) Å, V = 1930.6(5) Å^3, Z = 8, D_c = 1.501g·cm^{-3}, μ = 1.183 mm^{-1}, F(000) = 912; 2206 reflections (165 unique (R_{int} = 0.1040). The final refinement, for 137 refined parameters and 0 restrains, converged to wR(F2) = 0.0671 (R_w = 0.1560) for all unique reflections with I > 2σ(I) after merging. Elementary cells are reported in Figure 2.11.

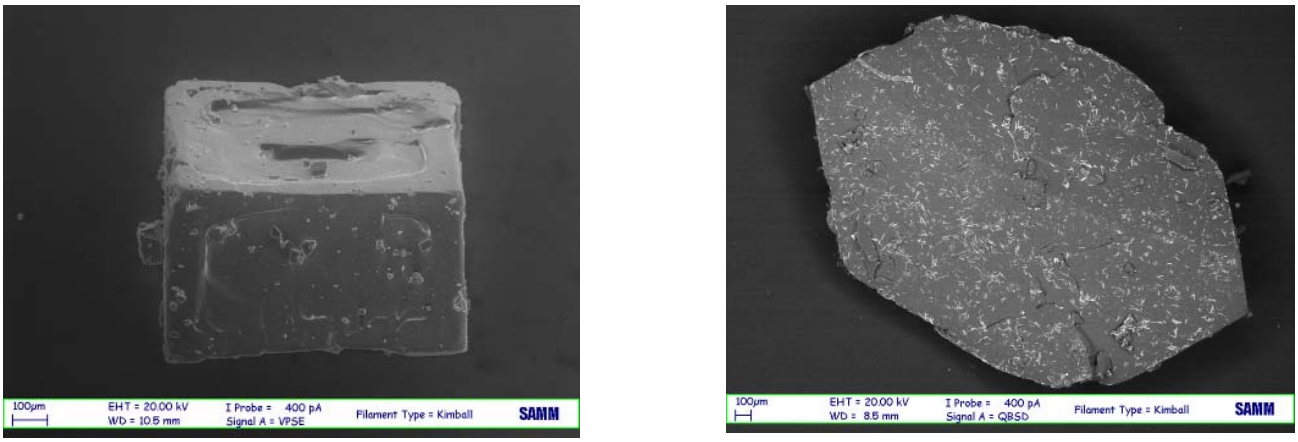
***meso*-Diglycerol dicarbonate (2b).** $C_8H_{10}O_7$, Mr = 218.16, space group $P2_12_12_1$ (no. 19), a = 6.366(5), b = 10.031(5), c = 14.889(5) Å, V = 950.8(9) Å^3, Z = 4, D_c =1.524 g·cm^{-3}, μ = 1.201 mm^{-1}, F(000) = 456; 1724 reflection (1454 unique, R_{int} = 0.0328). The final refinement, for 137 refined parameters and 0 restrains, converged to wR(F2) = 0.0475 (R_w = 0.1425) for all unique reflections with I > 2σ(I) after merging. Elementary cells are reported in Figure 2.11.



2a **2b**

Figure 2.11 - Elementary cells of *d,l*- diglycerol dicarbonate (**2a**) and *meso*-diglycerol dicarbonate (**2b**).

An interesting feature of the two pure distereoisomers was the different crystal shapes which make possible their manual separation (as tartaric acid by Pasteur). The *d,l*-isomer shows a characteristic cubic shape (Figure 2.12), whereas the *meso*-isomer shows flat hexagonal crystals. The *d,l*-isomer has been grown easily until 0.5 cm side.



2a **2b**

Figure 2.12 - SEM micrographs of single crystals of *d,l*-isomer (**2a**) and *meso*-isomer (**2b**)

2.4 – Reactivity of *d,l* and *meso*-DGDC.

Given the relative ease of preparation and separation of compounds **2a** and **2b**, these compounds constitute an important new outlet or building block for the use of glycerin. In particular, they can provide an important prerequisite for the development of a whole series of derivatives of glycerol which are stereoordered (for example, syndiotactic type glycerol oligomers of Figure 2.13), surprisingly never analyzed in the past. The current way of generating polyglycerols (under acid catalysis or better basic) is

not in fact able to control the position of the condensation (terminal and internal) and to induce stereochemical order, so the oligoglycerols available in the market are made from a complex mixture of products, differentiated primarily on the basis of the average number of condensed molecules of glycerol (typically 2 to 10). In addition, the alternatives developed industrially by Solvay use epichlorohydrin to get diglycerols from glycerol, and similarly to insert glycerol onto polyols, without regiochemical and streochemical control. Moreover they use very toxic chemicals. This inherently limits the synthesis of stereocontrolled polymers of glycerol.

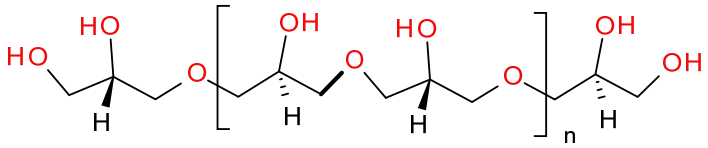


Figure 2.13 - Structure of sindiotactic 1,3-polyglycerol.

Bearing in mind that mixtures of polyglycerols are still characterized by high biodegradability and low toxicity (at least to the extent that the foreign polyglycerol ricinoleate has become a current food additive), the preconditions for the practical application of these products are certainly good. In this direction we wanted to do experiments in a preliminary way, some potential exploring some aspects of their chemical behavior and reactivity. The following points were more deeply investigated:

- Synthesis of *d,l*- and *meso*-DGDC.
- Metal complexation by using diglycerol dicarbonate.
- Condensation reactions of the *d,l*- and *meso*-DGDC with amines and alcohols.
- Approaches to the synthesis of stereoordered polyglycerols.

In the following chapters we revise our experimental activity with the main conclusion obtained subdivided in the four section above specified.

2.4.1 - Synthesis of pure *d,l*- and *meso*-diglycerol by hydrolysis of pure *d,l*- and *meso*-DGDC.

In the literature according to our knowledge, no report has appeared discussing analytical, physic-chemical data of *d,l*- and *meso*-diglycerol diastereoisomers, nor their synthetic route. So, to also the simple procedure of hydrolysis of the corresponding pure diastereoisomeric carbonates has great potential.

From the literature it is well known the hydrolysis of glycerol carbonate in the absence of catalyst up to 140°C was not observed, while at higher temperature, hydrolyzed to glycerol due to residual water present in the starting material. The total hydrolysis of glycerol carbonate in the presence of catalytic amount of bases such as sodium methoxide or potassium-tert-butylate (0.005 eq.), at 100°C takes place, where as in presence of catalytic amount of acids such as *para*-toluenesulfonic acid, or zinc chloride have no effect on glycerol carbonate, which remain unchanged after heating up to at 100°C. In the literature

enzyme-mediated enantioselective hydrolysis of cyclic carbonates is known[22] Racemic 4-(2-benzyloxy)ethyl-1,3-dioxolane-2-one was enantioselectively hydrolyzed by porcine pancreas lipase (PPL)[23] to give optically active (R)-4-(2-benzyloxy)ethyl-1,3-dioxolane-2-one and (S)-4-benzyloxybutane-1,2-diol (Figure 2.14).

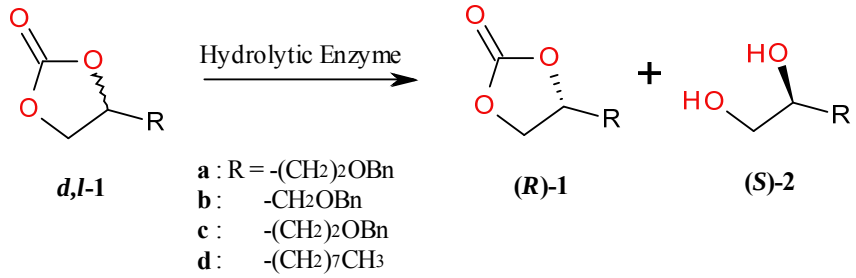


Figure 2.14 - Enantioselective hydrolysis of dioxolanones with the PPL hydrolytic enzyme.

For example, they performed enzymatic hydrolysis of dicarbonate with the PPL hydrolytic enzyme in 0.1 M phosphate buffer (pH 6.5) at 10 °C, noting that the hydrolysis leads to the optically active S configuration monocarbonate, while the remainder dicarbonate has a R configuration. In 12 hours the hydrolysis under these conditions leads to a conversion of 55%, recovering a (R)-optically active dicarbonate ($[\alpha]_D$ = +21, measured in methanol at 20 °C (c = 0.84 mg/ml)) in a 45% yield, and a (S)-optically active diol ($[\alpha]_D$ = -2.4, measured in methanol at 20 °C (c = 0.65 mg/ml)) in 48% yield. Allocation stereochemistry was made using the large correlations reported in the literature of hydrolysis of monocyclic carbonate.

Also the hydrolysis of 1,2-isopropylidene glycerol carbonate (solketal carbonate) by using acidic ion exchange resin, like Amberlite IR120, in 90% MeOH at 30°C is reported in good yields (84%).[24] Diglycerol diacetonide itself was analogously hydrolyzed in refluxing methanol in the presence of Dowex 50WX8 acidic resin in 82% yield. In this work it was also mentioned (without separation) the diasatereoisomeric nature of diglycerol, but characterization was done only by ^{13}C-NMR.[25]

Table 2.7 - Hydrolysis of pure *d,l*- and *meso*-DGDC in different conditions

Solvent	Catalyst (5 %)	Temperature (°C)	Time (h)	3a(3b) (Yield%)
H_2O	Amberlist-15	100°C	120	*d,l*- 93%
H_2O	H_2SO_4 10%	25°C	12	* 90 %
H_2O	H_2SO_4 10%	100°C	2	* 92 %
MeOH:H_2O 10/1	K_2CO_3	25°C	24	* 90-95%
MeOH	MeONa	25°C	24	*d,l*- 79 %)
MeOH	MeONa	25°C	24	* *meso*-80 %

Our attempt to hydrolyze diglycerol dicarbonate *d,l*-DGDC and *meso*-DGDC were successful under acid and basic catalysis in different solvents and at different conditions, affording the diglycerols **3a** and **3b** in good yield under optimized conditions. The hydrolysis reaction preserve the stereochemistry at C-2 carbon (Figure 2.15) and no racemization at the center was observed in all conditions tested. The best results obtained in the experiments are reported in Table 2.7.

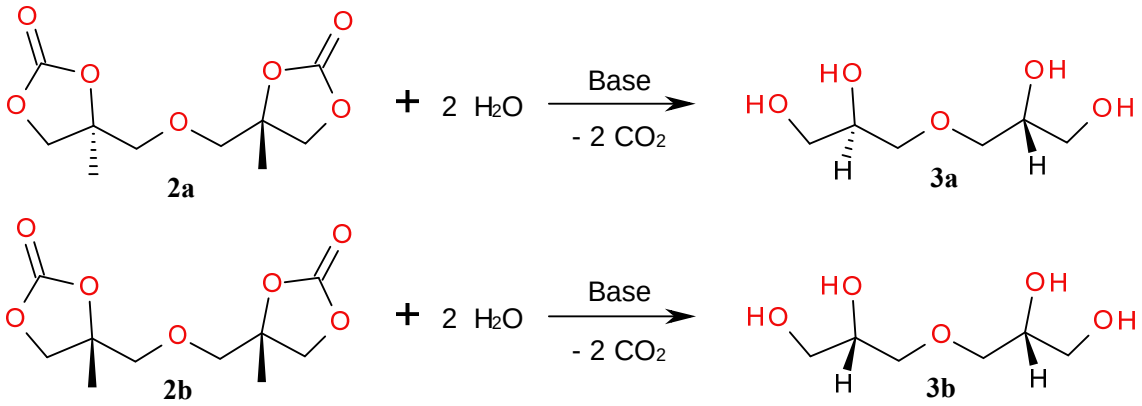


Figure 2.15 – Synthesis of pure *d,l*-α,α-DG (**3a**) and *meso*-α,α-DG (**3b**) by hydrolysis of DGDC isomers.

The best result were obtained at room temperature with potassium carbonate in methanol:water 10/1 or with 10% sulfuric acid in water. The relatively slow hydrolysis can be accelerated by heating both with homogeneous (H_2SO_4) and heterogeneous (Amberlist 15) catalysts in yield higher than 90%. Yet, heterogeneous catalyst Amberlist 15 requires at 100°C 120 hours at reflux to complete the hydrolysis. This is in part related to the limited solubility of DGDC in water and our attempt to solve the problem by using a cosolvents, i.e. methanol. However, sodium methoxide in methanol was a less effective catalyst, producing at room temperature lower yield in longer times.

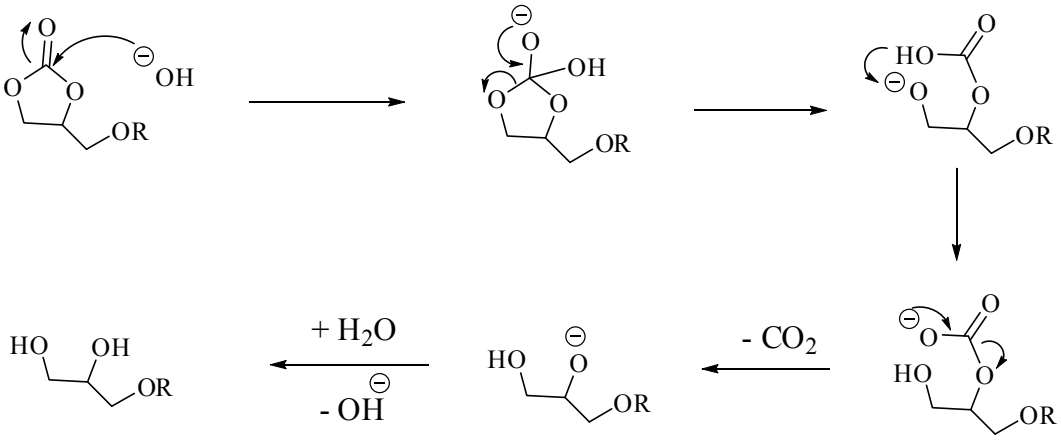


Figure 2.16 - Proposed mechanism of hydrolysis of DGDC.

A mechanistic interpretation was proposed for reaction under basic catalysis in water which involves the addition of hydroxide anion HO^{-} to carbonyl carbon atom forming a tetrahedral intermediate, which undergo ring opening with formation of alkoxide anion and emicarbonic ester. A fast intramolecular proton transfer is expected from the acidic proton of this intermediate and the alkoxide, followed by elimination of carbon dioxide, and subsequent protonation of the new formed alkoxyde anion from the medium (Figure 2-16).

Isolation of the product was carried out by evaporation of the solvent and purification of the crude product so obtained by fast column chromatography on silica gel to remove the catalyst. The stereochemical identity at the C-2 center was ascertained by ^{1}H-, ^{13}C-NMR and mass analysis. ^{1}H-NMR easily distinguish the two isomers *d,l-* and *meso*-diglycerol owing to characteristic multiplet signals of methylene hydrogens alpha to the ethereal oxygen and of methylene hydrogens at terminal position (Figure 2.17). Also in ^{13}C-NMR two signals were observed at different chemical shift for *d,l-* and *meso*-diglycerol as shown in Figure 2.18.

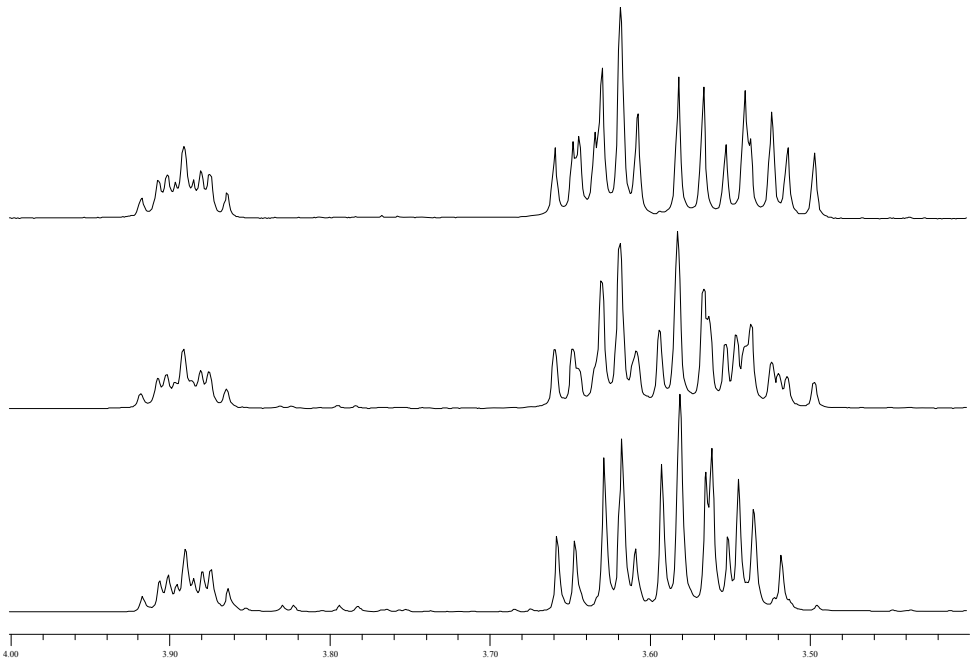


Figure 2.17 - ^{1}H-NMR spectra of mixture *of d,l- and meso*-diglycerol.

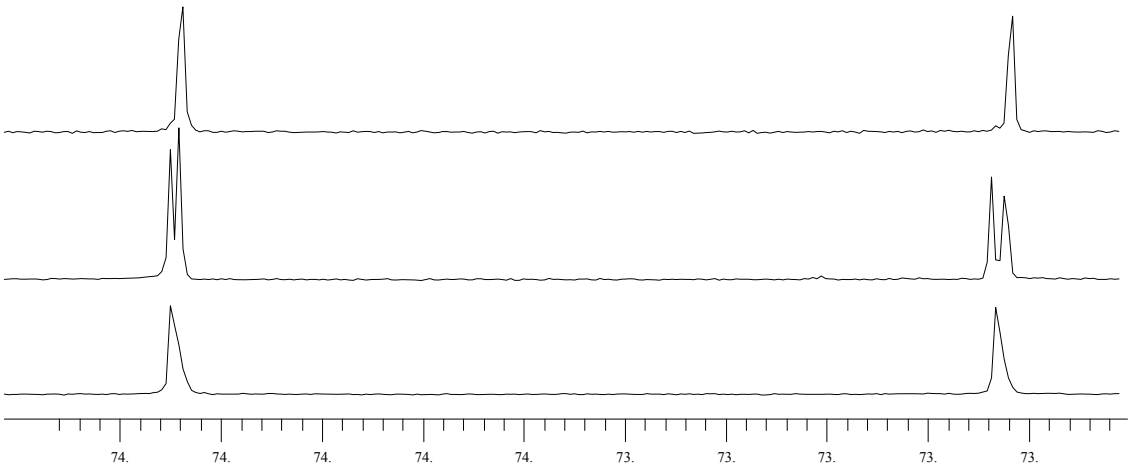


Figure 2.18 ^{13}C-NMR of different mixtures of *d,l*- and *meso*-diglycerol.

The ^{13}C-NMR of diglycerol was particularly diagnostic because of the absence of peak at 155 ppm which is of carbonyl absorption (C=O) of the 1.3-dioxolan-2-one of DGDC, and the three carbons of glycerol shifted to higher field than aliphatic carbon of the DGDC due to the loss of the deshilding effect linked to the electron withdrawing carbonate group. Figure 2.19 is diagnostic for this purpose as it compares the spectrum of the *d,l*-diglycerol obtained (a) with the one of *d,l*-diglycerol dicarbonate (b).

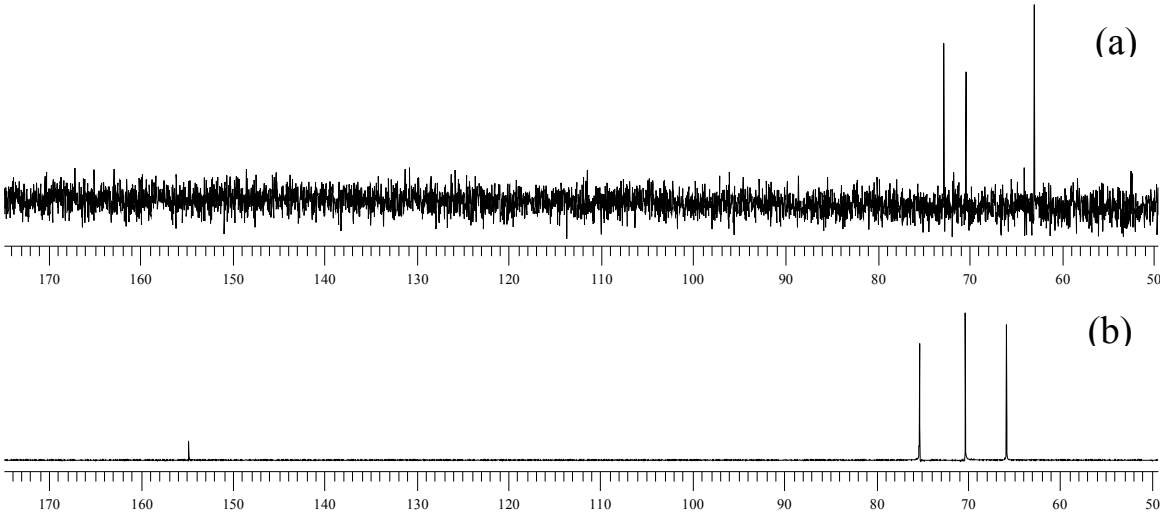


Figure 2.19 - ^{13}C-NMR spectra (in DMSO-d_6): (a) *d,l*-diglycerol, (b) *d,l*-DGDC.

2.4.2 Metal Complexation by Diglycerol Dicarbonate.

The structure of polyethers **2a** and **2b** is not far from the structure of polyoxyethylene glycol (PEG) and this is the reason why we expect to have good metal ion (M^{+}) complexing ability. The coordination may also facilitate decarboxylation to polyols, thus increasing further the complexing properties (Figure 2.20).

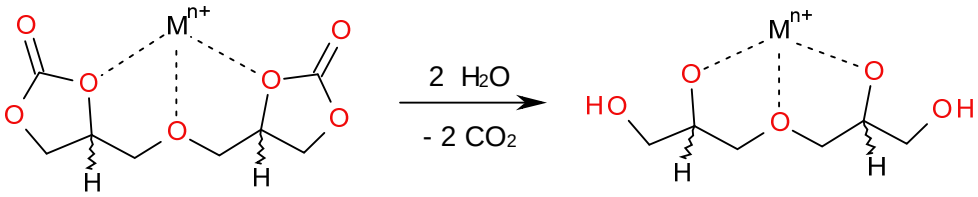


Figure 2.20 – Possible catalysis of DGDC-metal complexes in the decarboxylation reaction to DG.

These complexes can find applications such as agents for removal of cations in the field of personal hygiene and environmental aspects, as expected high biodegradability. In addition, complexes of this type are probably active in the transfer of carbonate groups and may represent new selective reagents for the carbonatation of multy functionalized derivatives transformed from the corresponding complex of diglycerol.

We test the complexing ability of DGDC using zinc cation as model, mainly because this ion showed a special catalytic activity in the synthesis and decomposition of DGDC (see section 2.2.1). The equilibrium constant K_{11}, (i.e. the stability constant for the formation of the 1:1 complex SL, namely, K_{11} = [SL]/[S][L], all concentrations being expressed in molar units and S is the metal ion and L is the DGDC) was the main target of the measure. This information is obtainable in several ways, but we select the techniques called the continuous variation and mole ratio methods by using the ^{1}H-NMR nuclear magnetic resonance spectroscopy. This technique assess the progress of the chemical shift ($\Delta\delta$) of the reference ligand induced by the presence of increasing amounts of the metal. The measurements were done in acetone-d_6 as solvent, with $Zn(NO_3)_2$ as source of the zinc cation for the poor coordinating properties of the bonded nitrate. In Figure 2.21 is reported the experimental trend of $\Delta\delta$ of ethereal methylene hydrogen of 2a against the ratio between zinc ion and diglycerol dicarbonate.

The ethereal oxygen of the molecule acts as a strong basic center and the methylene hydrogens close to this atom undergo a shift to lower fields as a result of coordination. It is worth noting that coordination is valuable even though acetone is used for reasons of solubility, a solvent which is also effective in complexing zinc ion.

The data of Figure 2.21 does not present the typical shape of the titration curve with a sharp jump, but it is more typical of systems in which there are multiple different complexes stoichiometry between ligand and metal. Fitting of these data according to a typical approach for these systems[26] provides a binding constant of formation of 1:1 complex of 16 and the one of 2:1 complex of 4.5. These values are

relatively low but are a clear sign of the importance of metal coordination by DGDC and help to understand the role of zinc in catalysis that we have seen.

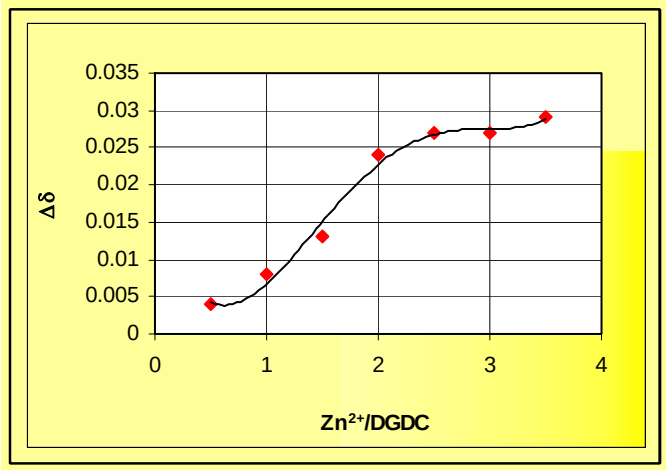


Figure 2.21 - Trend of the methylene hydrogen chemical shift on Zn^{2+}/DGDC ratio in CH_3COCH_3; DGDC = 9.72×10^{-2} M, $[Zn(NO_3)_2]$ = $57\text{-}42\times10^{-3}$ M, 25°C.

The attainment of structural details of these complexes may also help to rationalize the role of zinc in the activation of carbon dioxide in chemical reactions, as in the case of condensation reactions between epoxides and CO_2 to polycarbonates and biochemical environments. Until now, we do not succeed in isolating crystalline materials to submit to X-ray single crystal structure determination.

2.4.3 - Condensation reactions of the diglycerol dicarbonate 2a and 2b with alcohols and amines

To assess the potential of diglycerol dicarbonate as a curing agent for polyethers, polycarbonates and polyurethanes, we investigate the reactivity of diglycerol dicarbonate toward nucleophilic substitution with oxygen- and nitrogen nucleophiles, firstly with simple alcohols and amines as models and then with diols and diamines.

Alcoholysis and ammonolysis of DGDC were mainly carried out under basic catalysis or in the presence of zinc salts. Reaction of DGDC with alcohols R-OH [i.e. R=CH_3, methanol] in autoclave at 140°C in the presence of $NaHCO_3$ as catalyst, leads with a rather significant yield (53%) of dimethyl ether of α,α'-diglycerol **4** (Figure 2.22). The methyl ether structure of the compound was confirmed by ^{1}H-NMR and ^{13}C-NMR spectroscopy. Better yields (80%) were obtained when the solvolysis was performed in the presence of zinc nitrate (3% w/w).

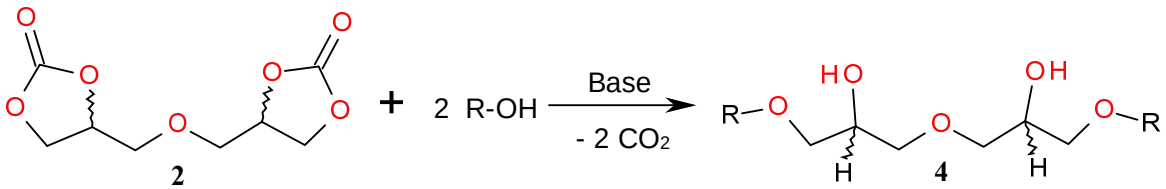


Figure 2.22 - Alcoholysis reaction of DGDC with alcohols under catalysis of a base.

In a similar way, the reaction of diglycerol dicarbonate with PEG 200 [R = $(CH_2CH_2O)_n$ H] at 140°C and at ordinary pressure for 3 hours was carried out to get a product mixture compatible with the structure of PEG ether of diglycerol, on the basis of molecular weight of main component (500-620 uma by mass spectrometry) with a relative distribution of product similar to the one of the starting PEG 200.

It was also verified that the treatment of diglycerol dicarbonate with a molar excess (5:1) of dibutylammine at 60°C for 12 hours provides the corresponding diglycerol dicarbamate derivative (Scheme 2.7). NMR analyses confirmed that the compound obtained is a mixture of two regioisomers, with preference for the terminal one (6:1).

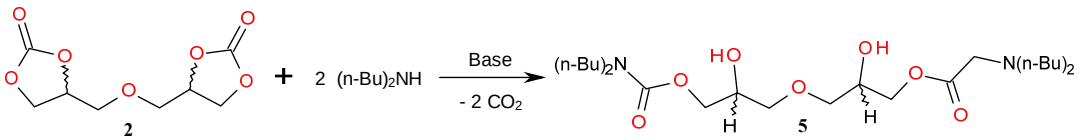


Figure 2.23 - Aminolysis reaction of diglycerol dicarbonate with dibutylammine.

In all these compounds, infrared analysis clearly indicates the presence of OH group (broad peak at 3400-3500 cm^{-1}) and urethane carbonyl group (C=O 1720 cm^{-1}), while the carbonyl group of cyclic carbonate at 1820 cm^{-1} is totally absent. Attempts to carry out this condensation at temperatures higher than 140°C result in progressive darkening of the mixture with decrease of the IR absorption band of carbonyl group, suggesting that decarboxylation is accompanied by the replacement of an oxygen atom of diglycerol with an amino group, in analogy to what happens in thermal decomposition of polyurethanes.

The reactivity observed is reminiscent of what reported previously in the literature for 1,3-dioxolane-2-ones,[27] in particular as concerns the catalyzed substitution by phenols, thiophenols, and anilines. The list of catalyst useful in these reactions is quite long and includes phosphines, alkali metals, tertiary amines, alkali metal halides, hydroxides, carbonates and alkoxides. A general reaction scheme was proposed as illustrated in Figure 2.24. in which the nucleophile (Nu^-) can be RO^- or RNH^-. The nucleophilic attack can take place at either carbonyl sp^2 carbon to give after ring opening two regioisomeric carbonates (or carbamates) or at saturated C-O bonds affording after carbon dioxide loss ethers (or amines). With primary amines the initially formed carbamate can undergo further intramolecular substitution to regioisomeric 1,3-oxazolin-2-ones.

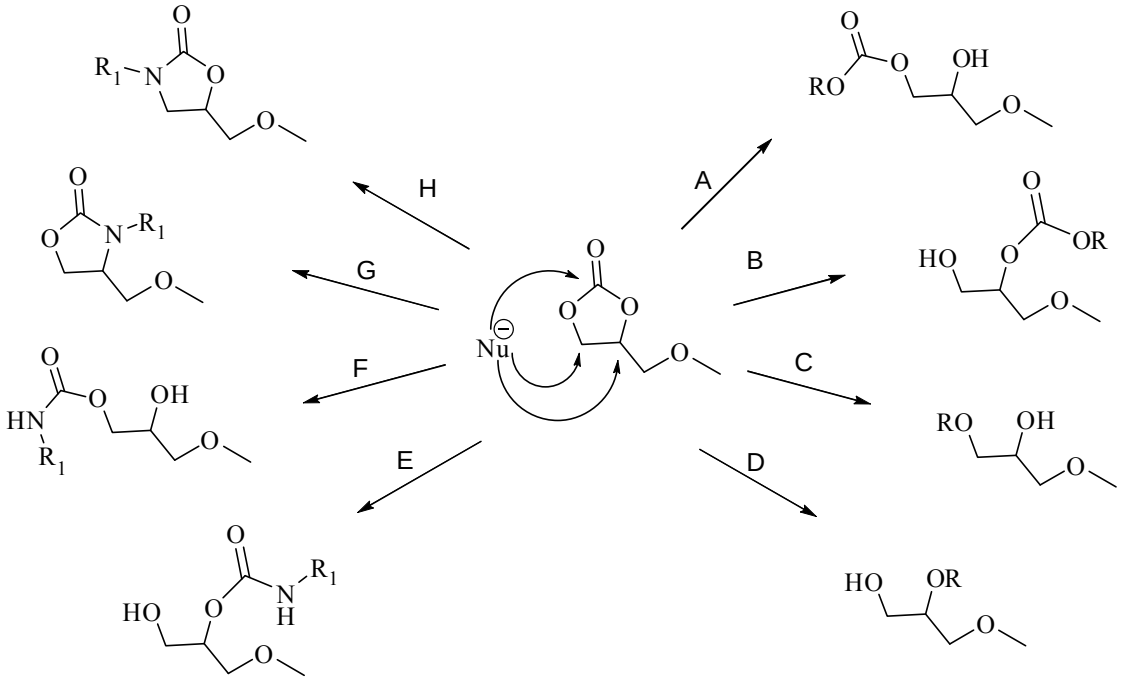


Figure 2.24 - Alternatives in addition of nucleophiles to glycerol carbonate.

In particular, five-membered carbonates were found to react with phenols in the presence of basic catalysts at temperature in the range 100-200°C by loss of carbon dioxide to give arylglycerol regioisomers (Figure 2.24, path C and D). Aliphatic alcohols react differently via a generalized transesterification route (Figure 2.24, path A and B) at lower temperature in the range 100-125°C. Anilines under basic catalysis were found to react at temperature in the range 100-200°C by the loss of carbon dioxide to give oxazolidinone derivatives (Figure 2.24, path G and H), whereas primary or secondary amines react at lower temperature to give regioisomeric hydroxyalkyl urethanes (Figure 2.24, path E and F) and at higher temperatures, by water loss, to 1,3-oxazolidin-2-ones(Figure 2.24, path G and H). The different reactivity of carbonyl group vs. saturated carbon has been attributed to the HSBA principle, in which the carbonyl group is the harder electrophile, as a result of its polarized positive charge and sp^2 hybridization, whereas the methylene carbons represent the softer electrophiles, due to their sp^3 orbital and their saturated carbon atom, which has a weaker positive charge. Accordingly, soft O- and N-nucleophiles were found to add selectively at the softer electrophile carbon atom of cyclic carbonate moiety affording mono and disubstituted diglycerol derivatives with complete retention of C-2 configuration.[28]As concerns the ratio between regioisomers, Baizer et al. found in the reaction of ethylamine with propylene carbonate a value of 70/30 for secondary alcohol/primary alcohol,[29] and similar ratios was observed with other primary amines. Reaction of linear carbonates with aliphatic amines gives mainly urethanes.

Attempts to extend the reaction of *d,l*-DGDC with other aliphatic and aromatic amines, i.e. benzyl amine, methyl amine anilines, anilines, produced complex reaction mixtures not easy to separate and characterize. During this analysis we found that more soft nucleophile carbamates reacted with *d,l*-DGDC more cleanly affording mixtures more easy to purify. Specific attention was devoted to ethyl N-(4-

methylphenyl)carbamate owing to its selective conversion into mono and di oxazolidinone products. Starting material **6** was prepared by a known procedure as shown in Figure 2.25.[30]

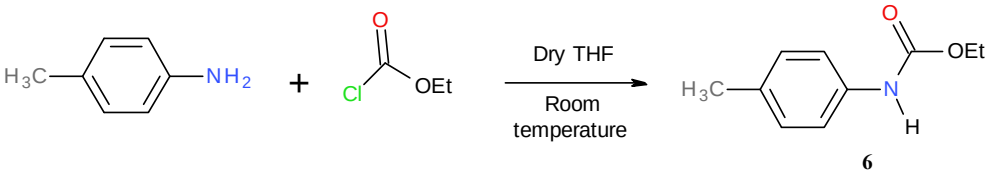


Figure 2.25 - Synthesis of ethyl N-(4-methylphenyl)carbamate from toluidine.

For the condensation reaction of diglycerol dicarbonate with ethyl N-(4-methylphenyl)carbamate neat conditions and K_2CO_3 as catalyst were used at 150°C. At this temperature the reaction was found to be complete in 11 hours. Workup of the reaction mixture (see experimental part) affords the dioxazolidinone **7a** and mono oxazolidinones **8a** and **9a** (Figure 2.26).

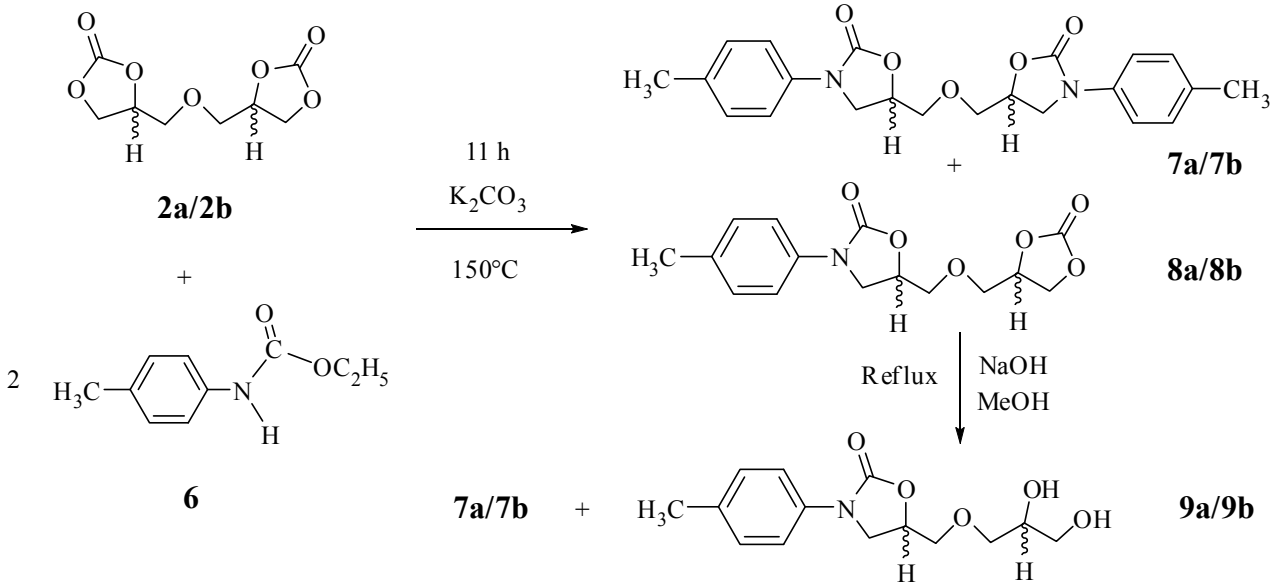


Figure 2.26 - Reaction of ethyl N-(4-methylphenyl)carbamate with *d,l/meso*-DGDC.

In particular, derivative **7a** was obtained in 59-60% yield when a molar ratio1:3 of DGDC to N-(4-methylphenyl)carbamate was used, whereas with higher ratios (1:1 or 1:2) mixture of mono-substituted product **9a** and disubstituted product **7a**. The results reported in **Table 2.8** are representative of these experiments.

Table 2.8 Oxazolidinone product distributions in the reaction of DGDC with ethyl N-(4-methylphenyl)carbamate (EC) depending on the molar ratio of reagents.

Reactions	Molar ratio DGDC:EC	**7a**	**8a**	**9a**
1	1:3	59%	7	5%
2	1:2	52%	10	8%
3	1:1	45%	15	10%

Compounds **7a** & **8a**, having the same Rf values on TLC, were evaluated by HPLC after recovery of pure reference products by hydrolysis with NaOH in methanol. Under these reaction conditions, compound 7a was found to be stable and only carbonate of compound **8a** got deprotected to compound C. This last compound was easily separated owing to its high polarity by column chromatography and then by crystallization from methanol. White shiny crystals of disubstituted compound were obtained by direct crystallization from methanol of the crude reaction mixture and submitted to X-ray structure determination.

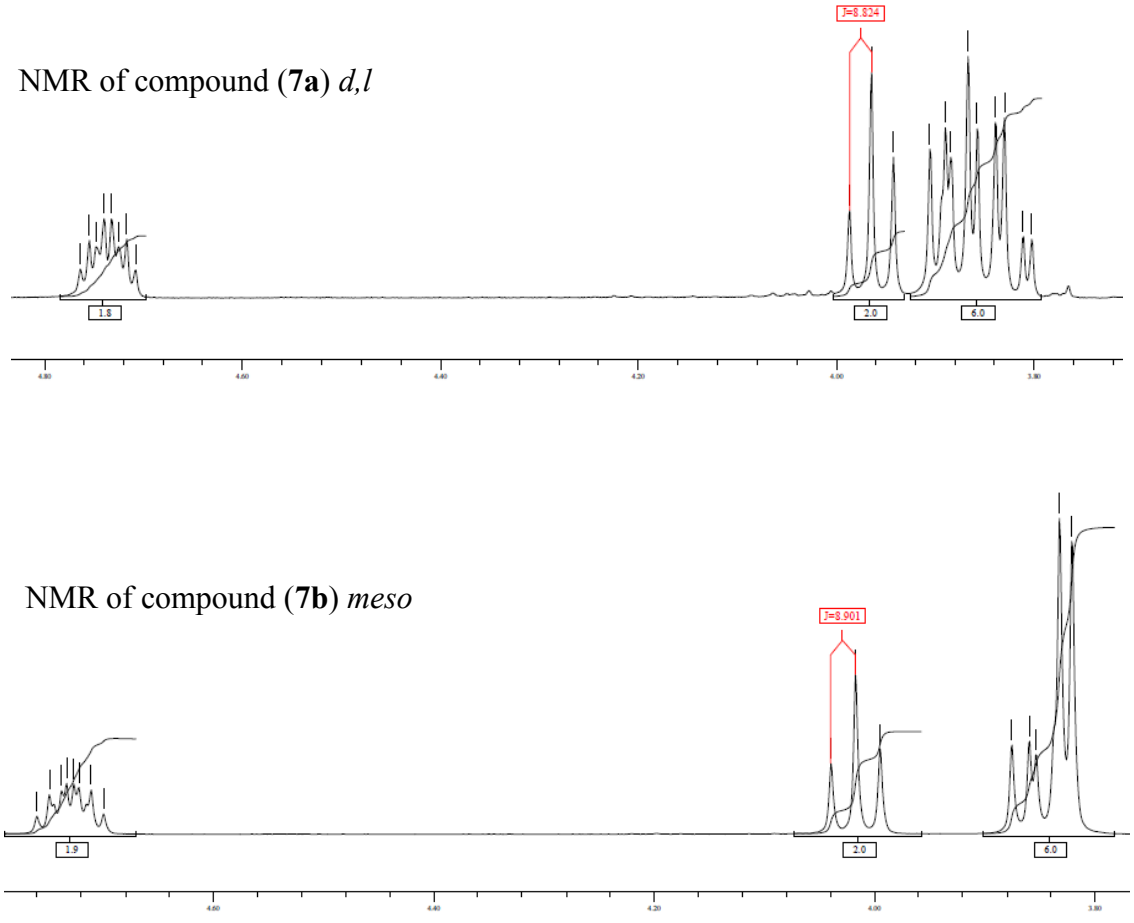


Figure 2.27 – ^{1}H-NMR spectra of compounds *d,l* **(7a)** and *meso* **(7b)**.

Analogous reactions carried out on *meso*-DGDC confirm that the process is stereoselective affording disubstituted products **7a** with retention of configuration. Structural attributions were made with the help of ^{1}H-NMR, ^{13}C-NMR, IR, mass spectroscopy. Nearly identical IR, mass and ^{13}C-NMR spectra were obtained for *d,l*- and *meso*-dioxazolidinones but the compounds were easily distinguishable with the help of ^{1}H-NMR (Figure 2.27) on the basis of the characteristic multiplet of methylene hydrogens alpha to ethereal oxygen. Moreover, the diastereoisomers show different melting point: *d,l* disubstituted has a m.p 125-126°C (from methanol), and *meso* disubstituted has a m.p 152-153°C (from methanol),

Reaction of *d,l*- and *meso*-DGDC with alcohols and phenols

Extension of the substitution reaction to O-nucleophiles confirms that simple aliphatic alcohols are challenging to react selectively to give the corresponding ether, resulting commonly into the mixed transesterification product of the carbonate group of DGDC. On the contrary, reactions with phenols, were more selective for the etherification reaction with preference for addition to position 1 of diglycerol. Generally, minor amount of monosubstituted products were also detected by HPLC or isolated by column chromatography.

The reaction was deeply investigated on 4-isopropylphenol under neat conditions at 120°C in the presence of catalytic amount of K_2CO_3. The reaction with *d,l*-DGDC (**2a**) was complete in 6 hours, affording three products, one disubstituted **10a**, and two mono-substituted (carbonate **11a** and triol **12a**), as reported in Figure 2.28. Similar reaction on *meso*-DGDC (**2b**) afforded the corresponding products **10b**, **11b**, and **12b**. All compounds were purified by using column chromatography and the white shiny crystals of disubstituted compound **10a** and **10b** were obtained by crystallization from hexane (with different melting point 68-69°C for **10a** and 50-51°C for **10b**).

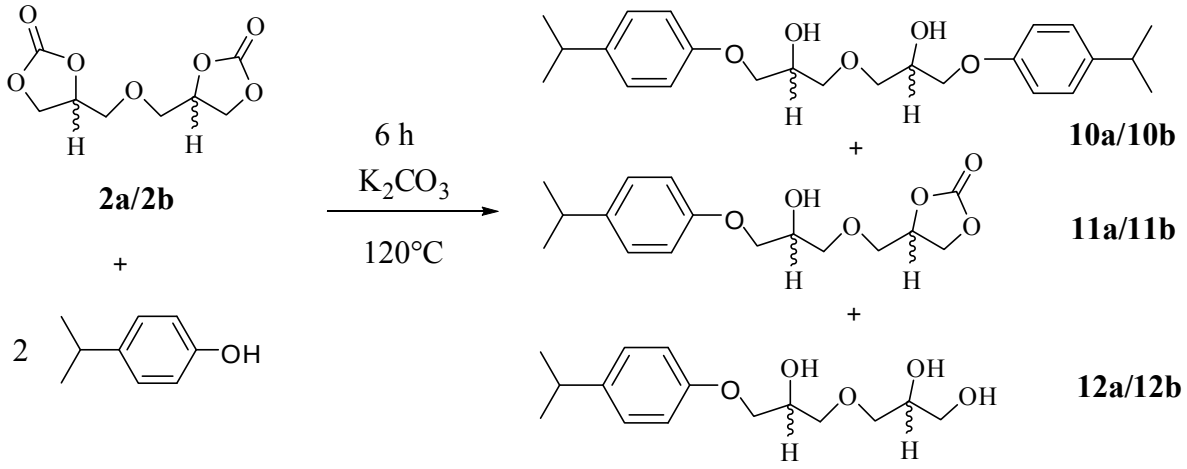


Figure 2.28 - Reaction of isopropyl phenol with *d,l/meso*-DGDC to give phenoxy-DG

Using combined analyses by ^{1}H-NMR, ^{13}C-NMR, IR, Mass and X-Ray crystallography the structure of compounds was established, confirming the retention of configuration in the main substitution product **10a** and **10b**. ^{1}H-NMR spectra were again particularly diagnostic with characteristic multiplet for the methylene hydrogens alpha to ethereal oxygen (Figure 2.29).

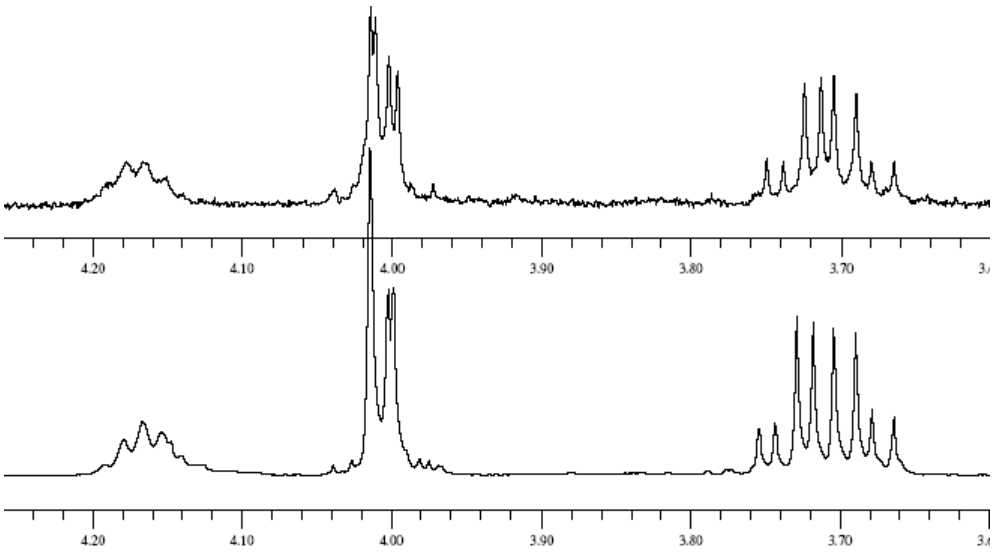


Figure 2.29 - ^{1}H-NMR of disubstituted *d,l*-**10a** and disubstituted *meso*-**10b**

Also IR spectra were usefull to clarify the presence of dioxolanone ring in compound **11b** as can be deduced from the characteristic peak of carbonyl group at 1793 cm^{-1} for the *meso* compound (Figure 2.30), absent in the di-addition product **10b** (Figure 2.31).

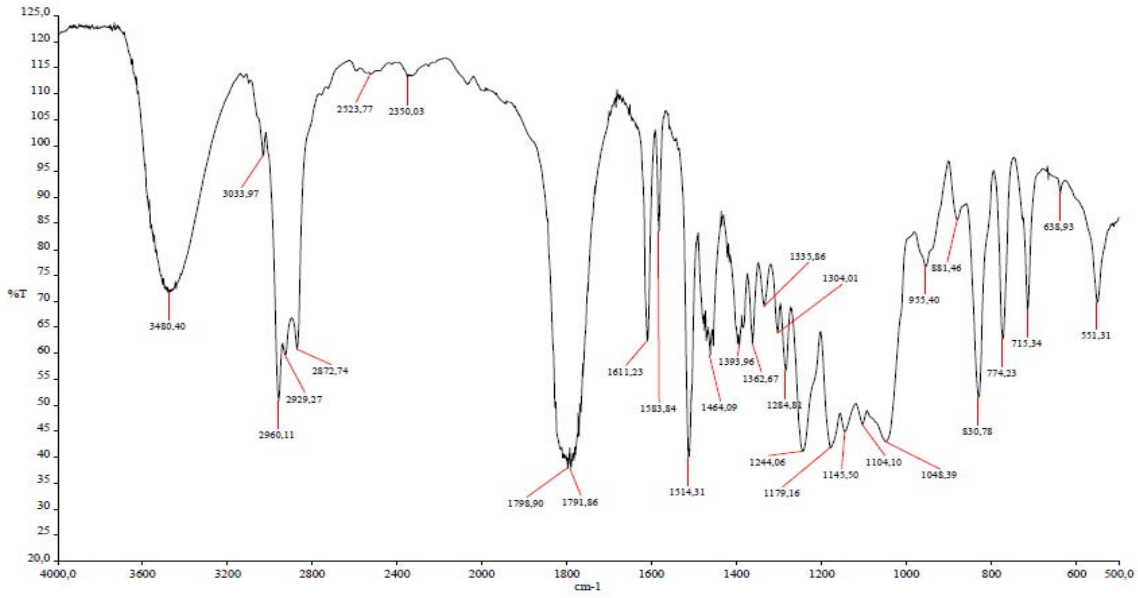


Figure 2.30 - IR spectra of mono substituted *meso*-**11b.**

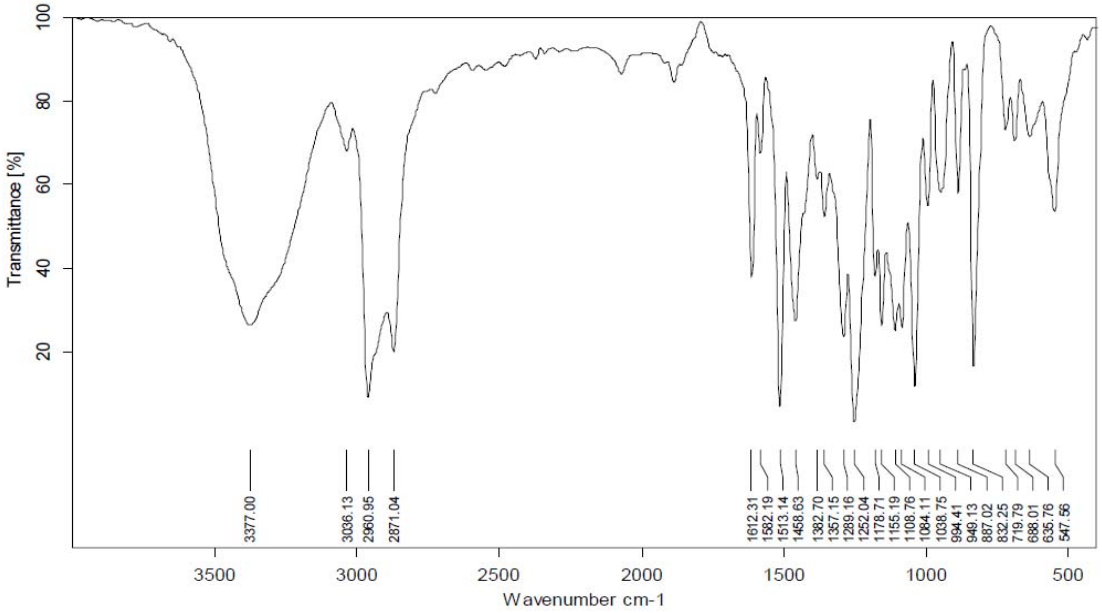


Figure 2.31 – IR spectra of disubstituted *meso*-diphenoxy-GC **10b**.

A definitive answer to the relative stereochemistry of the two stereogenic centers of diphenoxy-GC were obtained by X-ray single crystal analysis of compound **10a**. The Ortep plot of Figure 2.32 clearly confirm the retention of configuration (*d,l*-**10a** from *d,l*-**2a**).

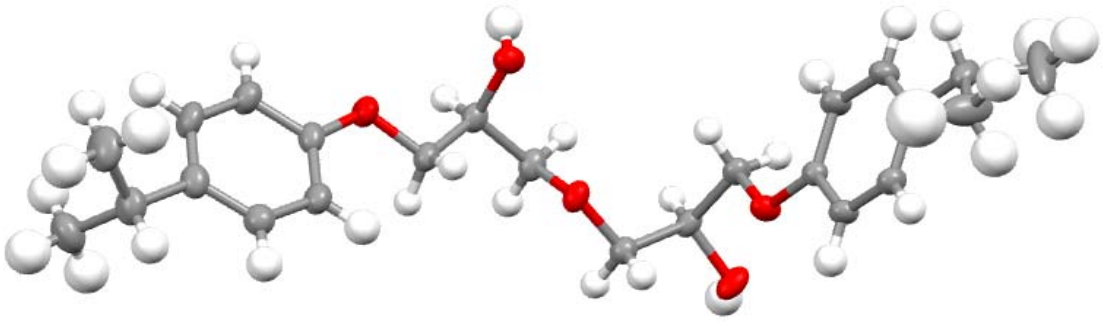


Figure 2.32 - Structure of disubstituted product *d,l*-**10a** determined by X-Ray single crystal analysis.

Disubstituted derivatives **10a** and **10b** become highly prevalent when the ratio DGDC to 4-isopropylphenol was used in molar ratio 1:2.2. A further improvement in the yield of the reaction was accomplished adding the phenol batch wise to prevent its sublimation at the temperature used (m.p. 59°C).

The preference of the reaction for terminal positions of DGDC was remarkable and quite useful in the context of use of DGDC as chain extender in polymer preparation. This selectivity is uncommon in nucleophilic substitution to 5-member cyclic carbonates, so detailed investigation was carried out to define the presence of stereoisomers in which the phenoxy group was present in position 2 of GC. After some preparative and analytical investigation with different techniques, we succeed in identifying GC-MS conditions to quantify the isomer, which is indicated in Figure 2.33 as arrow, is in the range of 2%.

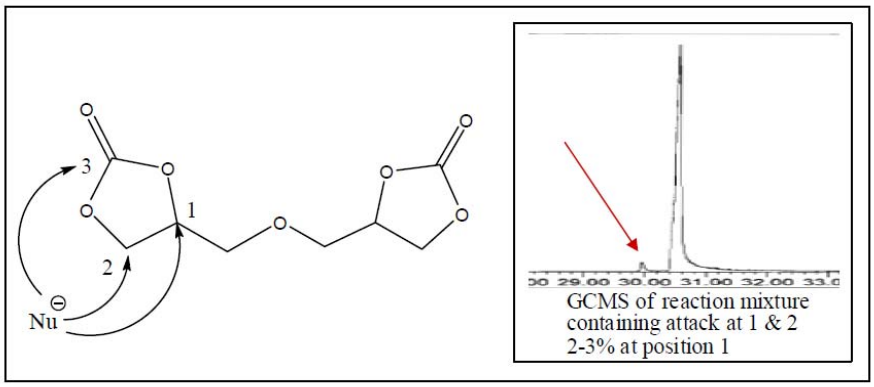


Figure 2.33 – Alternatives nucleophilic attacks on DGDC - GC-MS of **10a** from crude mixture.

The mass spectra of two peaks were similar with minor differences in intensity (see experimental part). Structural identity of compounds was also confirmed by ^{13}C- and ^{1}H-NMR analyses. A sample sufficiently enriched of this compound was in fact isolated by successive crystallizations of the mother liquors, affording the ^{1}H-NMR spectra of Figure 2.34. Absorption of the tertiary hydrogen on carbon 2 of

phenoxy-1,3-propandiol moiety was observed at 4.14, which compare well with the one reported in literature for the parent derivative at 3.99- 4.12 ppm.[31]

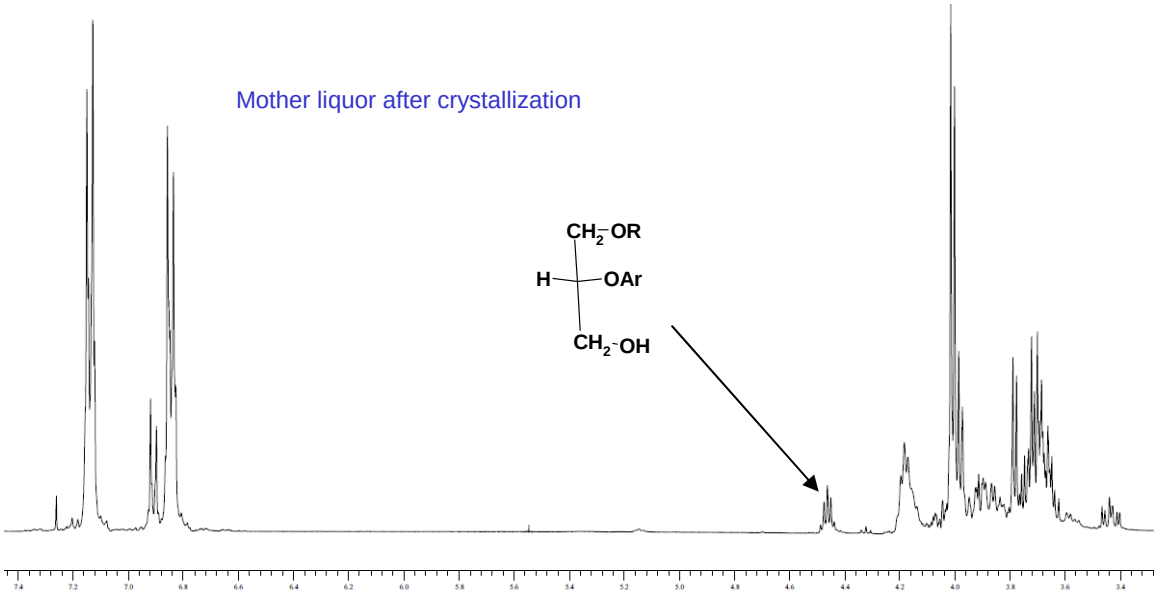


Figure 2.34 – ^{1}H-NMR spectrum of purified phenoxy product **11a** of DGDC at glycerol carbon 2.

The selectivity observed for terminal position is more in line with a direct nucleophilic substitution by the phenoxy group at the less hindered position 1 than the alternative addition to the glycidol intermediate formed by carbon dioxide extrusion from the carbonate (Figure 2.35). Nucleophilic addition to epoxides is known to give mainly addition products at the less substituted side but the selectivity is never higher than 90%.

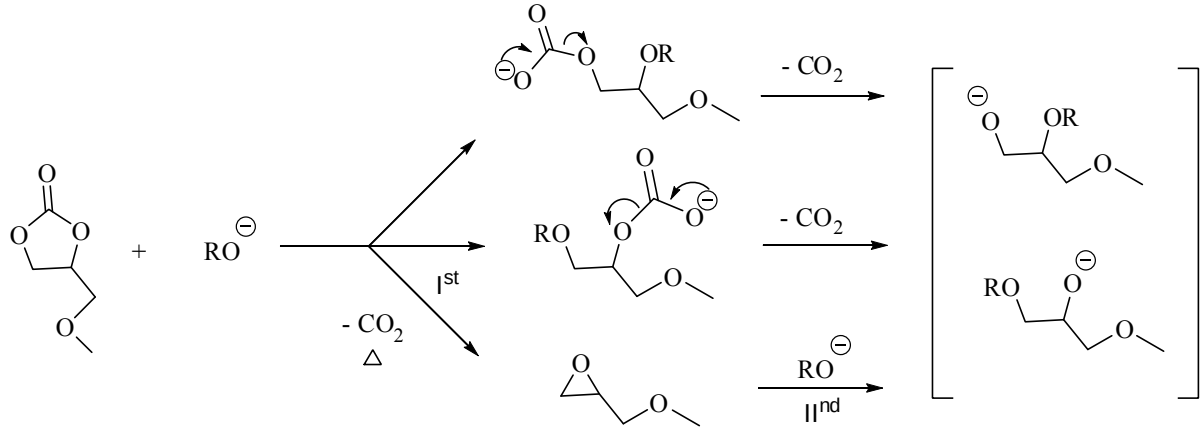


Figure 2.35 Alternative mechanisms of the reaction of glycerol carbonate with O^{-} nucleophiles.

In order to better understand the fate of the reaction and recover some insight on the mechanism of the substitution, a kinetic study of the reaction of DGDC with 4-isopropylphenol was investigated. The simplified model of Figure 2.36 was applied to evaluate the rate constant involved in the process (k_1 and k_2).

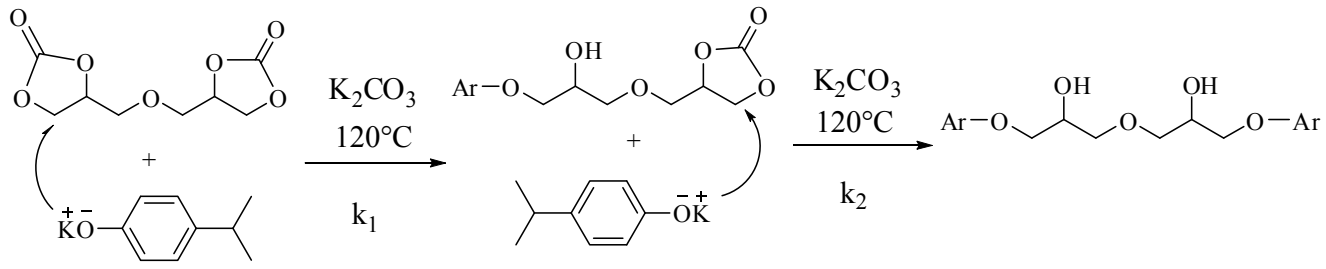


Figure 2.36 – Kinetic model for consecutive nucleophilic substitution of 4-isopropylphenol on DGDC.

The reaction was investigated on neat *d,l*-DGDC and 4-isopropylphenol mixture in molar ratio 1:2 at 120°C in the presence of catalytic amount of potassium carbonate (5%). HPLC analyses of samples withdrawn from the reaction mixture at selected times were used to follow the decay of starting phenol and formation of diphenoxy derivative **10a** and monophenoxy derivative **11a** (Figure 2.37).

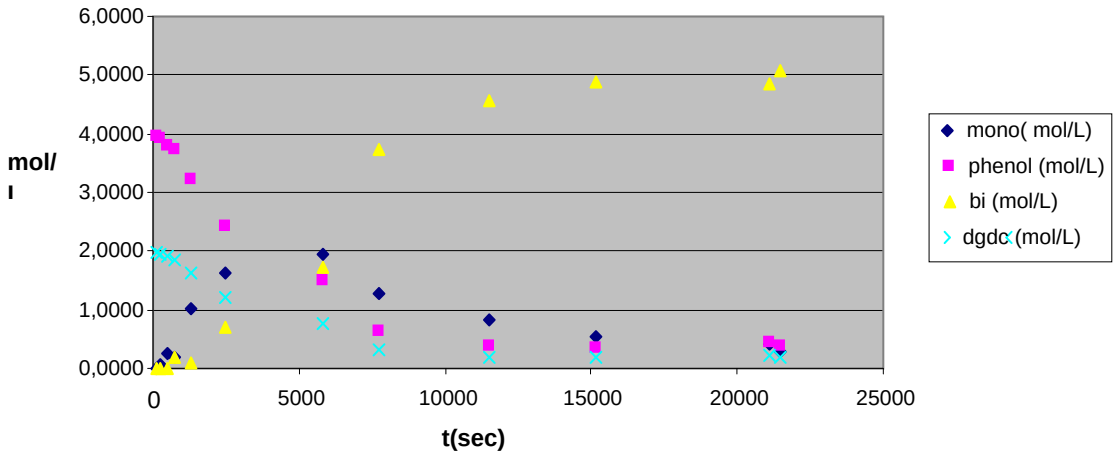


Figure 2.37 - Kinetic of the reaction of DGDC with 4-isopropylphenol followed by HPLC.

Mathematical elaboration of data for reagent and product concentrations on time allow to deduce the second order rate constants of the consecutive reactions $k_1 = 9.57 \cdot 10^{-5}$ and $k_2 = 1.44 \cdot 10^{-4}$ $M^{-1}s^{-1}$. The slightly higher rate constant k_2 over k_1 for the disubstitution explains the relevance of disubstituted product also under stoichiometric ratio of reagents and can be attributed to an enhancing effect due to the presence of phenoxy group firstly introduced, probably favored by the association with starting phenol.

2.5 - Stereo-ordered Poly(hydroxy ethers) by the Condensation of Bisphenols with Diglycerol Dicarbonate.

Polymers and oligomers containing reactive functional groups are vitally important in polymer science, especially for the preparation of thermosetting systems. Polymers containing epoxy, hydroxyl, isocyanate, amine and carboxylic acid groups are widely used commercially in applications such as protective coatings, adhesives and composites. Functional groups can also be used to modify the properties of a polymer such as adhesion. Many of the functional groups currently in use have limitations in terms of reactivity or may have environmental hazards associated with them. Thus, the development of new functional groups and new benign polymers is an active area of investigation in polymer science.

In this context, cyclic carbonates are of specific interest for a series of reasons: the carbonate group is highly polar, its reaction with amines yields hydroxy urethanes without the use of hazardous isocyanates, and its reaction with alcohols affords hydroxy carbonates and/or hydroxy ethers. Depending on the functionality of the cyclic carbonate and amine bearing materials, either linear or cross-linked polyurethanes, polycarbonates and polyethers can be produced.[32] In recent years derivatives of glycerol carbonate were more specifically investigated as raw materials for the synthesis of "green" chemicals, e.g. solvents, surfactants, and materials, i.e. moisture insensitive nonisocyanate polyurethanes and other heterochain polymers, but no report have appeared on the use of DGDC as difunctional monomer or cross-linker. This point stimulated our interest for the synthesis of functional polymer from this material[33] in combination with our finding on large scale separation of *d,l*- and *meso*-isomers of DGDC.

In particular, we were interested to extend the use of our diastereoisomers to the synthesis of analogous of poly(hydroxyl ethers) of diphenols and more specifically of poly(hydroxy ether of bisphenol-A) also known as phenoxy resin (Figure 2.38).

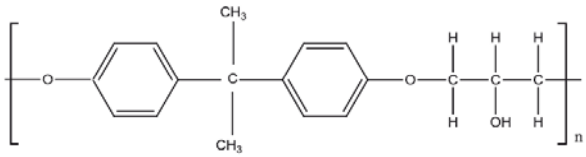
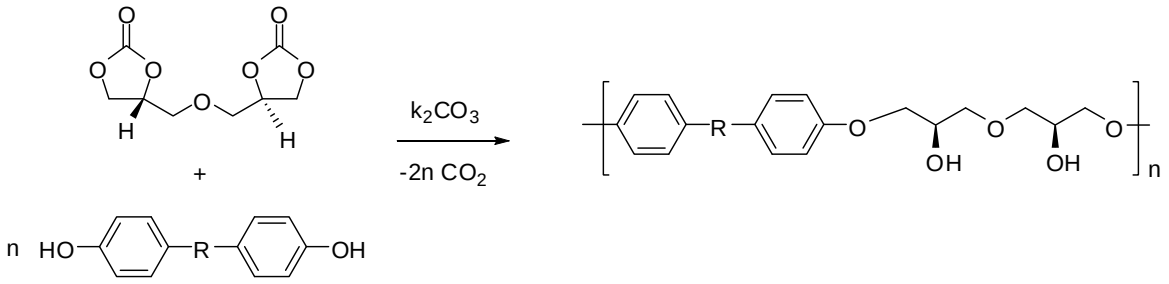


Figure 2.38 – Structure of poly(hydroxy ether of bisphenol-A)

These are amorphous thermoplastics of linear chain containing ether linkages in their backbone and pendant hydroxyl groups conferring high cohesive strength and good impact resistance. This resin is a tough and ductile material and has good oxygen barrier properties and has been used as general material in many fields such as coating, adhesive, laminates, and packaging, as material[34] but mainly it is used blended with other polymers[35] or charged with nanofillers in nanocomposites materials[36]. Preparative methods for these polymers involve polycondensation of diglycidol ether of bisphenol A or, more recently, ring opening of cyclic carbonate by potassium salts of diphenols at 70-90°C.[37] The polymers were characterized by linear structure with a minimized amount of branches.

Our extension of this last reaction to *d,l*-DGDC (**2a**) and *meso*-DGDC (**2b**) with substituted diphenols (**13**) would make available poly(hydroxyl ether)s of general structure **14a** and **14b** (Figure 2.39).



13; R = $C(CH_3)_2$ **14a (14b)**; R = $C(CH_3)_2$

Figure 2.39 – Stereoselective synthesis of poly(hydroxyl ether)s **14** by reaction of *d,l*-DGDC (**2a**) and *meso*- DGDC (**2b**) with bisphenols **13**.

As model reaction we investigate the bisphenol A (Figure 2.39, R = $C(CH_3)_2$) using the conditions previously developed with simple phenols, i.e. in neat conditions at 130-200°C in the presence of catalytic amount (0.1-10%) of potassium carbonate. A nearly stoichiometric amount of carbon dioxide was evolved from the medium during the reaction and a transparent colorless (or light yellow) glassy material was obtained by cooling the reaction mixture. Significant results were obtained when the polycondensation reaction was carried out at 180°C for 6 h and optimization was attempted by changing reagent and catalyst concentrations. Purification of the polymer was carried out by precipitation from dioxane/water. The highest molecular weight reached (M_v = 40.000 from gel permeation analysis) was obtained after 6 hour of reaction with strictly stoichiometric ratio of reagents.

Molecular weight determinations were more easily carried out by ^{1}H-NMR following the characteristic peaks of aromatic groups and carbonate end groups. In fact, the condensation reaction produce signals for internal phenyl ether groups (two doublets at δ 6.78 and 7.07) quite different from the terminal phenoxyl group (two doublets at δ 6.63 and 6.96) as evidenced by the spectra of figure 2.40 taken in the early stage of polymerization.

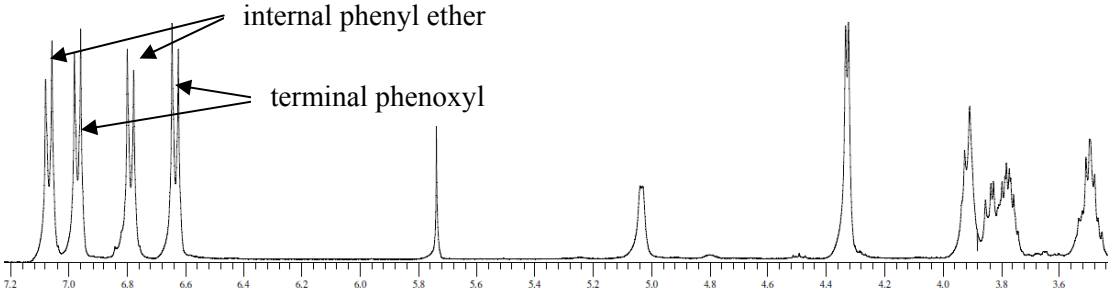


Figure 2.40 – ^{1}H-NMR of polymer **14a** at the early stage of polymerization.

^{1}H-NMR is also useful to identify if the end group in the polymer is phenol or carbonate. Apart the characteristic features of the aromatic region, the carbonate residue can be easily quantified from the characteristic peaks associated to hydrogens belonging to the dioxolanone ring (Figure 2.41).

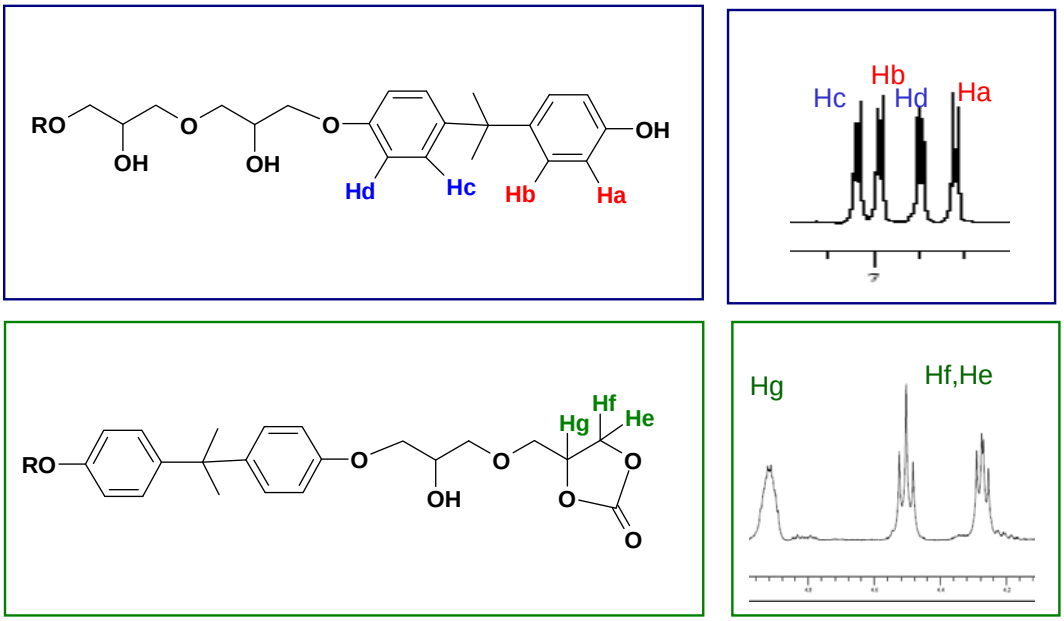


Figure 2.41 – Selected regions of ^{1}H-NMR spectra of polymer **14a** useful to quantify the bisphenol or carbonate function as end groups.

Quantitative determinations of molecular weight were deduced from integration of aromatic hydrogens of the polymer, taking into account the ratio between all aromatics and the terminal ones (at δ 6.63 and 6.97) and multiplying by the molecular weight of a unit (400) for two.

Moreover, comparison between ^{1}H-NMR spectra of the polymer **14a** and **14b** (R = $C(CH_3)_2$) and compound **10a** (**10b**) confirms also for these material the complete preservation of stereochemistry at the stereogenic centers with strong preference for substitution at terminal positions.

In Table 2.9 are collected representative conditions and yield of polymer **14** obtained in different trials, along with the main physical properties (Tg and M_v) of crude and purified polymer.

From these data a clear dependence of molecular weight of the polymer from reagents ratio and catalyst amount can be deduced, whereas the glass transition temperature of the material obtained was relatively insensitive on synthesis conditions.

Table 2.9 - Polycondensation of *d,l*-DGDC (**2a**) and *meso*-DGDC (**2b**) with bisphenol A - key properties of the obtained polymer.

2	[2]/[13]	catalyst (%)	t (h)	Tg (°C)	$\overline{M}$ *
2a	0.41	10	1	n.a.	1000
2a	0.66	10	1	n.a.	2000
2a	0.74	10	1	n.a.	3000
2a	0.82	10	1	70	6000
2b	0.82	10	1	65	6000
2a	0.87	10	1	72	12000
2a	0.91	10	1	n.a.	29000
2a	0.99	10	1	75	38000
2a	0.99	1	0.5	n.a.	800
2a	0.99	1	1	n.a.	9000
2a	0.99	1	2	n.a.	18000
2a	0.99	1	3	n.a.	22000
2a	0.99	1	4	74	24000
2a	0.99	1	5	73	26000

*Molecular mass deduced by ^{1}H-NMR analysis; n.a. = not available

The kinetic of the polycondensation reaction of **2a** with bisphenol A (**13**) with reagents in molar ratio close to 1:1 in neat and in the presence of 1% K_2CO_3 by collecting samples at selected time and immediately recording the ^{1}H-NMR spectra of crude sample dissolved in fixed amounts of $CDCl_3$. The ^{1}H-NMR traces are collected in Figure 2.42. Quantitative elaboration of these data, as above indicated, allows to deduce the data collected in Figure 2.43 (star marks).

A sharp increase in molecular weight is observed between 4 and 6 hours at 180°C and a maximum MW of 40.000 uma was obtained. The trend is typical of a stepwise polycondensation reaction with polymerization rate close to the one of phenol and cyclic carbonate compounds.

In the figure 2.43 are also reported (rhomboidal marks) the results of analogous polymerization reactions at fixed time carried out using different ratio of the two reagents. The asymptotic trend in MW on reagent ratio is typical of polycondensation reaction, where is well known that high molecular weight can be obtained only at strictly stoichiometric conditions.

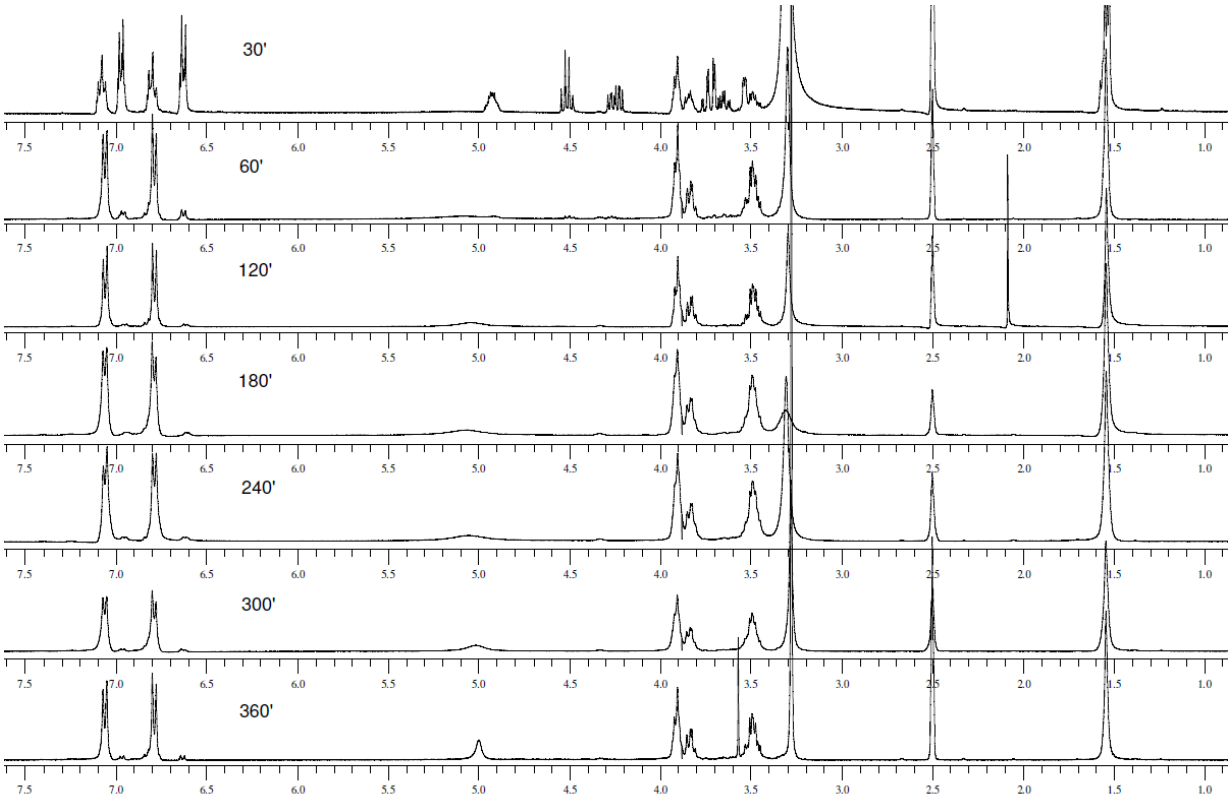


Figure 2.42 – Time dependence of ^{1}H-NMR spectra in the course of polymerization of *d,l*-DGDC with bisphenol A (molar ratio 1:1) at 180°C.

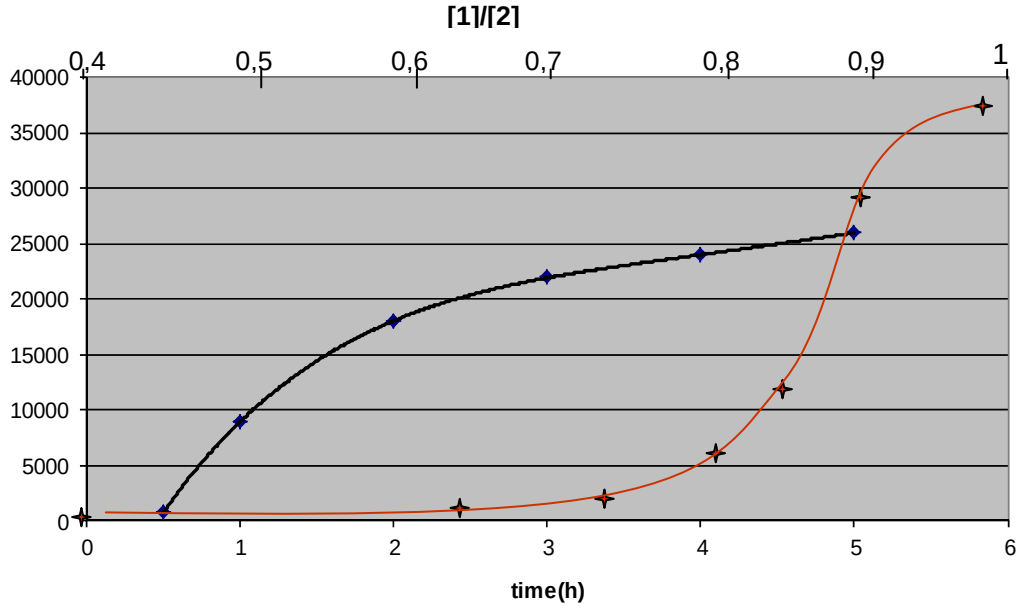


Figure 2.43 - Effect of time (conditions: T = 180°C; [**2a**]/[**13**]/K_2CO_3 1.1:1:10^{-2}) and monomer ratio (T = 180°C; h = 1.25; **2a**/K_2CO_3 1:0.1) in the bisphenol A polycondensation

It must be noticed that, when the polymer was purified by precipitation from dioxane:water 3:1, the end aromatic groups were significantly reduced as showed by the ^{1}H-NMR spectrum of Figure 2.44, clearly indicating a fractionation of the polymer towards high molecular weight components. After two precipitations from this solvent mixture a M_v of 110000 was obtained.

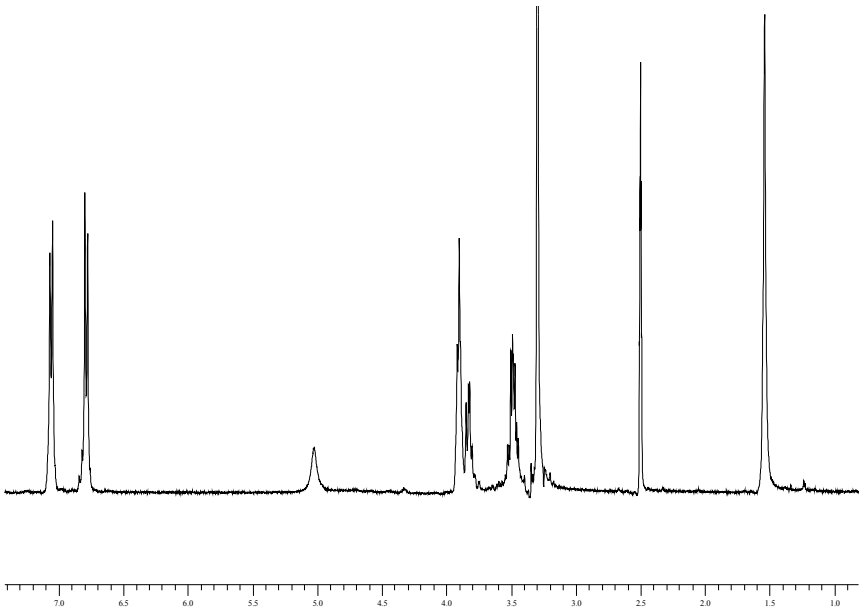


Figure 2.44 - ^{1}H-NMR spectrum of purified polymer **14a**.

FT-IR analysis (Figure 2.45) confirms the polyether structure of crude and purified polymer **14a**, because no carbonyl absorption was observed at 1791 cm^{-1} (linear C=O) or at 1750 cm^{-1} (cyclic carbonate). Table 2.10 collects the remaining peaks information**.**

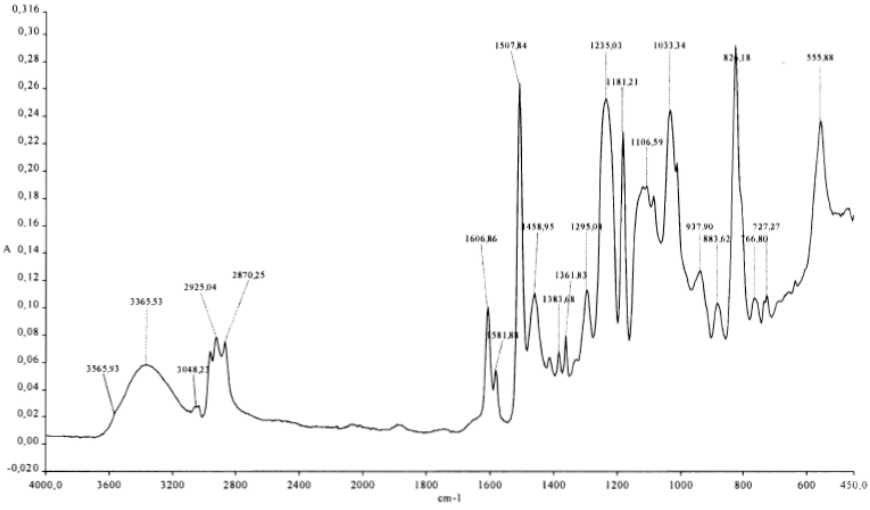
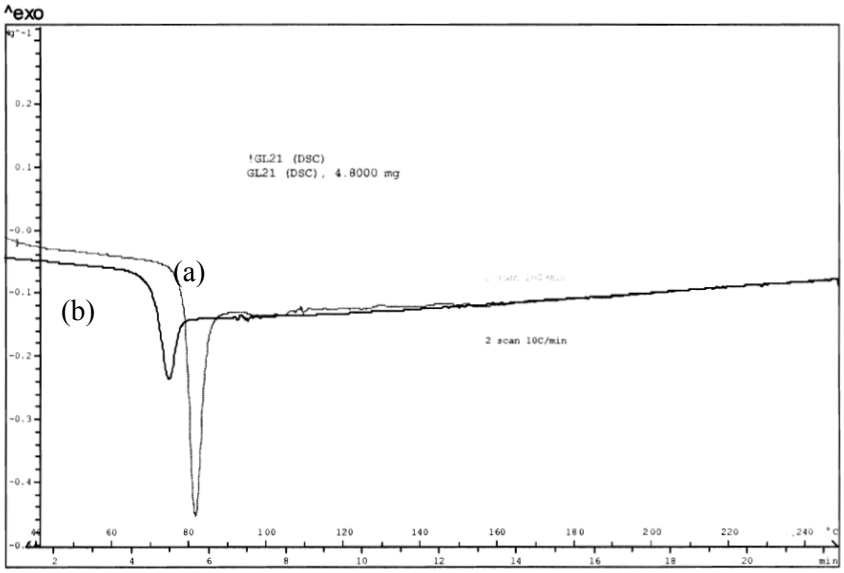


Figure 2.45 - FT-IR analysis of polymer **14a**, supporting its strictly polyether structure.

Table 2.10 - FT-IR absorption of functional groups in polymer **14a**.

Freq. (cm^{-1})	Functional Group
3566	-OH str.
3365	-OH str. water
3048	-CH str Aromatic
2870, 2925, 2961	-CH str aliphatic
1606, 1580, 1507, 1459	C=C str, Aromatic
1459	$-CH_2-$
1383	$-CH_3$
1106	R-O-R, -C-OH
1033	R-O-R
1235, 1181	R-O-Ar
826	CH arom. out of plain
550	Bending of Ar. ring

Thermoanalytical techniques were further applied to monitor heat effects associated to relevant transition in polymers **14a** and **14b**. Differential scanning calorimetry (DSC) analysis (from -25°C to 250°C at 10°C heating rate) revealed that the materials are completely amorphous with no significant transition temperatures and enthalpies of fusion and crystallization. In the first scan the glass transition temperature (Tg) was detected at about 78°C and a remarkable enthalpic relaxation was observed (figure 2.46a). In the second scan after annealing at 60°C (under the same experimental conditions) a Tg at about 70°C and a minor enthalpic relaxation were detected (Figure 2.46b).



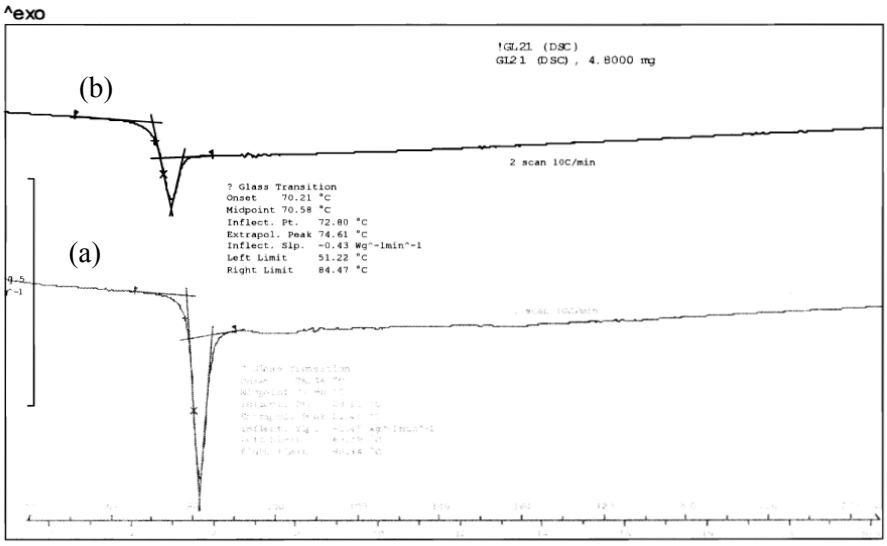


Figure 2.46 – Differential scanning calorimetry (DSC) analysis of polymer **14a**
(a) first scan, (b) second scan.

To further investigate the thermal dependence of polymer **14** from stereochemistry of starting DGDC (*d,l* and *meso*) and on preparative conditions, a series of DSC analyses were carried out. Representative conditions and related DSC traces of polymer **14** are collected in figure 2.47. These data allows to conclude that the glass transition temperature is insensitive to stereochemistry of diglycerol framework and that is also not very dependent on molecular weight, if higher than 20000.

	DGDC	T (h)
1	*d,l-*	2.75
2	*d,l-*	1.4
3	*meso-*	1.4

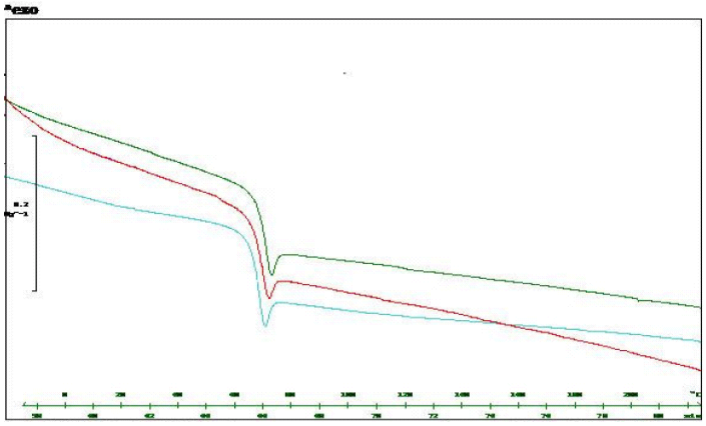


Figure 2.47 - Thermo gravimetric analysis (TGA) of polymer **14a** and **14b** (different preparations).

Thermogravimetric analysis (TGA) of the polymer were also investigated to recover information on thermal stability of the material and the nature of volatile materials produced. The TGA of polymer **14a** under nitrogen (Figure 2.48) shows a decomposition curve without significant emissions of volatile components at low temperatures and a thermal decomposition (TD-1/2) around 390°C. The pyrolysis produces a residue (about 8%) presumably associated to the catalyst K_2CO_3 in the preparation of the polymer. TGA analysis of the polymer **14a** sample precipitated from dioxane:water and free of inorganic residues (by microanalysis) revealed a carbon residue at 850°C of 3.5%, but the sharp peak of polymer decomposition remains around 390°C. These data confirm the remarkable stability of the polymer at high temperatures, even better than the one of typical phenoxy resins.

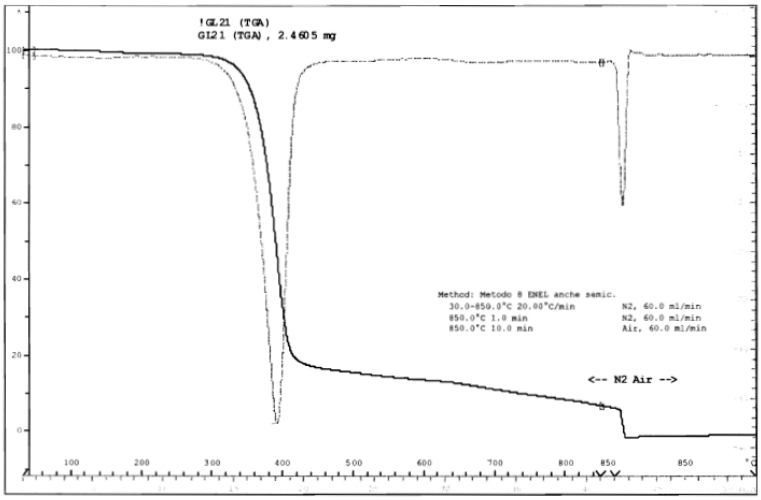


Figure 2.48 - Thermo gravimetric analysis (TGA) of crude polymer **14a**.

Conclusion. All the data collected indicate that poly(hydroxyl ethers) obtained by condensation of stereo pure α,α'-diglycerol dicarbonate and bisphenol A are a promising next generation materials with high chemical resistance and good mechanical and adhesion properties. Using appropriate diphenols (less toxic than bisphenol A), this class of polymers can become interesting alternatives to phenoxy resins more environmentally friendly and safe. Moreover, the use of the safe carbonate functional group allows to reach polymerization conditions at moderate temperatures and without the use of dangerous derivatives as glycidyl ethers. Finally, the presence in the polymer of hydroxyl functional groups make them tunable through appropriate functionalization, covering a broad range of applications. The potentiality of stereo regularity in the polymer backbone on properties of final material, here preliminary investigated, has not yet proved significant but it is under further screening.

2.6 EXPERIMENTAL

Materials or reagents

All materials were purchased form commercial suppliers; α,α'-diglycerol was purchased from Fluka (92% purity), diethyl carbonate and diethyl carbonate from Aldrich, solvents like acetonitrile, methanol, hexane, ethyl acetate, acetone dichloromethane and potassium carbonate were purchased from Carlo Erba. NMR spectra were determined with TMS as internal standard, on a Bruker 250 MHz or 400 MHz instrument. Chemical shifts are reported in ppm with the solvent residual peak as internal standard ($CHCl_3$: δH= 7.26 ppm; $CDCl_3$: δC= 77.0 ppm; [D_6]DMSO: δH= 2.50 ppm, δC= 39.52 ppm). ESI-MS spectra were performed with an Esquire 3000 plus ion-trap mass spectrometer equipped with an ESI source. GC-MS analyses were performed on an Agilent *6890* gas-chromatograph equipped with a 5973 mass-detector, using a HP5MS column (30 m x 0.25 mm x 0.25 μm); the following temperature program was used: 40°C (1')//2°C/min//45°C (1')//10°C/min//200°C (1')//20°C/min //280°C (10'). IR spectra were registered with a Perkin Elmer 2000 FTIR instrument. Chromatographic separations were performed using Merck Kieselgel 60 silica gel. Melting points were determined with a Buchi 535 instrument and are uncorrected. HPLC analyses were performed on Varian 9010 equipped with a diode array detector using a column Purospher Star RP-18 endcapped column (125 mm × 2.0 mm, particle size 5 μm) preceded by a C18 guard column (4 × 4, 5 μm), both supplied by Merck (Darmstadt, Germany) using a gradient mixture of acetonitrile/methanol (1:1-1:0, v/v, 10 min).

2.2 Synthesis of 4,4'-[oxybis(methylene)]bis(1,3-dioxolan-2-one) (diglycerol dicarbonate, DGDC)

A. Thermal - General procedure.

In a round bottom flask equipped with a Vigreux column and distillation condenser, diethyl carbonate (2.5 mol) was added to the mixture of α,α'-diglycerol (1 mol) and sodium bicarbonate (0.04 mol) as a catalysts. The reaction was carried out at 140°C, with a stirring at 100 rpm. The ethanol was distilled out at 80°C and then diethyl carbonate until 120°C (approximately 2 hr). The reaction was stopped and allowed to stand at room temperature overnight, and the white solid formed filtered to give the mixture of *d,l*-DGDC and *meso*-DGDC with 80 % yield. *d,l*-Diglycerol dicarbonate was obtained by crystallisation from dichloromethane after seeding with pure *d,l*-isomer. Crystallization of *d,l*-isomer can be obtained also in water (1:10 weight ratio) after neutralization with acetic acid. The mother liquid were concentrated and crystallized with chloroform to obtain the *meso*-isomer.

B. Microwave irradiation - General procedure

A two neck 250-ml round bottom flask, previously weighed and calibrated, then equipped with a Vigreux column and water-cooled distillation condenser, was prearranged in a microwave Milestone Microsynth oven and charged with diethyl carbonate (240.16 g, 2.033 mol), α,α'-diglycerol (140.19 g, 0.844 mol) and sodium bicarbonate (2,835 g. 34 mmol). The reaction was MW irradiated at atmospheric pressure under magnetic stirring. The microwave reactor was programmed by setting a limit of initial power of 500 W for 3 minutes to reach temperatures of 140°C, followed by a power of 300 W to maintain the reaction temperature at 140°C for 40 minutes. The reaction mixture initially appeared heterogeneous but became homogeneous as the temperature increases. It was observed that around 120°C unreacted diethyl carbonate distilled out, while approximately ethanol distilled out at 80°C. During the distillation of ethanol the

power used to maintain constant temperature is increased up to 250 watts and then drop back to about 60 watts. This can be taken as indication of the end of the reaction and irradiation was stopped. The reaction mixture was then allowed to cool and during the cooling phase formation of small crystals was observed. The system was left to stand until room temperature was reached, and then the reaction mixture was dissolved by stirring in dimethoxyethane at 60°C and allowed to cool for 24 hours at r.t.. A crystalline precipitate was filtered and the mother liquor was further left to stand for another 24 hours at 5°C. Thus was obtained the formation of another solid which looks different from the first precipitated. The first solid precipitated was crystalline, transparent, white, and the second was more amorphous, opaque, gray pearl. From the solution of the crude mixture of reaction in dimethoxyethane at 60°C *meso*-diastereoisomer crystallizes first with a high degree of purity in the form of translucent prisms. Then, after several hours, precipitates the diastereoisomer *d,l*- of impure *meso*- in the form of opaque flakes.

The mother liquor was analyzed by GC-MS which showed that there was still a significant amount of DGDC. The mother liquor was concentrated by removing the solvent by means of vacuum pump and rotavapor, and dissolved in deionized water in hot (40°C). The two diastereoisomers precipitated. The yield in moles of the crystalline DGDC, calculated with respect to diglycerol, was approximately 65%.

***d,l*-diglycerol dicarbonate 2a** (30-45 % yield), White solid, mp 103-104°C (from water), 105-106°C (from MeOH), 102-103°C (from DCM); ^{1}H-NMR (400 MHz; $CDCl_3$; Me_4Si) in δ: 4.80 (2H, m), 4.51 (2H, t, *J* = 8.2 Hz), 4.40 (2H, dd, *J* = 5.7and 8.5 Hz), 3.85 (2H, dd, *J* = 3.4 and 11.4 Hz), 3.78 (2H, dd, *J* = 3.17 and 11.4 Hz), ^{1}H-NMR (400 MHz; $(CD_3)_2CO$; Me_4Si) 5.00 (2H, m), 4.62 (2H, t, *J* = 8.3 Hz), 4.38 (2H, dd, *J* = 6.2 and 8.3 Hz), 3.89 (2H, dd, *J* = 3.1 and 11.4 Hz), 3.82 (2H, dd, *J* = 3.8 and 11.4 Hz),; ^{13}C-NMR 400 MHz ($(CD_3)_2CO$, δ): 156.7; 77.2; 72.6; 67.7,; MS *m/z* (ESIMS) 257 (M^+ + K), 241 (M^+ + Na); 219 (M+1, 22), 132(3), 102(7), 87(46), 70(19), 57(100), 43(67), 31(23).; IR ν_{max} (KBr)/cm^{-1} 1793.

***meso*-diglycerol dicarbonate 2b** (27-32 % yield). White solid, mp 86-87°C (from water), mp 84.5-85.5°C (from 1,2-dimethoxyethane), 82-83°C (from DCM); ^{1}H-NMR (400 MHz, $CDCl_3$; Me_4Si) in δ: 4.82 (2H, m), 4.52 (2H, t, *J* = 8.4 Hz), 4.32 (2H, dd, *J* = 5.8 and 8.8 Hz), 3.82 (2H, dd, *J* = 4.0 and 11.0 Hz,), 3.77 (2H, dd, *J* = 4.4 and 11.0 Hz,); ^{1}H-NMR (400 MHz, $(CD_3)_2CO$, Me_4Si) in δ: 5.00 (2H, m), 4.60 (2H, t, *J* = 8.3 Hz), 4.38 (2H, dd, *J* = 5.8 and 8.6 Hz), 3.90 (2H, dd, *J* = 2.7 and 11.4 Hz), 3.82 (2H, dd, *J* = 4.5 and 11.4 Hz),; ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 4.93 (2H, m), 4.53 (2H, t, *J* = 8.5 Hz,), 4.26 (2H, dd, *J* = 6.2 and 8.4 Hz,), 3.77 (2H, dd, *J* = 2.6 and 11.6 Hz,) and 3.68 (2H, dd, *J* = 4.4 and 11.6 Hz,); ^{13}C-NMR (100.6 MHz, $(CD_3)_2CO$, Me_4Si) 156.6, 77.3, 72.8, 67.8; MS *m/z* (ESIMS) 257 (M^+ + 39), 241(M^+ + 23), 219(M+1, 12), 132(2), 102(6), 87(46), 70(19), 57(100), 43(61), 31(23); IR ν_{max}(KBr)/cm^{-1} 1785.

2.4.1 Synthesis of pure *d,l*- and *meso*-diglycerol by hydrolysis of pure *d,l*- and *meso*-DGDC

Hydrolyses of *d,l*-*DGDC* (and *meso*-DGDC) with catalyst K_2CO_3. DGDC (2.18 g, 10.0 mol) K_2CO_3 (0.44 g) and a mixture of methanol/water 10:1 (20 mL) were taken in round bottom flask and stirred at room temperature for 24 h, with complete conversion of DGDC to diglycerol. The reaction mixture was concentrated and purified by RP18 SiO_2 column chromatography eluting with acetonitrile. The yield of *d,l*-DG (**3a**) and *meso*-DG (**3b**) was 90-95% in both experiments.

Hydrolysis of *d,l*-DGDC (and *meso*-DGDC) with Amberlist-15 as catalyst. In a 25 ml round bottom flask, diglycerol dicarbonate (0.1834 g), Amberlist-15 resin (0.3631 g) and water (10 ml) were taken and refluxed for 5 days. After the completion of the reaction by TLC analysis, the resin was filtered and the

solvent was evaporated under vacuum on rotavapor. The yield of DG obtained was 93%. The resin used Amberlist-15 has previously been titrated with NaOH (0.1 M). The mixture was subjected to ^{13}C-NMR analysis for identification.

Hydrolysis of *d,l*-DGDC (and *meso*-DGDC) with H_2SO_4 as catalyst. The use of homogeneous acid catalysts (sulfuric acid 10% by weight 100:1 ratio by weight) makes it possible to achieve complete hydrolysis in 12 hour at 25°C and in 2 hour at 100° C. The yields of GC were 90% and 92%, respectively.

Hydrolysis of *d,l*-DGDC (and *meso*-DGDC) with sodium methoxide as catalyst. *d,l*-DGDC (415 mg, 19 mmol), sodium methoxide (11 mg, 0.19 mmol, 10% by weight) and methanol (11 mL) were stirred for 24 hours at room temperature. The reaction was controlled by TLC (90% DCM : 10% MeOH). After completion of reaction, DG compound was purified by column chromatography with eluent DCM (80 ml)/MeOH (10 ml) affording 290 mg of pure *d,l*-diglycerol (79% yields). Tony K.M Shing, and Yong-Li Zhong carried out the hydrolysis of five memberd cyclic carbonate by using sodium methoxide in methanol.[38]

***d,l*-Diglycerol (α,α) (3a).** Highly viscous liquid; bp > 280°C at 10 mmHg, ^{1}H-NMR 400MHz (D_2O, δ (ppm)): 3.89 (2H, m), 3.50-3.70 (8H, m).^{13}C-NMR 250 MHz (DMSO-d6, δ (ppm)): 72.8, 70.38, 62.96. MS m/z (re l. int.): 167 (M+1, 8), 135(4), 117(43), 105(9), 93(26), 87(16), 75(51), 61(36) 57(100), 45(87), 43(76), 31(37).

***meso*-Diglycerol (α,α) (3b).** White solid mp 34-35°C; MS (m/z) 166.18; ^{1}H-NMR 400 MHz(D_2O, δ (ppm)): 3.89 (2H, m), 3.65 (2H, m), 3.58 (2H, m). ^{13}C-NMR (D_2O, 100.6 MHz, DSS as internal standard) δ (ppm) 75.7, 73.1, 65.3, 56.0, 21.7, 17.6.

2.4.3 Condensation reactions of the diglycerol dicarbonate 2a and 2b with alcohols and amines

Condensazione reaction of *d,l*-DGDC with dibutylamine. In a 50 ml round bottom flash *d,l*-DGDC (**2a**, 4.36 g, 20 mmol) tin(II) 2-ethylhexanoate (120 mg) and dibutylamine (5,2 g, 0.04 moli) were charged and, then, under nitrogen, the system was heated at 130°C for 4 hours. The mixture is cooled at 100 °C and 80 ml of hot toluene is added. The slurry is left under stirring until an homogeneous solution is obtained, then is slowly cooled until 10 °C. At this temperature the system is left for 1 hour, then the formed solid is filtered (7,9 g, yield 82%). The compound obtained (**5a**) shows the following analytical data: IR ν_{max}: 1720 cm^{-1} (str urethane C=O), 3400 cm^{-1} (broad OH). ^{1}H-NMR (250 MHz, $(CD_3)_2CO$, δ): 0.9 (t, 6H), 1.2-1.5 (m, 8H), 2,3 (t, 4H, NCH_2), 3.32 (m, 1H), 3.63 (m, 1H), 3.7-3.9 (m, 2H), 4.1 (m, 1H). No details on regioselectivity of the carbonate ring opening could be deduced owing to the absence of well isolated signals in *d,l*- and *meso*-isomers. ^{13}C-NMR were nearly identical.

Reaction of DGDC diastereoisomers with ethyl N(4-methylphenyl) carbamate.

Synthesis of ethyl *N*-(4-methylphenyl)carbamate(6). The compound was prepared according to the procedure reported in the supplementary data from the paper *Tetrahedron 62 (2006) 12351-12356.* A mixture of *p*-toludine (10 mmol), ethyl chloroformate (20 mmol), and TEA (20 mmol) were taken in anhydrous THF (100 ml) and stirred at room temperature for 1 hour. The solid was filtered off and the solution was evaporated under reduced pressure. The residue was dissolved in EtOAc (100 ml) and the organic phase was washed with water (2 x 100 ml). The organic phase was evaporated under reduced pressure to give yellow crystalline solid, Yield 83%. ^{1}H-NMR ($CDCl_3$): δ 7.37 (d, J = 8.2, 2H, 3-H and 5-

H or 2-H and 6-H), 7.13 (d, J = 8.2, 2H, 3-H and 5-H or 2-H and 6-H), 4.22 (q, J = 7.1, 2H, $COO\underline{CH_2}CH_3$), 2.33 (s, 3H, CH_3), 1.35 (t, J = 7.1, 3H, $COOCH_2\underline{CH_3}$).

Synthesis of *d,l*-5,5'-oxybis(methylene)bis(3-*p*-tolyloxazolidin-2-one) (7a). *d,l*-DGDC (0.0046 mol), ethyl N-(4-methylphenyl)carbamate (0.0137 mol) and K_2CO_3 (0.92 mmol, 20%) were stirred for 11 hours at 150°C. After the completion of reaction, DCM and aqueous NH_4Cl (1:1 10 ml) were added. The organic layer was separated, dried on sodium sulphate and concentrated. Crystallization afforded 1.07 g of 5,5'-oxybis(methylene) bis(3-*p*-tolyloxazolidin-2-one) (0.0027 mol, 59%). White solid, m.p 125-126°C (from methanol), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.28 (4H, d, *J* = 8.5 Hz), 7.07 (4H, d, *J* = 8.5 Hz), 4.73 (2H, m), 3.96 (2H, t, *J* = 8.8 Hz), 3.91-3.79 (6H, m), 2.30 (6H, s); ^{13}C-NMR ($CDCl_3$, 100,6 MHz) δ(ppm) 154.4, 135.3, 133.5, 129.4, 118.1, 71.9, 71.1, 46.8, 20.5; ESI-MS (MeOH + HCOOH 0.1%) *m/z* 419 (M^+ + Na), 397 (M^++H).

Synthesis of *meso*-5,5'-oxybis(methylene) bis(3-*p*-tolyloxazolidin-2-one) (7b). *meso*-DGDC (0.760 g, 3.48 mmol), ethyl N-(4-methylphenyl)carbamate (1.87 g, 10.44 mmol) and K_2CO_3 (0.096 g, 0.676 mmol, 20%) were stirred for 11 hours at 150°C. After the completion of reaction, DCM and aqueous NH_4Cl were added. The organic layer was separated, dried on sodium sulphate and separated and concentrated. Crystallization afforded 0.730 g of meso-5,5'-oxybis(methylene)bis(3-*p*-tolyloxazolidin-2-one) (1.84 mmol, 53%). White crystalline solid, m.p 152-153°C (methanol), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.38 (4H, d, *J* = 8.4 Hz), 7.14 (4H, d, *J* = 8.4 Hz), 4.71 (2H, m), 3.99 (2H, t, *J* = 8.9 Hz), 3.86-3.76 (6H, m), 2.31 (6H, s); ^{13}C-NMR ($CDCl_3$, 100,6 MHz) δ (ppm) 154.4, 135.5, 133.7, 129.4, 118.3, 72.1, 71.1, 47.0, 20.6. ESI-MS (MeOH + HCOOH 0.1%) *m/z* 419 (M^+ + Na), 397 (M^++H).

Reaction between *d,l*-DGDC and 4-isopropylphenol. *d,l*-DGDC (0.50 g, 23 mmol), 4-isopropylphenol (0.62 g, 48 mmol) and K_2CO_3 (32 mg, 2 mmol, 10%) were stirred for 3 hours at 120°C. Column chromatography of the cooled reaction mixture afforded 200 mg of unreacted 4-isopropylphenol, 530 mg of 1-[2-hydroxy-3-(4-isopropyl-phenoxy)-propoxy]-3-(4-isopropyl-phenoxy)-propan-2-ol (**10a**) (13 mmol, 57%) and 140 mg of 4-((2-hydroxy-3-(4-isopropylphenoxy)propoxy)methyl)-1,3-dioxolan-2-one (**11a**) (5 mmol, 20%) and 120 mg of 3-(2-hydroxy-3-(4-isopropylphenoxy)propoxy)propane-1,2-diol (**12a**) (4 mmol, 18%).

***d,l*-1-[2-Hydroxy-3-(4-isopropyl-phenoxy)-propoxy]-3-(4-isopropyl-phenoxy)-propan-2-ol (10a).** White solid mp 68-69°C (*n*-hexane); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.13 (4H, d, *J* = 8.6 Hz), 6.84 (4H, d, *J* = 8.6 Hz), 4.17 (2H, m), 4.06-3.96 (4H, m), 3.76-3.66 (4H, m), 2.86 (2H, septet, *J* = 6.7 Hz), 2.60 (2H, d, *J* = 4.8 Hz), 1.22 (12H, d, *J* = 6.7 Hz); ^{13}C-NMR ($CDCl_3$,100,6 MHz) δ (ppm) 156.6, 141.5, 127.2, 114.4, 72.7, 69.2, 69.0, 33.2, 24.1; EIMS: *m/z* 402 (M^+, 11%), 175 (23), 136 (20), 133 (27), 121(100), 91(37).

***d,l*-4-((2-hydroxy-3-(4-isopropylphenoxy)propoxy)methyl)-1,3-dioxolan-2-one (11a).** Oil, ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.14 (2H, d, *J* = 8.6 Hz), 6.85 (2H, d, *J* = 8.6 Hz), 4.81 (1H, m), 4.45 (1H, t, *J* = 8.4 Hz), 4.33 (1H, dd, J = 6.0 and 8.6 Hz), 4.14 (1H, m), 3.99 (2H, m); 3.80-3.64 (4H, m), 2.86 (1H, septet, *J* = 7.0 Hz), 2.24 (1H, d, *J* = 4.8 Hz); 1.22 (6H, d, *J* = 7.0 Hz); ^{13}C-NMR ($CDCl_3$,100,6 MHz) δ (ppm) 156.4, 155.9, 141.6, 127.3, 114.3, 75.0, 72.7, 70.5, 69.0, 68.7, 66.1, 33.1, 24.1; EIMS *m/z* (rel. int.) 310 (M^+ 14%), 295 (20), 136 (21), 121 (100), 91 (33).

***d,l*-3-(2-hydroxy-3-(4-isopropylphenoxy)propoxy)propane-1,2-diol (12a).** Oil, ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.14 (2H, d, *J*=8.6 Hz), 6.84 (2H, d, *J*=8.6 Hz), 4.16 (1H, m), 4.03-3.98 (2H, m), 3.90

(1H, m), 3.74-3.57 (6H, m), 2.86 (1H, septet, *J* = 6.7 Hz), 1.22 (6H, *J* = 6.7 Hz); EIMS *m/z* (rel. int.) 284 (M^+ 16%), 136 (25), 121 (100), 91 (29).

The same procedure used for reaction between *d,l*-diglycerol dicarbonate and 4-isopropylphenol was applied also to the *meso*-isomer, allowing to separate the following products:

***meso*-1-[2-hydroxy-3-(4-isopropyl-phenoxy)-propoxy]-3-(4-isopropyl-phenoxy)-propan-2-ol (10b). (XXX number)** White solid, mp 50-51°C (*n*-hexane); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.12 (4H, d, *J* = 8.6 Hz), 6.83 (4H, d, *J* = 8.6 Hz), 4.17 (2H, m), 3.99 (4H, m), 3.77-3.64 (4H, m), 3.08 (2H, bs), 2.85 (2H, septet, *J* = 7.0 Hz), 1.22 (12H, d, *J* = 7.0 Hz), ^{13}C-NMR ($CDCl_3$,100,6 MHz) δ (ppm) 156.6, 141.6, 127.3, 114.4, 72.6, 69.2, 69.0, 33.2, 24.1; EIMS *m/z* (rel. int.) 402 (M^+, 11%), 175 (23), 136 (20), 133 (26), 121 (100), 91 (38).

***meso*-4-((2-hydroxy-3-(4-isopropylphenoxy)propoxy)methyl)-1,3-dioxolan-2-one (11b).** Oil, ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.13 (2H, d, *J* = 8.6 Hz), 6.84 (2H, d, *J* = 8.6 Hz), 4.80 (1H, m), 4.46 (1H, t, *J* = 8.6 Hz), 4.35 (1H, dd, *J* = 6.0 and 8.6 Hz), 4.15 (1H, m), 4.05-3.94 (2H, m), 3.82-3.66 (4H, m), 2.85(1H, septet, *J* = 7.0 Hz), 2.66(1H, d, *J* = 5.1 Hz), 1.22(6H, d, *J* = 7.0 Hz); ^{13}C-NMR ($CDCl_3$,100,6 MHz) δ (ppm) 156.4, 154.8, 141.7, 127.3, 114.2, 74.9, 72.8, 70.6, 69.1, 68.7, 66.1, 33.2, 24.1; EIMS *m/z* (rel. int.) 310 (M^+ 23%), 295 (32), 136 (21), 121 (100), 91 (35).

***meso*-3-(2-hydroxy-3-(4-isopropylphenoxy)propoxy)propane-1,2-diol (12b).** Oil, ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.14 (2H, d, *J*=8.7 Hz), 6.84 (2H, d, *J*=8.7 Hz), 4.17 (1H, m), 4.04-3.97 (2H, m), 3.90 (1H, m), 3.74-3.57 (6H, m), 2.86 (1H, septet, *J* = 6.9 Hz), 1.22 (6H, *J* = 6.9 Hz); EIMS *m/z* (rel. int.) 284 (M^+ 10%), 136 (26), 121 (100), 91 (26).

2.5 Stereo-ordered poly(hydroxy ethers) by the condensation of bisphenols with diglycerol dicarbonate

Synthesis of oligomer 15a (4-[1-[4-[2-hydroxy-3-[2-hydroxy-3-[4-[1-(4-hydroxyphenyl)-1-methyl-ethyl]phenoxy]propoxy]propoxy]phenyl]-1-methyl-ethyl]phenol). The bisphenol A (2.0 g), *d,l*-DGDC (4,5 g) and potassium carbonate (0,6 g) were weighed in a two neck round bottom flask. The system was flushed with nitrogen for 2 min. and then the reaction flask was dipped in oil bath at 130°C for 6 h under nitrogen. The cooled reaction mixture was column chromatographed on flash SiO_2 using methyl-t-butyl ether to obtain as second crop, after small amount of starting bisphenol A, the diaddition product **15a** (52% yield) with the following analytical data: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.07 (2H, d, *J*=8.7 Hz, phenyl ether), 6.96 (2H, d, *J*=8.2 Hz, phenol), 6.78 (2H, d, *J*=8.7 Hz, phenyl ether), 6.63 (2H, d, *J*=8.2 Hz, phenol), 4.12-4.20 (2H, m), 3.77-3.64 (4H, m), 1.72 (6H, s); EIMS *m/z* (rel. int.) 587 ($M+1^+$ 19%), 509 ($M+ Na^+$, 100). Exact Mass: 586, 288 calcd. $C_{36}H_{42}O$ 586,29305. El. Anal. C 73.61% H 7.32% O 19.01%, calcd. C 73.70% H 7.22% O 19.09%.

Synthesis of polymer 14a (14b). The bisphenol A (**13**) (11.4 g, 50 mmol), *d,l*-DGDC (**2a**) (10.9g, 50 mmol) (or *meso*-DGDC **2b**) and potassium carbonate (0.5 g, 10% mol), were taken neat in two neck round bottom flask and flushed with nitrogen then reaction flask was dipped in oil bath which was at 180°C temperature, for 6 h, the reaction mixture was found to be viscous liquid stirred mechanically, a nearly stoichiometric amount of carbon dioxide was evolved during the reaction and a transparent colourless or light yellow glassy material was obtained by cooling the reaction mixture. Analytical data for the polymer are reported and discussed in the full text. IR cm^{-1}: 3566 (-OH str.), 3365 (-OH str. H_2O), 3048 (-CH str. Ar ring), 2870-2925-2961 (-CH str. aliphatic), 1606, 1580, 1507, 1459 (C=C str. Ar ring), 1459 (-CH_2-),

1383 (-CH_3), 1106 (R-O-R, CH-OH str.), 1033 (R-O-R), 1235, 1181 (R-O-Ar), 826 (CH bend Ar out of plain), 550 (Ar ring bend.).

Kinetic of polymerization for 14a. In an appropriate equipment were prepared 10 round bottom flashes charged under nitrogen with *d,l*-DGDC (**2a)** (2,28 g, 10 mmol) and bisphenol A (**13**) (2.18 g, 10 mmol) and K_2CO_3 (99 mg, 1% mol) was added. All flashes were poured in a thermostatic bath at 180°C under magnetic stirring and single flash was removed from the bath at appropriate time and immediately cooled in ice. A sample (50 mg), accurately weight, was dissolved in $CDCl_3$ (1 ml) and the solution was analyzed by ^{1}H-NMR. The obtained spectra are collected in Figure 2.42. The mean molecular weight of polymer obtained was deduced by quantification of hydrogens belonging to end and internal aromatic moiety as discussed in the text.

Determination of complexation constant between DGDC and Zinc nitrate. A solution of anhydrous zinc nitrate (50 mg) in acetone D6 (0.5 ml) was made and increasing amounts of DGDC (10-250 mg) were added and the ^{1}H-NMR spectra of the homogeneous system were registered. To evaluate the complexation equilibrium constants, the ^{1}H-NMR data were used following the general standard data elaboration for two subsequent equilibria 1:1 and 1:2 (S + L a SL and SL + L a SL_2 , respectively) with K_{11} and K_{12} the related equilibrium constants, via the following equation (where $\Delta = \delta - \delta_L$, $\Delta_{11} = \delta_{SL} - \delta_L$ e $\Delta_{12} = \delta_{SL2} - \delta_L$):

$$\Delta = \frac{\Delta_{11} K_{11} [L] + \Delta_{12} K_{11} K_{12} [L]^2}{1 + K_{11} [L] + K_{11} K_{12} [L]^2}$$

The simpler analysis of the experimental data taking into account only the 1:1 complexation equilibrium, according to the following typical expression, deviates significantly at high ligand [L] concentration.

$$\Delta = \frac{\Delta_{11} K_{11} [L]}{1 + K_{11} [L]}$$

The constants K_{11} and K_{12} were deduced by a regression of data according to the first equation by using the Mathcad 2000 program.

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Chapter – 3

Cascade or one pot three component solvent free synthesis of α-glycerolcarbamates.

Chapter - 3

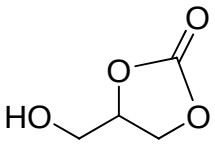
Cascade or one pot three component solvent free synthesis of α-glycerolcarbamates.

3.1 Introduction

Organic carbamates and hydroxyurethanes (i.e. urethanes containing hydroxyl group in the carbon backbone) are compounds of great interest having a wide range of applications[1] in pharmacology, agriculture, and chemical industry.[2] Methods to prepare carbamates and polyhydroxyurethanes are of special interest due to the biological activities of the molecules containing this functional group and the versatility of these polymeric materials. There are numerous routes to synthesize organic carbamates; the more commonly used methods are: a) alcoholysis of carbamoyl chlorides,[3] b) aminolysis of chloroformates,[4] c) transamidation,[5] d) oxidative amination of carbon monoxide,[6] e) reductive carbonylation of organic nitro compounds,[7] f) reaction of urea with alcohol in the presence of heavy metals,[8] g) reaction of carbon dioxide with ammonia,[9] and h) reaction of alcohols with isocyanates. The last reaction is the most widely used approach in polymer industry to synthesize polyurethanes, even if it is based on the use of toxic reagent isocyanates.[10] Also more simple N-monosubstituted carbamates are usually prepared by the reaction of an isocyanate with an alcohol or a phenol or by the reaction of a primary amine with a chloroformic acid ester; these methods normally, although not essentially, involve the use of phosgene to prepare the isocyanate or the chloroformic acid ester.

In recent years special attention has been devoted to the substitution of these dangerous reagents with more safe and green reagents, like carbon dioxide and organic carbonates, with these last considered as good substitutes for phosgene.[11] Alkyl and aryl carbonates were the most investigated reagents for this purpose, but the frequently drastic conditions used with these reagents prevented selective transformations on poly-substituted or structurally complex derivatives.

In recent years the approach to hydroxyurethanes via by aminolysis of cyclic carbonate through a ring-opening reaction has been significantly explored. The interest for these reactions arises mainly from the absence of volatile and non-volatile by-products and from the absence of chloro intermediates. Glycerol carbonate (GC) is of special interest in this context because it is considered a green substitute for important petro-derivative compounds such as ethylene carbonate or propylene carbonate. This compound can be synthetized by several methods via different carbonatating reagents (dialkyl carbonates, ureas, CO_2, CO, etc.) and different catalysts as mentioned previously in chapter - 1.

 Glycerol carbonate.	Colorless Liquid MW : 118.09 CAS : 931-40-8 Viscosity: 61.0 cts a 25°C Flash point: > 400 °C b.p.: 128-131°C a P= 0.1 mmHg DL_{50}: > 5000 mg/Kg,

GC is a quite reactive molecule which can be involved in a great number of substitution/addition reactions with various substrates containing negatively charged or uncharged nucleophilic species centered on nitrogen (N), oxygen (O), sulfur (S), and carbon (C). However, with this substrate the aminolysis reaction provides two hydroxyurethane isomers having the urethane function on the α- or β-carbon atom of glycerol moiety.[12] This finding is a general problem in the aminolysis of the unsymmetrical cyclic carbonates and a limited number of studies were focused on the effect of substituent, temperature and solvent on regioselectivity of this ring opening reaction. The results and related interpretations are frequently in conflict. For instance the rate constant of amine addition to cyclic carbonates was found to increase as the electron withdrawing character of the substituent increased,[13] but the contrary was concluded in another paper by Mikheev *et al.*[14]. Moreover, some report indicates that carbamates (**1** and **2**) can be easily isolated, whereas in other similar reactions only oxazolinones (**6** and **7**) were identified and in limited cases also ethanolamines (i.e. **3** and **4** of Figure 3.1) were reported. The main mono addition/substitution products detected in these reactions are summarized in Figure 3.1.

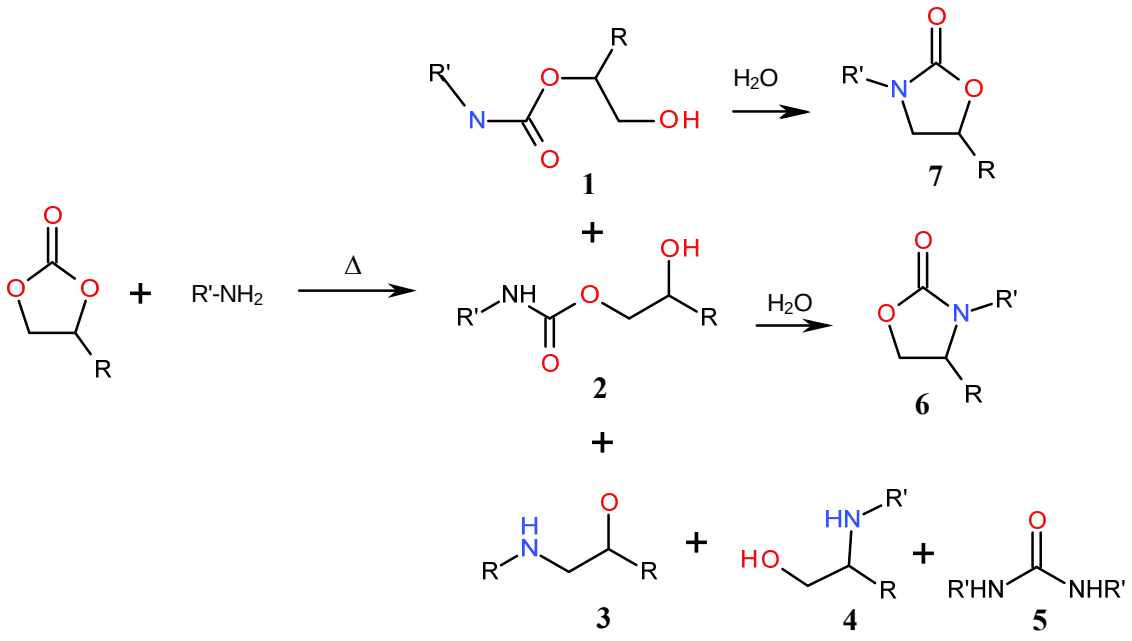


Figure 3.1 - Products reported in literature for aminolysis reaction of 5-membred cyclic carbonate derivatives by alkylamines.

A generally accepted vision of the reaction foresee that operating at low temperature (20-80°C) the aminolysis reaction results in hydroxyurethane isomers (**1** and **2**), whereas at elevated temperatures (>100°C), a second amine molecule is able to react with the hydroxyurethane and yields a substituted urea (**5**),[15] whereas at higher temperatures (> 130°C) isomeric oxazolidines (**6** and **7**) are formed by water elimination from hydroxyurethanes.

As concern the regioisomers obtained in these addition/substitution reactions, their ratio was found to depend on the reaction conditions, the functional group attached to the cyclic carbonate and the substituent's on the aliphatic amine. In particular, the ratio of carbamate derivatives with substituent on the alfa- and beta-carbon atom **3**/**4** or **2**/**1** was found to fluctuate from 1:1 to 9:1. Only limited analyses of factors affecting these values were carried out, but has been reported that in the presence of organic solvents, a somewhat high ratio of β- versus α-hydroxyl was observed.[16] Other studies conclude that the isomer distribution is insensitive to the reaction temperature and only slightly dependent on solvent polarity. One study investigated specifically the condensation of glycerol carbonate with butylamine in the presence and absence of a solvent in stoichiometric amounts, concluding that a ratio close to 1:1 can normally be expected.[17]

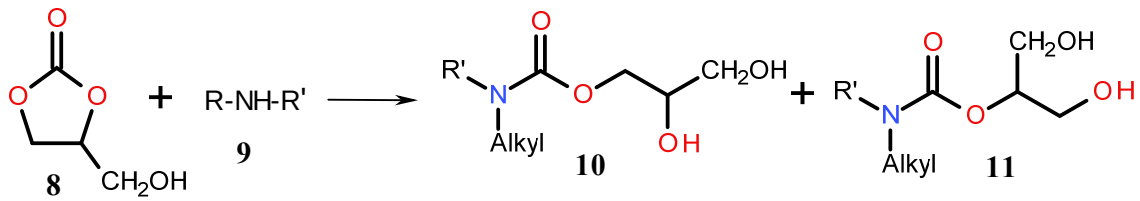
The kinetic features of the interaction of cyclic carbonates with amino groups were studied by Garipov *et al*.[18] These studies indicated that the reaction rate was dependent on the initial concentration of the amine (with reaction order from 1 at low concentration to 2 at high concentration), but is independent of the substituent on the ring. [19] When using water as a solvent, side reactions must be considered, such as hydrolysis, which decreases yields of products compared to those obtained when using organic solvents. Malkemus *et al*.[20] studying the reaction of ethylene carbonate with ammonia at 50°C to form hydroxyalkylurethane reports that secondary products were lacking and the reaction is clean first order in carbonate and ammonia. On the contrary, Ochiai et al.[21] in the aminolysis of bicyclic carbonate with aqueous ammonia found extensive hydrolysis of carbonate. The polyaddition of a hydrophobic bifunctional cyclic carbonate and hexamethylenediamine was reported in a patent as an efficient method to produce polyhydroxyalkylurethanes in aqueous media, although accompanied by significant hydrolysis of bicyclic carbonates into diols. In another paper the kinetic of reaction between functionalized five-membered cyclic carbonates and n-hexylamine concluded that the formation of urethanes with a secondary hydroxyl group increased when strongly electron withdrawing group are present in the cyclic carbonate but the isomer with secondary hydroxyl group was major product in all the cases.[22] Pasquier et al.[23] studied the model reaction of cyclic carbonates substituted by quaternary ammonium groups with n-propylamine in water finding a fast reaction (completed in 3 hr at room temperature) and an higher rate of ring opening than the one of hydrolysis. However, when the reaction was carried out in methanol instead of water under the same conditions, the hydrolysis dictated the product distribution. Very recently, parallel with our studies, in 2012 Basam Nohara *et al*.[24] has reported the synthesis of hydroxyalkylurethanes by the reaction of glycerol carbonate with several primary amine (terminated polypropylene glycol) and secondary amines. They investigated the effects of the solvent, the length of the alkyl chain and the class of the amine (primary or secondary) on the selectivity of α- versus β-isomers. The major product is always the isomer bearing a secondary hydroxyl group, demonstrating a distinct regioselectivity.[25]

From the analysis of literature above reported a complex picture emerges which does not provide a valuable and selective synthesis for 1-substituted glycerol N-alkylcarbamates nor clarify the main factors affecting product and isomer distributions. Therefore, we decide to approach the problem of the synthesis monosubstituted carbamates and, in particular, of glycerol N-alkylcarbamates using directly green alkyl carbonate reagents and glycerol as substrate in the presence of amines. This simplified strategy was elaborated starting from the results reported in chapter II and literature data on reactivity of 5-membered cyclic carbonates and simple dialkyl carbonates, where the latter are general slightly more reactive that the first, in comparison with the much higher reactivity of glycerol carbonate (GC).

The successful approach developed devises a new efficient synthetic route to difunctional and polyfunctional molecules based on building blocks from C-3 inherent natural polyol monomer glycerol. The approach can be usefully applied also in the assembling polymeric urethane materials and hybrid biomaterials from polyols and dialkyl carbonates.

3.2 Results obtained.

In order to develop our project, we first analyze the reactivity of glycerol carbonate (GC, **8**) towards representative alkyl amines (**9a-g**), in order to be confident with the results reported by other researchers and to recover more insight on this reaction, which is, or can be, involved in the process we are interested. We select as reference conditions the one developed in previous chapter on DGDC, namely absence of any solvent and use of potassium carbonate (or tertiary amine) as catalyst. The reactions carried out under these conditions were checked at different temperatures and with different distribution of reagents and found to afford at moderate temperature mainly the product of addition to carbonyl group with ring opening, i.e. glycerol N-alkyl carbonates **10a-g** and **11a-g**. Minor impurity was detected and efforts were made for their identification. The results of these experiments are summarized in Table 3.1.



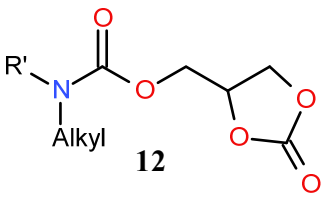
a; R = n-Bu, R'=H
b; R = n-hexyl, R'=H
c; R = n-$C_{12}H_{25}$, R'=H
d; R = 2-Ethexyl, R'=H
e; R = $(CH_2)_2Ph$, R'=H
f; R = $PhCH_2$, R'=H
g; R = R' = n-Bu

Table 3.1 – Catalyzed condensation of glycerol carbonate (**8**) with alkyl amines (**9**) to glycerol N-alkylcarbamates isomers (**10** and **11**).

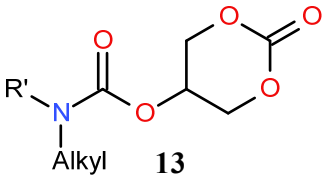
Entry	GC/AA	RNHR'	Catalyst	T (°C)	Time (h)	Yield (%) 10 + 11	10/11**
1	1.0	R=n-Bu, R'=H	0.03	25	24	81	1.02
2	1.0	R=n-Bu, R'=H	0.03*	50	12	82	4.7
3	1.0	R=n-Bu, R'=H	0.03	100	1	75	6.5
4	2.0	R=n-Bu, R'=H	-	50	24	83	6.2
5	1.1	R=Bz, R'=H	-	50	12	84****	6.0
6	1.1	R=n-$C_{12}H_{25}$, R'=H	0.03	50	12	70	5.8
7	1.0	R=$(CH_2)_2$Ph, R'=H	0.06	50	24	87	6.6
8	1.1	R=2-Ethexyl, R'=H	0.03	50	38	81	6.9
9	1.0	R=R'=n-Bu	0.03	80***	6	76	6.7
10	2.0	R=R'=n-Bu	-	80	24	85	7.0

*DABCO; ** Based on ^{1}H-NMR spectra; *** at 50°C after 24 h the carbamate's yield was only 5 %.
****at 25°C after12 h the carbamates yield was 63% with a distribution of isomers of 1.4

The results of table 3.1 indicate that the reaction is general, can be carried out without any catalyst if appropriately long times are taken, is strongly temperature dependent both as concern rate and regioisomer distribution. Side products are however formed which limit the yields in glycerol N-alkylcarbamates, namely glycerol N-alkylcarbamate carbonates (**12** and **13**) and glycerol dicarbamate (**14**).



12



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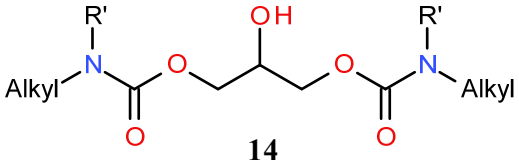
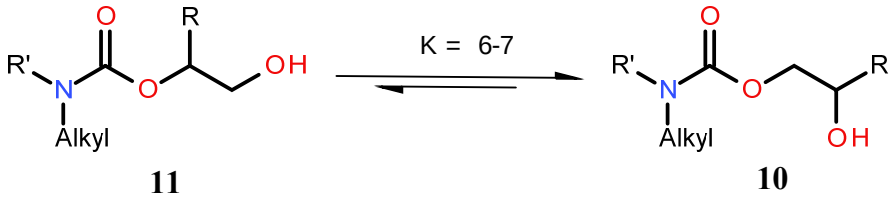


14

Compounds **12** and **14** were isolated in reactions with n-butylamine (**12a** and **14a**) and benzylamine (**12f** and **14f**) by chromatography, whereas compound **13** was inferred from NMR spectra and was present in trace amount. Compounds **12a** and **14a** were found reactive towards glycerol at moderate temperature to give glycerol carbonate and in the presence of benzylamine and glycerol to give glycerol N-benzylcarbamate, suggesting that trans-carbonatation and trans-cabamoilation are operative under these conditions. These reactions have a remarkable precedent in the use of urea as source of carbonyl group for the synthesis of dimethyl carbonate from methanol. These carbonyl transfer reaction can be usefully applied to reduce the relevance of the side products **12-14** carrying out the synthesis of glycerol carbamates in the presence of glycerol. The lower conversions on glycerol so realized with higher yield on converted glycerol carbonate are not limiting factors because the separation of glycerol N-

alkylcabamate is easily carried out by extraction with a medium polarity solvent if the amine used contains 6-8 carbon atoms.

The problem of the isomer distribution becomes more clear when pure diastereoisomers of butylamine, i.e. compounds **10a** and **11a**, were isolated. It was possible to verify their stability by heating independently at temperature in the range 50-100°C in the absence and presence of K_2CO_3. In the last condition NMR analysis have conclusively demonstrated that isomers convert each other and the equilibration of Figure 3.2 is complete at 60-80°C in the range of 6-12 hours, with isomer **10a** formed in preference (6.2-6.8).



11 **10**

Figure 3.2 - Isomerization of glycerol N-alkylcarbamates

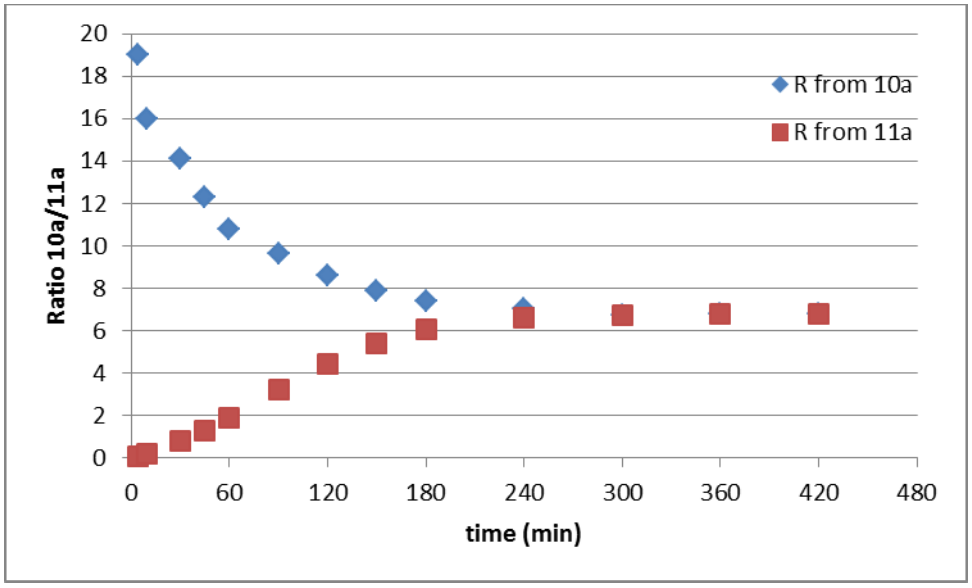


Figure 3.3 – Time dependence of the isomer ratio R in the equilibration of neat **10a** and **11a**

In Figure 3.3 are reported the results of these equilibration experiments on **11a** and **10a** at 80 °C as trend in the ratio **10a**/**11a** against time. Fitting of the data of Figure 3.3 was carried out taking the equilibrium as

a reversible first-order reactions for which the rate law has the following form (where [A] is the concentration of **10a** and [B] is the one of **11b** and k and k_{-1} are the direct and reverse rate constant).

$$v = -\frac{dx}{dt} = k[\mathrm{A}] - k_{-1}[\mathrm{B}]$$

Under this hypothesis and if initially only A is present, $[A]_0 = [A]$ and $[B]_0 = 0$ the following expressions can be derived for the decay of A and growing of B:

$$[\mathrm{A}] = \frac{k_{-1} + ke^{-(k+k_{-1})t}}{k + k_{-1}}[\mathrm{A}]_0 \qquad\qquad [\mathrm{B}] = \frac{k + ke^{-(k+k_{-1})t}}{k + k_{-1}}[\mathrm{A}]_0$$

Therefore, the ratio [A]/[B] can be derived as a value independent from $[A]_0$

$$\frac{[\mathrm{A}]}{[\mathrm{B}]} = \frac{k_{-1} + ke^{-(k+k_{-1})t}}{k - ke^{-(k+k_{-1})t}}$$

Fitting of data allows to deduce a rate constant $k = 0.021$ min^{-1} and $k_{-1} = 0.0029$ min^{-1} for the direct (**10a** → **11a**) and inverse (**11a** → **10a**) rate constants, respectively.

These data are significant contributions to a better understanding of the problem of carbamate regioisomers distribution, now amenable to a typical problem of kinetic and thermodynamic control of the reaction. In fact, at low temperatures the carbamate regioisomers distribution **10** and **11** is nearly statistic, whereas, when heated, the system equilibrates ta a mixture more rich in regioisomer **10** (typically with a ratio **10**/**11** of 6-7). This fact can help to understand the conflicting results reported in literature on the isomer distribution, certainly due to different temperature used in reaction and work up and to different reaction time, variables which were not considered so determinant.

The combined results of table 3.1 and figure 3.1 allow us to develop an easy procedure for the synthesis of isomeric glycerol N-alkylcarbonates starting from crude glycerol. The results of this study are part of a contract with an Italian company and will not be reported here.

In the course of the preparative reaction of glycerol carbonate from glycerol and dialkyl carbonate we noticed a remarkable difference in behavior between dimethyl carbonate (DMC) and diethyl carbonate (DEC). The yields with the latter derivative were always better in strictly controlled conditions, whereas relevant interferences were observed when water and other nucleophiles were present. This further has strengthened our persuasion that glycerol functionalization can occurs via in situ prepared glycerol carbonate if a sufficiently unreactive dialkyl carbonate is used to prevent its direct reaction with the nucleophile.

To test this hypothesis we investigate the reaction of dimethyl carbonate (DMC) and diethyl carbonate (DEC) with benzyl amine. We found that up to 90°C DEC do not react with benzylamine (and other primary amines) even after extended time and in the presence of a base like potassium carbonate, whereas DMC react at 90°C to give methyl N-benzylcarbamate and dibenzylurea in good yield in limited

time (9 h) (Figure 3.4). It was also verified that ethyl N-benzylcarbamate could not be formed below 130 °C and also a 130°C the reaction was remarkably delayed. On the contrary, DMC reacts quite efficiently even at 0-50°C with benzylamine. The formation of lower alkylcarbamates is a problem in these reactions because these compounds are of concern owing the potential toxicity evidenced by toxicological studies.

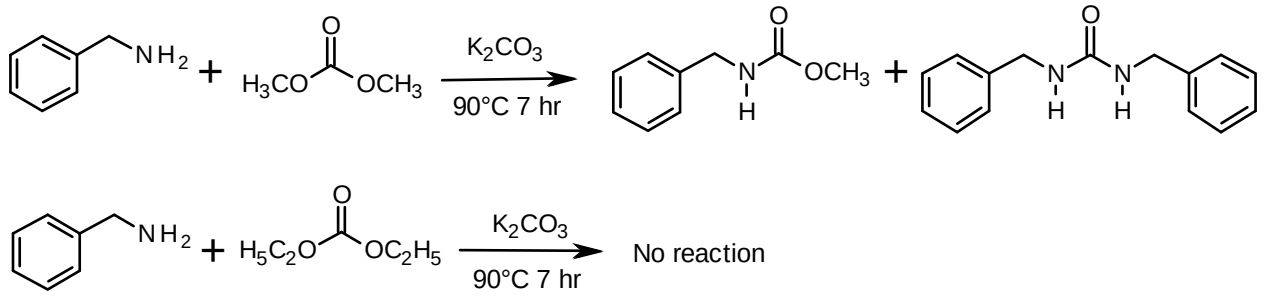


Figure 3.4 – Different reactivity of DMC and DEC toward benzylamine at 90°C.

This information was crucial for the possibility to carry out the one pot reaction between the three reagent, glycerol, an alkyl amine and diethyl carbonate (Figure 3.5).

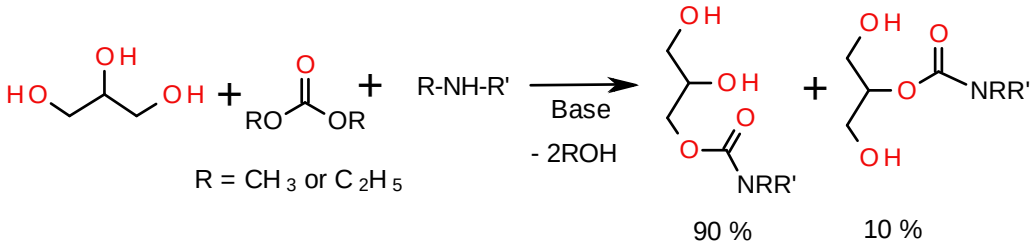


Figure 3.5 – Synthesis of glycerol N-alkylcarbamates by single step reaction of glycerol, dialkyl carbonates, and aliphatic amines

The approach was tested before on benzylamine and, then, other primary amines were investigated. In Table 3.2 are collected the investigated factors which affect the reaction such as temperature (from 0°C to 150°C), concentration of reagents and different catalyst. Specific attention was paid on carbamate isomer ratio because in literature has been concluded that, until this compound was prepared from glycidol or glycerol carbonate and at high temperature, this ratio cannot be higher than 2-3 in favor of terminal isomer and disubstitution is a relevant interfering reaction. Both these data appears as strong limitation in the practical application of the reaction on industrial scale.

Table 3.2 – K_2CO_3 catalyzed one-step condensation of benzylamine with glycerol and DEC.

Entry	Glycerol	DEC	Benzylamine	Catalyst	T (°C)	Time (h)	Yield (%)	10f:11f
1	1	1	1	0.03	50	48	98	90:10
2	1	1	1	0.03	150	2	90	90:10
3	1	1	1	-	50	48	20	80:20
4	1	1	1	-	100	6	65	90:10
5	1	1	1	0.20	50	24	70	90:10
6	1	2	2	0.06	50	24	75	75:25
7	2	1	1	0.03	50	35	85	85:15
8	7	-	-	-	150	6	-	-
9	1	2	1	0.03	50	3	70	90:10
10	1	0.5	1	0.03	50	7	50	90:10

The analytical data of Table 3.2 were inferred from ^{1}H-NMR spectra both as concern the yield (deduced from integration of methylene hydrogens at 4.38 δ and the one of trioxane at 5.15 δ, used as internal standard) and the isomer ratio (deduced by integration of the methylene protons of the methine proton of the glyceric moiety). Figure 3.6 is a typical example of the spectra of a crude reaction mixture obtained from the reaction with benzylamine and summarize the assignments made for the two isomers **10f** and **11f** and useful for quantitative determinations. In this example the reaction mixture containing 90% of terminal carbamate (**10f**) and 10% of the internal one (**11f**).

As reported in Table 3.2 the temperature has a positive effect on the rate of reaction but not on the yield, because at 150°C significant amount of oxazolidinone was formed and at 100 °C a lower ratio of isomers was observed. This suggests that the difference in thermodynamic stabilization between terminal isomer **10f** and internal isomer **11f** decreases as the temperature increase and 50°C appears as an optimum compromise between yield and selectivity for linear carbamate **10f**. Also at 0°C the reaction was possible but requires long time for completion and so that glycerol carbonate accumulates in the reaction mixture.

The value of the isomer ratio **10**/**11** observed in these experiment carried out at 50 °C was higher than the one observed with glycerol carbonate itself and unexpected. However, this trend was confirmed when we extended the reaction to other primary amines under the best condition established for benzylamine, as reported in table 3.3. Generally, the isomer ratio was lower with simple linear alkyl amines than benzylamine, but higher with dialkyl amines.

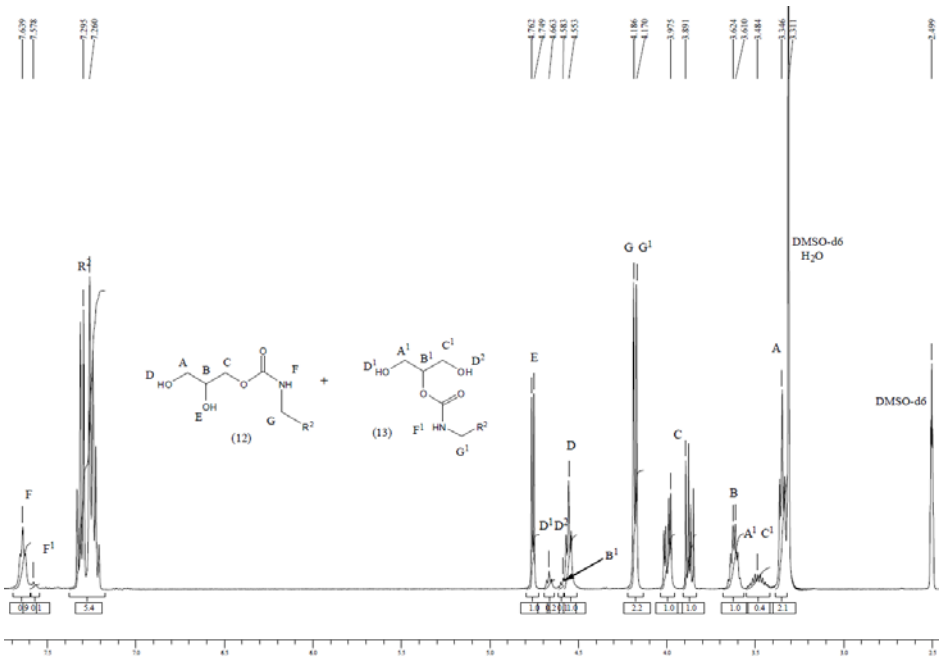


Figure 3.6 – ^{1}H-NMR spectra of reaction mixture of glycerol, benzylamine and DEC at 0°C, with hydrogen assignment for quantitative determination of carbamate isomer ratio.

Table 3.3 – Carbamate yield and isomer ratio in the single step condensation of glycerol with alkylamines and diethylcarbonate in the presence of K_2CO_3 (50 °C, 12 h)

Entry	Amine	Products 10+11	Yield (%)	Ratio* (10/11)
1	1-hexylamine	**10b+11b**	71	62:38
2	Benzylamine	**10f+11f**	99	90:10
3	1-Dodecylamine	**10c+11c**	89	65:35
4	disopropylamine	-	0	-
5	dibutylamine	**10g+11g**	25	92:8
6	1,6-hexamethylenediamine	**10h+11h**	85	85:15

Steric hindrance limits significantly at 50°C the yield with dibutylamine (but the reaction is again possible at higher temperature, 80°C). However with more crowded system N-nucleophiles (i.e. diisopropylamine) the reaction totally fails. This finding is in line with literature data of reactivity of alkyl carbonates with secondary and tertiary amines, i.e. N-methyl or NN'-dimethyl substituted amines.[26]

In Figure 3.7 are reported for comparison the results obtained at 50°C with benzylamine for the one step procedure here developed and for the two step procedure involving the isolation of glycerol carbonate and its reaction with the amine.

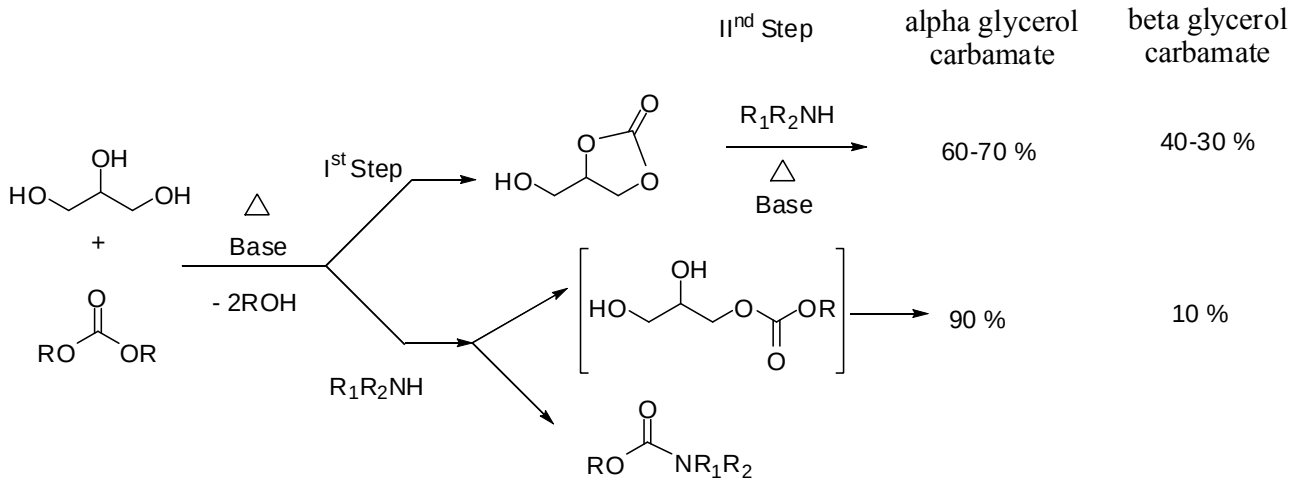


Figure 3.7 – Comparative behavior of one step and two step reactions of glycerol, benzylamine and DEC

Another relevant finding of this one-step procedure was the quite limited amount of di-carbamate and carbamate-carbonate products. These derivative arises from further reaction of mono-carbamate with dialkyl carbonate to give the intermediate carbamate-carbonate derivative, which in turn will undergo the attack by the amine. The lower reactivity of diethyl carbonate seem to slow down further this consecutive reaction and the introduced carbamate function seems to inhibit the formation of the new carbonate intermediate. We verify this aspect carrying out model experiments on isolated α-glycerol N-benzylcarbamates with DEC and benzylamine at different temperature and we verify that the second substitution was quite unefficient even at higher temperatures. Instead, at high temperatures cyclisation of α-glycerol carbamate starts to give the oxazolidinone product and DEC works more as dehydration agent.

We also verify that ethyl *N*-benzyl carbamate (a possible intermediate of the reaction) was not involved in this one-step reaction with benzylamine and it was unable to quickly react with glycerol to form directly the glycerol N-benzylcarbamate. Experiments carried out in the temperature range 50-150°C indicates that this substrate is totally unreactive at lower temperature (< 100°C) and converts into dibenzyl urea at higher temperatures. These results are visually summarized in Figure 3.8.

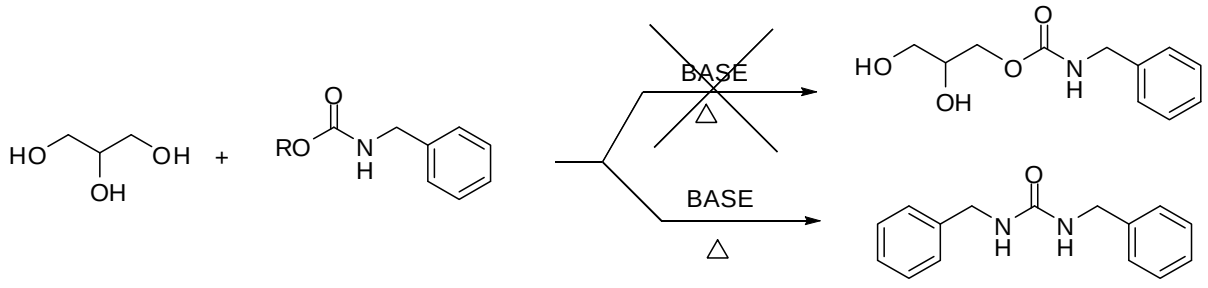


Figure 3.8 – Reactivity of ethyl *N*-benzyl carbamate in glycerol at different temperatures.

The one step reaction is not restricted to glycerol and its telomers but it was verified that can be applied to other 1,2- and 1,3-glycols as reported in table 3.4.

Table 3.4 – Yield and carbamate isomer ratio in the single step condensation of some glycols with benzylamine and diethyl carbonate at 50°C temperature.

Entry	Alcohol	Amine	Product 10+11 (Time in hours)	Yield (%)	*(10:11)
1	Glycerol	Benzylamine	**10f+11f (49 h)**	99	90:10
2	αα'-diglycerol	Benzylamine	**2e/3e (4 h) ****	70	90:10
3	ethylenglycol	Benzylamine	**mono/di (24 h)**	100(70%)	Mono:di 70:30
4	1,3-propanediol	Benzylamine	**mono/di (12 h)**	100(50%)	Mono:di 72:28

* Based on ^{1}H-NMR spectra, **at 130°c temperature.

We next briefly analyze the importance of catalysis on the reaction, taking into account that the reaction was in any case possible also in the absence of catalyst. We select some basic catalyst to compare with potassium carbonate, the apparently best catalyst previously identified. The one more tested were potassium hydroxide and potassium t-butoxide, in all cases under neat conditions. The results of these experiments are reported in Table 3.5. For comparative purposes in the last three row of Table 3.5 are reported also the results obtained by using dimethyl carbonate (DMC) instead of diethyl carbonate (DEC) in a similar one-pot procedure.

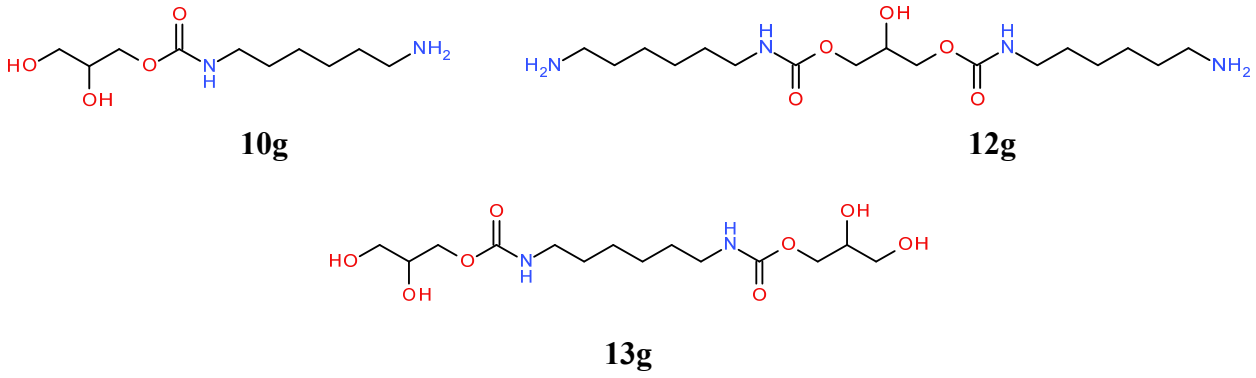
Table 3.5 – Influence of different catalysts on the one step synthesis of glycerol N-benzylcarbamate.

Entry	Glycerol	DEC	Benzylamine	Catalyst (3%)	T (°C)	Time (h)	Yield (%)
1	1	1	1	K_2CO_3	50	49	99 %
2	1	1	1	NO catalyst	150	1/2	90 %
3	1	1	1	KOH	25	7	75 %
4	1	1	1	KOH	50	5	70 %
5	(4+)	1	1	KOH	50	11	100 %
3	1	1	1	K-t-butoxide	25	8	80 %
4	1	1	1	K-t-butoxide	50	1	99 %
5	1	2	2	K-t-butoxide	50	1	90 %
6	1	DMC	1	K_2CO_3	50	11	80 %
7	1	1	1	K_2CO_3	25	25	50 %
8	1	1	1	K_2CO_3	5	8	0 %

These data confirm that the higher reactivity of DMC makes difficult to apply the one-pot procedure for the synthesis of glycerol carbamates due to the strong interference of the direct reaction of the amine with the carbonate to give the harmful methyl N-benzylcarbamate by-product. Also the use of lower reaction temperatures does not eliminate this side reaction.

The results of table 3.5 clearly indicate that other catalyst are active and that the more basic potassium t-butoxyde is particularly effective, making possible to reduce the reaction time to 1h, with again optimum isomer ratio in favor for the terminal one. With this catalyst also work at room temperature in moderate time becomes possible. As previously observed, the reaction without catalyst occurs also at moderate temperature but is generally less clean with a lower ratio of terminal to internal isomers.

A final comment deserves the one-step reaction of 1,6-hexanediamine because of the possible relevance in the preparation of polymeric glycerol carbamates (polyurethanes). Under the mild condition used in the one-step reaction, only mono (**10g**) and diaddition products terminated with the amine function (**12g**) or with the diol function (**13g**) were observed (Figure 3.9). The relative ratio of the products was found to depend on the amount of amine and glycerol used with an obvious preference for monoaddition products at lower molar ratio of amine to glycerol.



10g **12g**

13g

Figure 3.9 – Mono- and di-carbamate products in reaction of 1,6-hexanediamine with glycerol and DEC

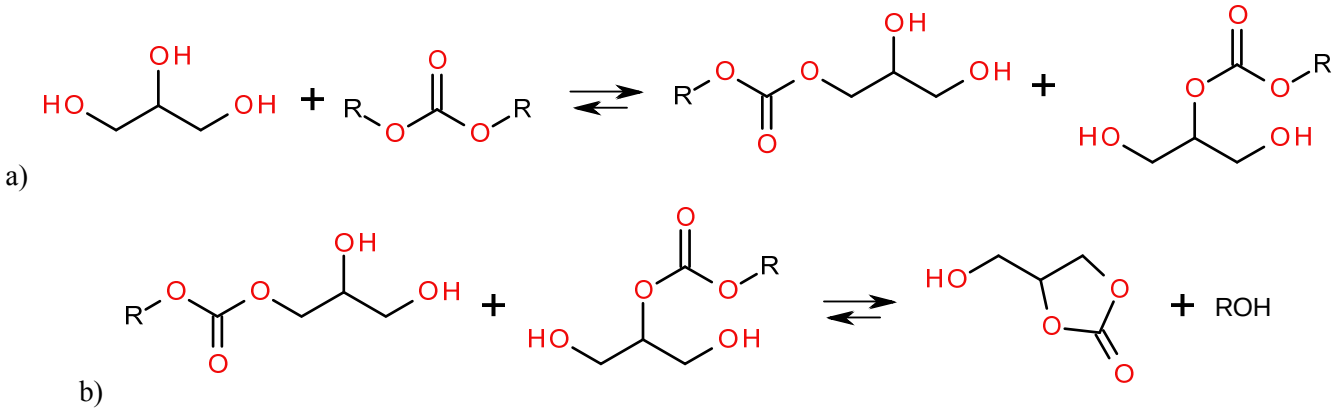
All these products are relevant because they can be used as oligomers for chain extension for thermoplastic polymers or for direct polymerization to hydroxypolyurethanes or mixed polyesters and polyamides at higher temperature. This last aspect need to be further investigated in order to reduce the importance of the intramolecular cyclization to oxazolidinone. A specific aspect to be underlined in these diamine reactions is the strong preference for terminal substitution in accord with the general trend observed in these one-step reactions. This fact can have relevance on the properties of the polymer making possible to reach an higher molecular weight and better mechanical performances. These aspects are again to develop. We have preliminary verified also that the condensation with 1,6-hexanediamine is compatible with other diols, i.e. ethylenglycol and 1,3-propandiol, expanding so further the variety of carbamate intermediate available for functional polymer preparation.

3.3 Discussion

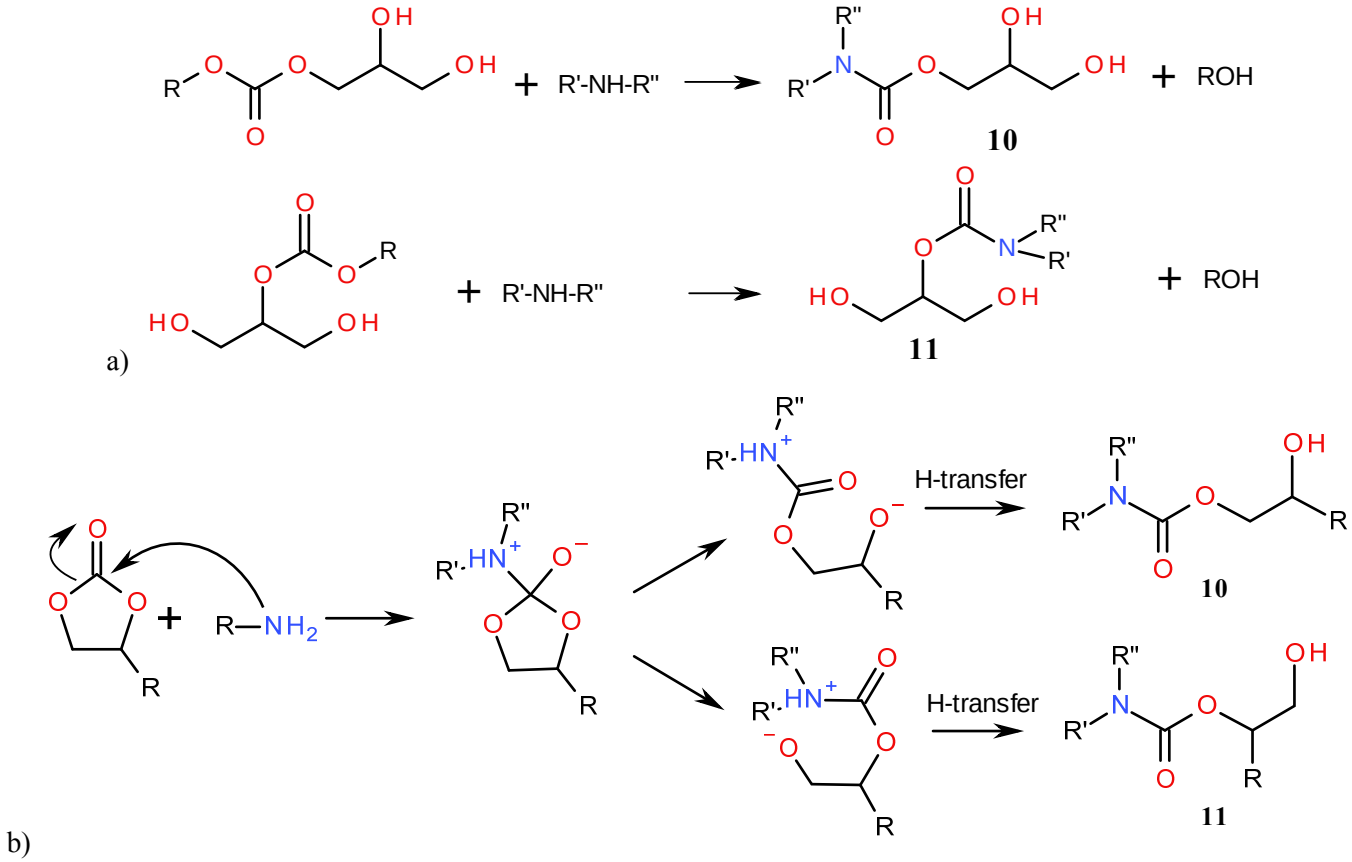
The results of the one-step reaction investigated clearly indicate that the approach is effective and easy to be transferred on industrial scale. It overcomes some problem identified in the reaction of glycerol carbonate and appears to be easily extended to other glycols, alcohols and phenols (in the last case competitive phenol substitution can prevail at low amine concentration).

The main point to be discussed is the apparent facility and good selectivity of this cascade one-pot reaction in which glycerol carbonate does not need to be prepared or isolated. Our hypothesis to explain the results can be summarized in the complex scheme of Figure 3.10 in which were distinguished the stages of transcarbonation of glycerol by dialkyl carbonate (step Ia to linear carbonates and step IIb to GC), the phase of aminolisis of linear carbonates (step IIa) and cyclic carbonate (step IIb), and the stage of intramolecular transcarbamoilation (step III). In the scheme were not taken into consideration the formation of six membered cyclic carbonates of glycerol because it is known that these species even formed converted efficiently to the more thermodynamically stable five-membered isomers. From the scheme is also omitted the specific role of the basic catalyst (K_2CO_3, KOH, t-BuOK) because the reaction is possible also in their absence. From experimental data reported in previous paragraph, the specific involvement of the catalyst seems to be restricted to the trans-carbonatation and the trans-carbamoilation steps, but the involvement in the amine nucleophilic substitution cannot be excluded because these reactions are known to be controlled by a network of hydrogen bond in which ions can play a significant role.

Step I – trans-carbonatation



Step II – Aminolysis of glycerol carbonates



Step III – trans-carbamoilation

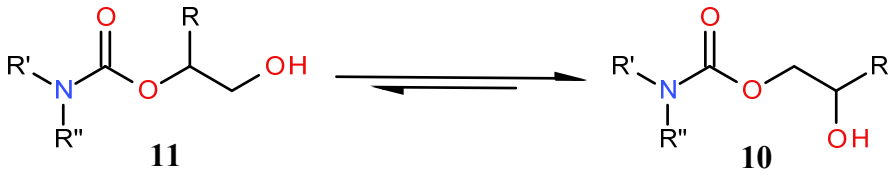


Figure 3.10 – Mechanistic stages involved in the one-step synthesis of glycerol carbamates.

To explain the efficiency of the reaction with diethyl carbonate our hypothesis is that initial trans-carbonatation occurs to give linear glycerol carbonates at both alfa and beta position, but with high preference for the first for steric reasons. The consecutive reaction of these intermediates can give the intramolecular cyclization to glycerol carbonate (GC) in a relatively slow process compared with the addition of the amine to carbonates to give the alfa and beta glycerol N-alkylcarbamates (**10** and **11**, respectively). The alfa and beta selectivity in this hypothesis can arise from the relative distribution of the two linear glycerol carbonates and can explain the higher ratio of **10**/**11** generally observed in this one-pot reaction if compared with the results of aminolysis of glycerol carbonate. Obviously, this last reaction can be present in the system if the amine concentration is low or if the temperature is low, because these

intramolecular processes are generally considered fast. In both cases the rate of bimolecular nucleophilic substitution reaction will be lower and monomolecular intramolecular trans-carbonatation will become important. This was observed working at 0° where glycerol carbonate was found to accumulate in the medium (^{1}H-NMR analysis) but its presence was not detected at 50 °C or higher temperatures. However, in this hypothesis the reactivity of the linear carbonate toward primary and secondary amines must be higher than the one of cyclic glycerol carbonate (GC). Kinetic information on this point are lacking but our previous data on mixed carbonates, i.e. glycerol tricarbonate, are in this direction because the central linear carbonate of this derivative was found to be four time more reactive than the cyclic one.[27]

The equilibration of regioisomers alfa and beta via intramoleculra carbamoil group transfer is a process superimposed to the overall reaction and will depend on both temperature and presence of catalyst.

At low temperature two facts will concur to favor the alpha isomer under our one stage process: a thermodynamic stabilization (because alpha diastereoisomer prevails always on beta isomer in equilibration experiments) and possibly a kinetic preference related to the higher amount of alpha linear carbonate than beta internal carbonate in the initial trans-carbonatation reaction. In this regard, it is noteworthy to notice that at 0°C the reaction of glycerol carbonate with butylamine affords the alpha and beta isomers in near 1:1 ratio, whereas the one-step process provide a ratio of 9:1. This data supports our preference for a kinetic selectivity related to the involvement of alpha linear glycerol carbonate. In this hypothesis appears also plausible the preference for the opening of the linear mixed carbonate on the side of glycerol instead of ethyl group. Intramolecular hydrogen bonding can assist the nucleophilic substitution by the amine on glycerol side of the mixed carbonate.

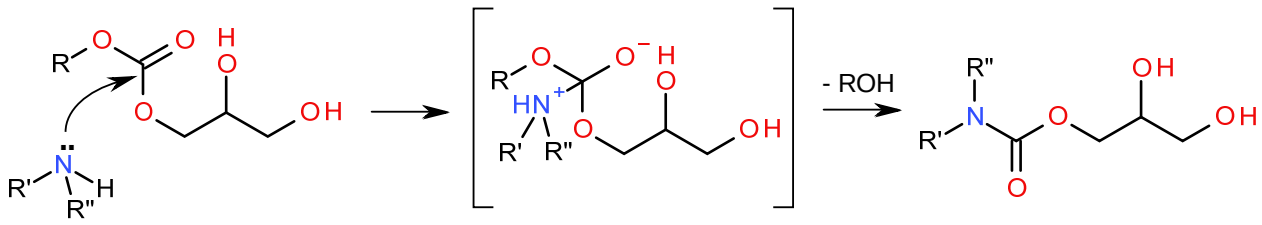


Figure 3.11 – Hydrogen bond directed nucleophilic substitution of amines on mixed glycerol carbamates.

In reaction with glycerol carbonate (GC) the selectivity of the aminolysis reaction favored the alpha isomer but the length of the alkyl chain in the amine was found to affect the regioselectivity of the ring-opening with increase of beta isomer, the more the alkyl chain increased. The ratios of alpha to beta isomers in the reaction with GC were so dependent on amines and on the reaction temperature (differently from what recently reported).[28] The alpha/beta values obtained on a specific amine with GC were always lower than the one observed in the one-step reaction, which reach values of 9:1 or higher.

Diethyl carbonate (DEC) appears to behave quite differently in these reactions respect to the more commonly used dimethyl carbonate (DMC) and the difference appears mainly to be of kinetic nature. DMC was in fact reactive in these one pot reaction, also at temperature of -20°C, but formation of methyl N-alkyl carbamates was always a relevant side reaction. Moreover, in reactions of DMC at higher temperatures glycerol carbamate-carbonate and glycerol di-carbamate products were always relevant side products as observed in similar reactions with GC itself. The higher reactivity of DMC is therefore a limit for selective transformation on polyfunctional molecules and this suggest that a careful choice of alkyl residues on dialkyl carbonate or mixed carbonates can be usefully exploited in the synthesis of complex molecules. The behavior of DEC seems not simply related to an higher steric hindrance on nucleophylic substitution to carbonyl group induced by ethyl instead of methyl substituents on carbonate but a significant role must also be played by the decrease in polarity going from DEC to DMC, stressed by the use of the reagents in our neat conditions. This change in polarity can affects both the solvation in the transition state of the nucleophilic substitution and the formation of hydrogen bonds between reagents amine and dialkylcarbonate.

The absence of reactivity of DEC with primary and secondary amines in the temperature range 25-130°C is not exceptional if the report of Porta *et al.*[29] is taken in consideration in which propylamine was found to react with diethyl carbonate to give the corresponding carbamate only in the presence of metal salts such as $AlCl_3$. On the contrary methoxycarbonylation of amines, including anilines, by dialkyl carbonates has been disclosed in several patents under quite broad conditions. Lissel *et al*. [30] reported that the reaction was possible in the presence of K_2CO_3 and 18-crown-6-ether and,[31] but Porta *et al*. was unable to observe substitution when $FeCl_3$ and $AlCl_3$ were used as catalysts. Futhermore, lead compounds were described as active catalysts for the synthesis of methyl N-phenylcarbamates from anilines and DMC.[32]

The reactivity of carbonate esters depends upon the electrophilicity of carbonyl carbon; the factors that help increase in the electrophilicity of carbonyl carbon may therefore increase the rate of reaction. Electron-withdrawing substituent on the oxygen will facilitate the nucleophilic attack whereas electron-donating substituents with retards.[33] However, the final reactivity will depend on the p*K*a of attacking amine[34] and the steric hindrance at nitrogen due to huge alkyl substituents. It is generally believed that aminolysis proceeds smoothly when the p*K*a values of attacking amine are about 4–5 units higher than that of the leaving group (e.g. alkoxide or aryloxide).[35] Similarly, alcoholysis of substituted urea is accelerated by electron-donating group on alcohol and slowed down by electron-withdrawing groups, provided that hindrance factor is not coming into play.[36] On the other hand, electron donating substituents on phenyl urea increase reactivity of urea, while decreased by electron-attracting substituents on aryl group.[37] Carbonate reactivity towards diphenyl urea follows the same rule increasing with the leaving group ability of methoxide and phenoxides,[38] which is consistent with the trend observed in aminolysis of carbonates.[39] The reactivity of alkyl carbonates towards ureas was found to decrease in the order dimethyl carbonate > diethyl carbonate > dibutyl carbonate. On this basis it was concluded that carbonyl carbon of dimethyl carbonate is the most electrophilic center and dibutyl carbonate is the least.[37] A similar kind of reactivity was earlier observed for alcohols in transesterification of DMC and was attributed to the steric factors rather than electronic effect of various alcohols.[40]

It must be underlined that in all reactions studied no substitution of OH group of glycerol by the amine nitrogen was detected. This transformation is reported in Figure 3.12 exemplified for linear mixed carbonates to give N-alkylated isoserinol deivatives.

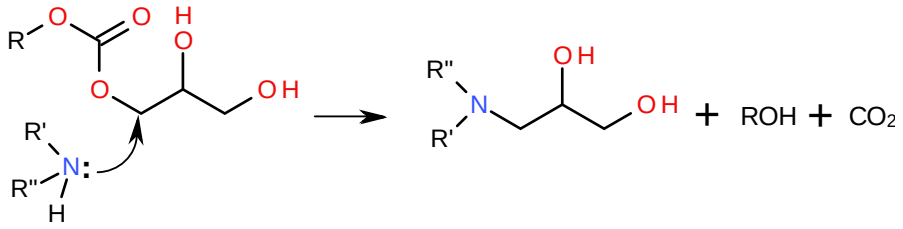


Figure 3.12 – Nucleophilic substitution of amines to saturated C-O bond of mixed glycerol carbamates.

This reaction has been reported in literature with some amines with dimethyl carbonate at high temperature and by us with anilines. It is generally believed that DMC reacts with amines by two different reaction pathways, due to the presence of two electrophilic centers on dimethyl carbonate: *i*) a nucleophilic attack of Nu^- to the carbonyl carbon of the dimethyl carbonate, producing the carboxyalkylated product **A** and the corresponding alcoholate anion CH_3O^- (path-a, $B_{Ac}2$ type mechanism), and subsequently second attack of amine produces urea product **B**. *ii*) A nucleophilic attack of Nu^- to the methyl carbon of the carbonate with the formation of the methylated product **C** and of the methyl carbonate anion $CH_3OCO_2^-$ (path-b, $B_{Al}2$ type mechanism). The $CH_3OCO_2^-$ anion is unstable specie which easily undergoes decomposition to CH_3O^- and CO_2. Although a clear cut-off between these two pathways is not possible, reaction conditions, more specifically the temperature and the nature of the catalyst, often allow discriminating between the carboxyalkylation and the alkylation reactions. The effect of the temperature on the reactivity and the use of dialkyl carbonates, with emphasis on DMC, have been extensively investigated by Tundo group.[41]

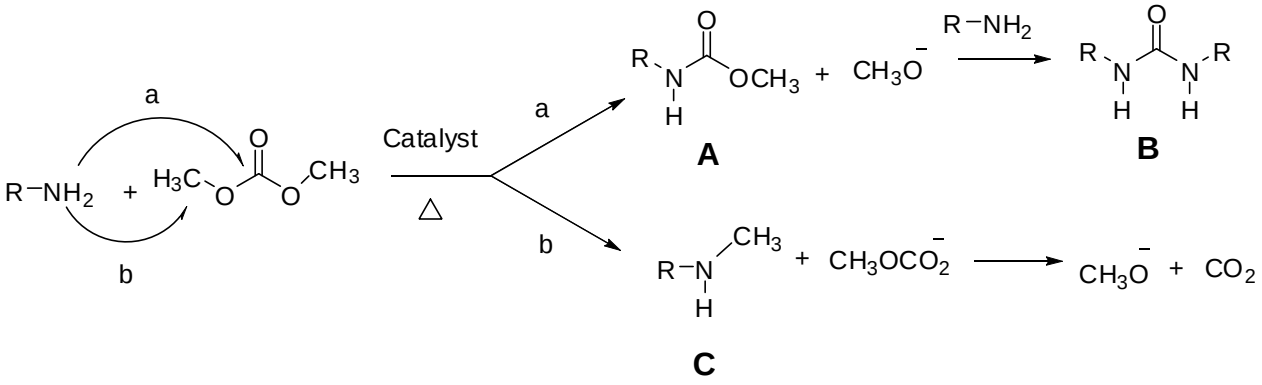


Figure 3.13 -Reactivity of amines towards dimethyl carbonate.

When an alkaline carbonate was used as catalyst, it is generally observed that below or at the reflux temperature of DMC (T ≤ 90 °C), a methoxy carbonylation reaction takes place almost exclusively. A $B_{Ac}2$ (bimolecular, base catalyzed, acyl cleavage, nucleophilic substitution) mechanism operates: the nucleophile attacks the carbonyl carbon of DMC, giving the transesterification product. At higher temperatures instead (usually at T ≥ 120 °C), DMC acts primarily as a methylating agent through a $B_{Al}2$ (bimolecular, base-catalyzed, alkyl cleavage, nucleophilic substitution) mechanism: the nucleophile attacks the methyl group of DMC, giving the methylation product.[40] Solvation phenomena can be accounted for this behavior: as described in literature for the hydrolysis of methyl esters in gas phase,[42] the reduced (or absent) solvation of nucleophiles makes the attack to the less hindered (even though less electrophilic) alkyl carbon preferred with respect to the carbonyl carbon of DMC. At high temperature, the $B_{Al}2$ mechanism becomes the major reaction pathway and, accordingly, highly selective alkylation reactions of several nucleophiles can be carried out using DMC as the methylating agent.[40] Primary aliphatic amines were found to present a less clear behavior than anilines, because their higher nucleophilicity posed severe limitation to the reaction selectivity, due to not only the double *N*-methylation but primarily, to the formation of carbamates.[43] Apparently, $B_{Ac}2$ and $B_{Al}2$ mechanisms, i.e. the attack of the amine to the carbonyl ($B_{Ac}2$) and to the methyl ($B_{Al}2$) groups of DMC, were possible without any discrimination.

From the data of our research we can conclude that with alkylamines and DMC or DEC the N-substitution to C-O bond of glycerol is possible only with soft nucleophiles (anilines) and at high temperatures but not under the mild conditions used in the one-step process investigated. For this reason we cannot exclude that the alkylation of amines by dialkyl carbonates can involve the firstly formed carbamates and their thermal decomposition instead of a direct nucleophilic attack on the C-O bond of dialkyl carbonate or the mixed carbonates.

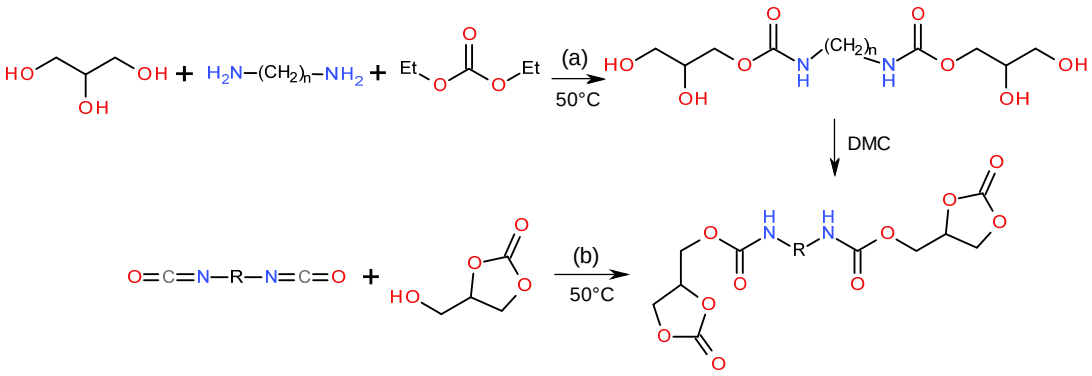


Figure 3.14 - Synthesis of bis(cyclic carbonate) from a diisocyanate and glycerin carbonate

The potentiality of the synthesis of glycerol carbamates by the one-step method was further confirmed in experiments with diamines, i.e. 1,6-hexanediamine. Selecting appropriate amounts of reagents, mono and disubstitution products were possible to be obtained as major products (see experimental part) allowing to isolate these potentially useful new monomer for polyurethanes, polyesters and polyamides. The high preference for substitution in the alpha position of glycerol and the possibility to further functionalize these carbamates with the more reactive DMC, allowed to prepare the bis(cyclic carbonate) carbamate Scheme 10a (figure 3.14), recently described in a patent as important monomer for polymer manufacture and synthetized from glycerol carbonate and diisocyanate product Scheme 10b (figure 3.14),.[44]

A final comment deserves the method we select to determine the ratio of α versus β hydroxyurethanes. In the literature this has generally been established by spectroscopic methods, in particular by ^{1}H-NMR[45] or by ^{13}C-NMR.[46] We select only ^{1}H-NMR to evaluate this value taking into account the signals assignable to hydrogens of methylene and methyne CHOCO group close to the carbamate function which were sufficiently separated in 400 or 500 MHz instruments. The preference for this method was related to the fact that ^{1}H-NMR spectra were also diagnostic in detecting and quantifying other products in case present in the reaction mixture, i.e. glycerol carbonate, dialkyl ureas, methyl N-alkylcarbamates, etc.. Carbonyl carbon signals in ^{13}C-NMR, that appeared at 159.18 and 158.88 ppm in the alfa and beta derivatives, respectively, were found to be less useful owing to their low intensity and the high time for relaxation of nuclei involved. However, initially HPLC analyses were used to confirm the ^{1}H-NMR results, namely in the benzylamine case. Some attempt were carried out to follow the reaction by on-line analyses with infrared spectroscopy following the disappearance of the C=O bond of the carbonate function (1786 cm^{-1}) and the appearance of the urethane unit (1697 cm^{-1}). The measurements were problematic under the neat conditions used in this study mainly for viscosity reasons, but were usefully applied in diluted solution of "transparent" solvents, i.e. acetonitrile. In this study was found that the two other characteristic bands of carbamate at 1543 cm^{-1} (–OC(=O)NH-R) and carbonate at 1250 cm^{-1} (C(=O)–O– C) were less useful because were in part superimposed to glycerol and dialkyl carbonate absorption. A parallel preliminary on-line investigation using a Raman spectroscopy (Raman Kaiser Optical System RXN2, 785 nm NIR, laser 400 mW) with an immersion sapphire probe under these diluted conditions, confirmed that this technique has high potentiality to monitor these reactions.

Conclusion

In this study a new method has been established for the one-step synthesis of the α-glycerolcarbamates by using three component system (glycerol, dialkyl carbonates, and aliphatic amines or polyamines). The reaction is compatible with a large variety of primary and secondary amines and involve quite mild conditions and minor excess of reagents in the absence of co-solvents. Factors affecting the selectivity at terminal to internal carbamate isomers were investigated and the key role of the intermediate *in-situ* formed linear carbonate ester of glycerol for selective substitution at the terminal position was ascertained.

Stability and reactivity studies indicate that consecutive reactions of glycerol N-alkylcarbamate can limit the second attack and reaction conditions can be selected to avoid disubstitution. This inhibition of further substitution is presumably related to intramolecular hydrogen bond on both carbamate and/or the intermediate carbonate consecutively formed. Experiments with 1,6-hexanediamine demonstrates that the reaction can be extended to the preparation of polymeric glycerol carbamates (polyurethanes) with good productivity and selectivity. The envisaged reaction is very attractive involving two inexpensive and readily available raw materials in a chemical cycle that overall, result in the chemical fixation of CO_2. Moreover, this reaction also provides a route to up-grade waste glycerol produced in large quantities during the production of biodiesel.

EXPERIMENTAL

^{1}H- and ^{13}C- NMR spectra were determined with TMS as internal standard, on a Bruker 400 MHz instrument. Chemical shifts are reported in ppm with the solvent residual peak as internal standard (DMSO-d_6: δH= 2.50 ppm, δC= 39.52 ppm). ESI-MS spectra were performed with an Esquire 3000 plus ion-trap mass spectrometer equipped with an ESI source. GC-MS analyses were performed on an Agilent *6890* gas-chromatograph equipped with a 5973 mass-detector, using a HP5MS column (30 m x 0.25 mm x 0.25 μm); the following temperature program was used: 40°C (1')//2°C/min//45°C (1')//10°C/min//200°C (1')//20°C/min //280°C (10'). IR spectra were registered with a Perkin Elmer 2000 FTIR instrument. Chromatographic separations were performed using Merck Kieselgel 60 silica gel. Melting points were determined with a Buchi 535 instrument and are uncorrected.

General procedure: In a 100 ml round bottom flask glycerol, alkyl carbonate, amine and base were taken and stirred the reaction mixture on oil bath at temperature and for hours as indicated in respective tables. All the reactions were studied with time-on-line analysis of products via a ^{1}H-NMR and TLC analysis. After completion of reaction excess of alkyl carbonate and alcohol produced during the reaction were distilled out under vacuum and the reaction mixture was chromatographed to obtain pure products α- and β- glycerolcarbamates along with di substituted products. The purified products were characterized with the help of ^{1}H- and ^{13}C- NMR, IR, Mass analysis techniques.

Reaction of glycerol with DMC and benzyl amine (molar ratio 1:1:1). In a 100 ml round bottom flask glycerol (0.01086 mol), dimethyl carbonate (0.01086 mol), benzyl amine (0.01086 mol) and K_2CO_3 (0.003 mol) were taken and stirred the reaction mixture on oil bath at temperature and for hours as indicated in table no-3.5. The reaction has been studied with time-on-line analysis of products via a ^{1}H-NMR and TLC analysis. After completion of reaction, excess of DEC and ethanol produced in the reaction were distilled out under vacuum and the residue was analyzed by ^{1}H-NMR to recover the ratio between glycerolcarbamates isomers (α-/β- 63:37). The reaction mixture was chromatographed to obtain pure products α- and β- glycerolcarbamates, whose structure was confirmed by comparison with authentic samples prepared through the ensuing procedure.

Reaction of glycerol with DEC and benzyl amine and K_2CO_3 (molar ratio 1:1:1:0.03). In a 100 ml round bottom flask glycerol (0.01086 mol), Diethyl carbonate (0.01086 mol), benzyl amine (0.01086 mol) and K_2CO_3 (0.003 mol) were taken and stirred the reaction mixture on oil bath at 50°C temperature and for 18 hours as indicated in table no-3.5. The reaction was monitored via ^{1}H-NMR and TLC analysis (MeOH/ethyl acetate 1:9 v/v as eluent). After completion of reaction, excess of DEC and ethanol were distilled out under vacuum and the reaction mixture was chromatographed using as solvent a mixture of

hexane/ethyl acetate (5:95 v/v) to obtain pure products α- and β-glycerolcarbamates in ratio 90:10 (via ^{1}H-NMR).

1-(2,3-Dihydroxypropyl)-N-benzylcarbamate (α-glycerolcarbamate). Amorphous white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.65–7.62 (m, 1H, NH), 7.33–7.20 (m, 5H, Ph), 4.76-4.74 (d, 1H, CH-OH), 4.56–4.53 (t, 1H, CH_2-OH), 4.18-4.17 (d, 2H, Ph-CH_2), 4.01–3.97 (m, 1H-1, CH_2OH), 3.89– 3.84 (m, 1H-2, CH_2OH), 3.65–3.58 (m, 1H, CH_2-CH-CH_2), 3.36–3.33 (m, 2H, -CH_2-OCO-NH-Ph); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 156(C=O), 140(C_{IV}-Ar), 128.2, 127.0, 126.7 (CH–Ar), 69.8 (C-1), 65.8 (C-2), 62.8 (C-3), 43.7 ($PhCH_2NH$); EISI-MS m/z: 248 $[M(225)+Na]^+$; IR (KBr) cm^{-1}: 3310 (OH), 3086, 3065, 3032, 2939 (N–H, CH_{Ar}), 1685 (C=O), 1556 (NHCO).

2-(1,3-Dihydroxypropyl)-N-benzylcarbamate (β-glycerolcarbamate). Amorphous white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.59–7.56 (m, 1H, NH), 7.33–7.20 (m, 5H, Ph), 4.69-4.66 (t, 2H, 2CH_2-OH), 4.60-4.58 (m, 1H, CH_2-CH-CH_2), 4.18-4.17 (d, 2H, Ph-CH_2), 3.54–3.43 (m, 4H, CH_2-CH-CH_2); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 156(C=O), 140 (C_{IV}-Ar), 128.2, 127.0, 126.7 (CH–Ar), 75.6 (C-2), 60.1 (C-1, C-3), 43.7 ($PhCH_2NH$); MS m/z 248$[M(225)+23(Na)]^+$; IR (KBr) cm^{-1}: 3310 (OH), 3086, 3065, 3032, 2939 (N–H, CH_{Ar}), 1685 (C=O), 1556 (NHCO).

Reaction of glycerol with DEC and benzylamine and K_2CO_3 (molar ratio 1:1:1:0.02). The same reaction conditions were applied as reported in previous reaction using glycerol (0.01086 mol), diethyl carbonate (0.01086 mol), benzylamine (0.01086 mol) and K_2CO_3 (0.00217 mol) at 50°C for 22 hr. The residue was analyzed by ^{1}H-NMR to recover the ratio between glycerolcarbamates isomers (α-/β- 9:1) and chromatographed to obtain monocarmamates and the disubstituted product.

[3-(benzylcarbamoyloxy)-2-hydroxy-propyl] N-benzylcarbamate. White solid m.p. 102-3°C. MS-EISI m/z 397 (M[358] + 39[K]), 381 (M[358] + 23[Na]), Exact Mass: found 299.1538, calcd. 299.1529 Anal. Found: C, 63.55; H, 6.16; N, 4.73. $C_{19}H_{22}N_2O_5$ requires C, 63.67; H, 6.19; N, 7.82%.

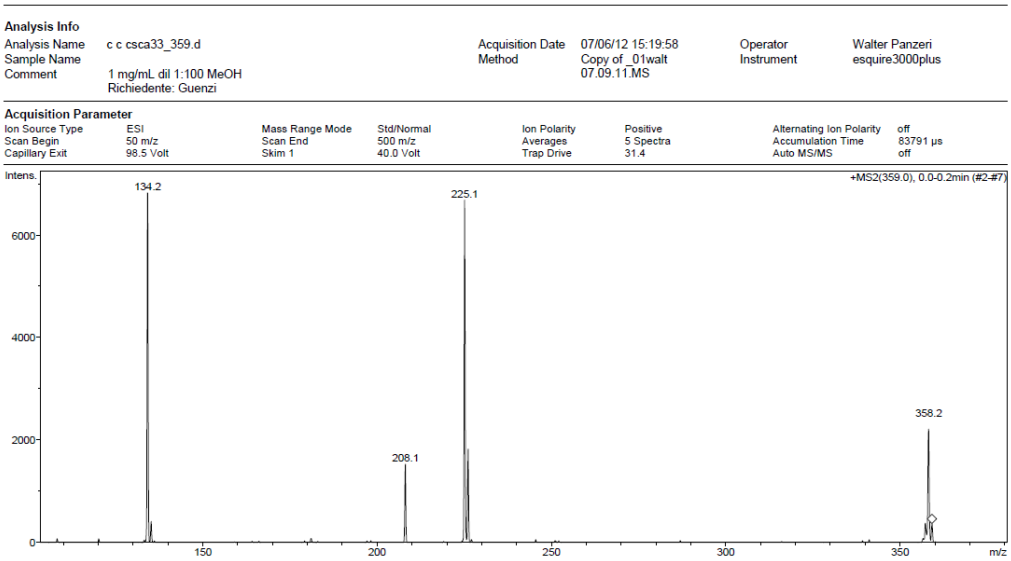


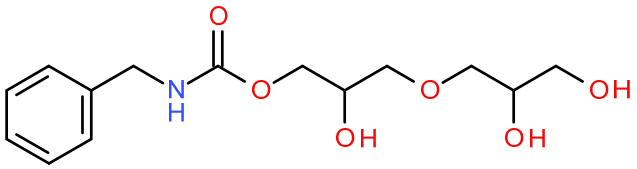
Figure 3.15 – Mass spectrum of reaction of benzylamine, glycerol and DEC (1:1:1:0.02).

Reaction of glycerol with DEC and benzylamine (1:1:1). In a 100 ml round bottom flask glycerol (0.01086 mol), diethyl carbonate (0.01086 mol) and benzylamine (0.01086 mol) were taken and stirred the reaction mixture on oil bath at 100°C for 26 hr. The reaction was monitored via ^{1}H-NMR and TLC analysis (methanol/ethyl acetate (1:9 v/v) as eluent). After completion of reaction, excess of DEC and ethanol produced in the reaction were distilled out under vacuum and the reaction was analyzed by ^{1}H-NMR giving a ratio of α- to β-glycerol carbamates of 80:20 (Yield 85%).

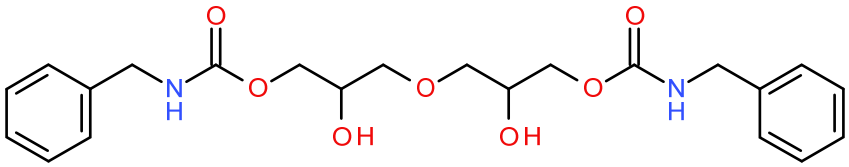
Reaction of glycerol carbonate with benzyl amine and K_2CO_3 (1:1:1:0.03). In a 100 ml round bottom flask glycerol carbonate (0.0087 mol), benzyl amine (0.0087 mol) and K_2CO_3 (0.00026 mol) were taken and stirred the reaction mixture on oil bath at 50°C temperature and for 6 hr. The reaction was monitored by ^{1}H-NMR and TLC. ^{1}H-NMR analysis of the resulting reaction mixture indicates a ratio between α- and β-glycerolcarbamates of 60:40. Single isomers were isolated as pure products (α- 51% yield; β- 34% yield) by column chromatography with the some solvent mixture indicated previously and the compounds were found to have the same analytical data as above reported.

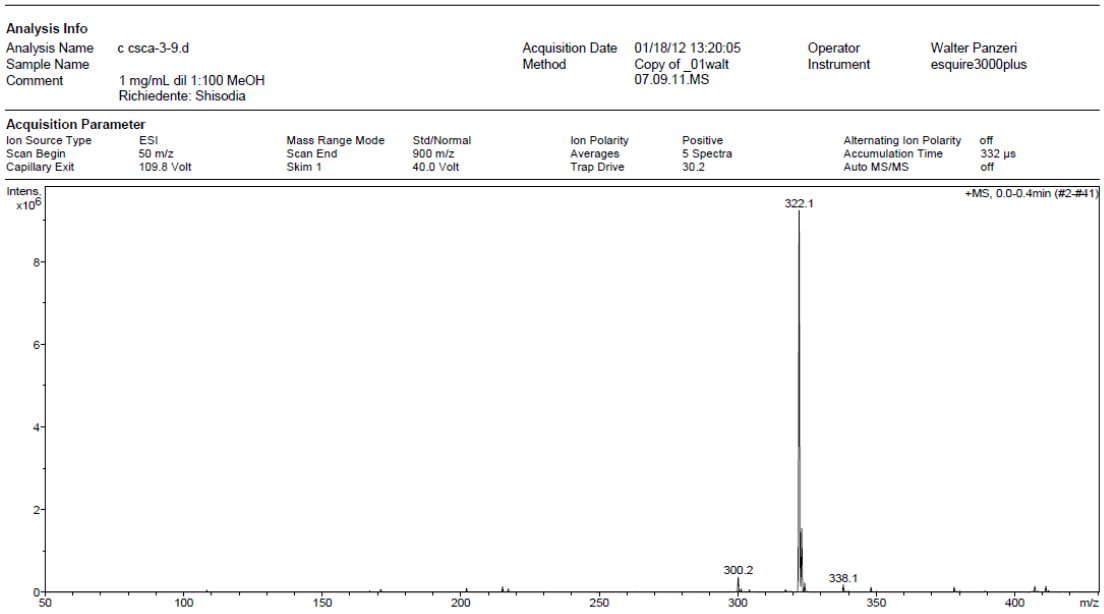
Reaction of αα'-diglycerol with DEC and benzylamine (molar ratio 1:2:2). In a 100 ml round bottom flask diglycerol (0.006 mol), diethyl carbonate (0.012 mol), benzylamine (0.012 mol) and K_2CO_3 (0.0018 mol) were taken and stirred the reaction mixture on oil bath at 130°C for 4 hours. The reaction was monitored by TLC (methanol/ethyl acetate 1:9 v/v as eluent). After the completion of reaction, excess of DEC and ethanol were evaporated on rotavapor under vacuum and solid reaction mixture was chromatographed to obtain pure products. Mass analysis indicates that the reaction mixture contains mono- and disubstituted products.

[3-(2,3-dihydroxypropoxy)-2-hydroxy-propyl] N-benzylcarbamate. MS-EISI m/z 338 (M[299] + 39[K]), 322 (M[299] + 23[Na]), Exact Mass: found 299.1376, calcd. 299.1369 Anal. Found: C, 56.21; H, 7.16; N, 4.77. $C_{14}H_{21}NO_6$ requires C, 56.18; H, 7.07; N, 4.68%.



[3-[3-(benzylcarbamoyloxy)-2-hydroxy-propoxy]-2-hydroxy-propyl] N-benzylcarbamate. MS-EISI m/z 471 (M[432] + 39[K]), 455 (M[432] + 23[Na]), Exact Mass: found 432.1886, calcd. 432.1897 Anal. Found: C, 61.01; H, 6.60; N, 4.37. $C_{14}H_{21}NO_6$ requires C, 61.10; H, 6.53; N, 6.48%.





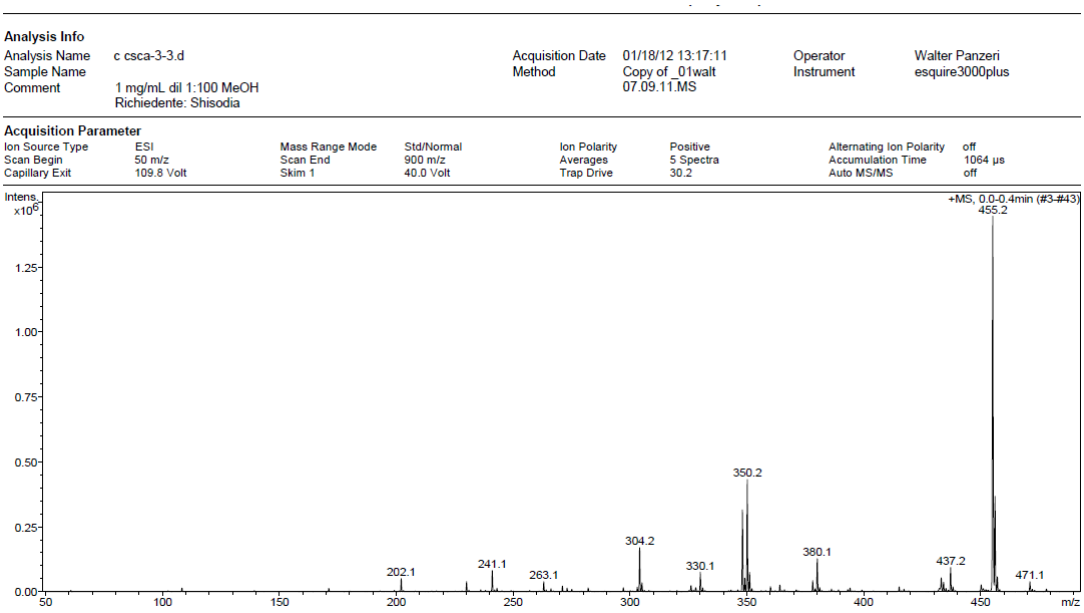


Figure 3.16 – Mass spectrum of crude reaction mixture of benzylamine with α,α-diglycerol and DEC

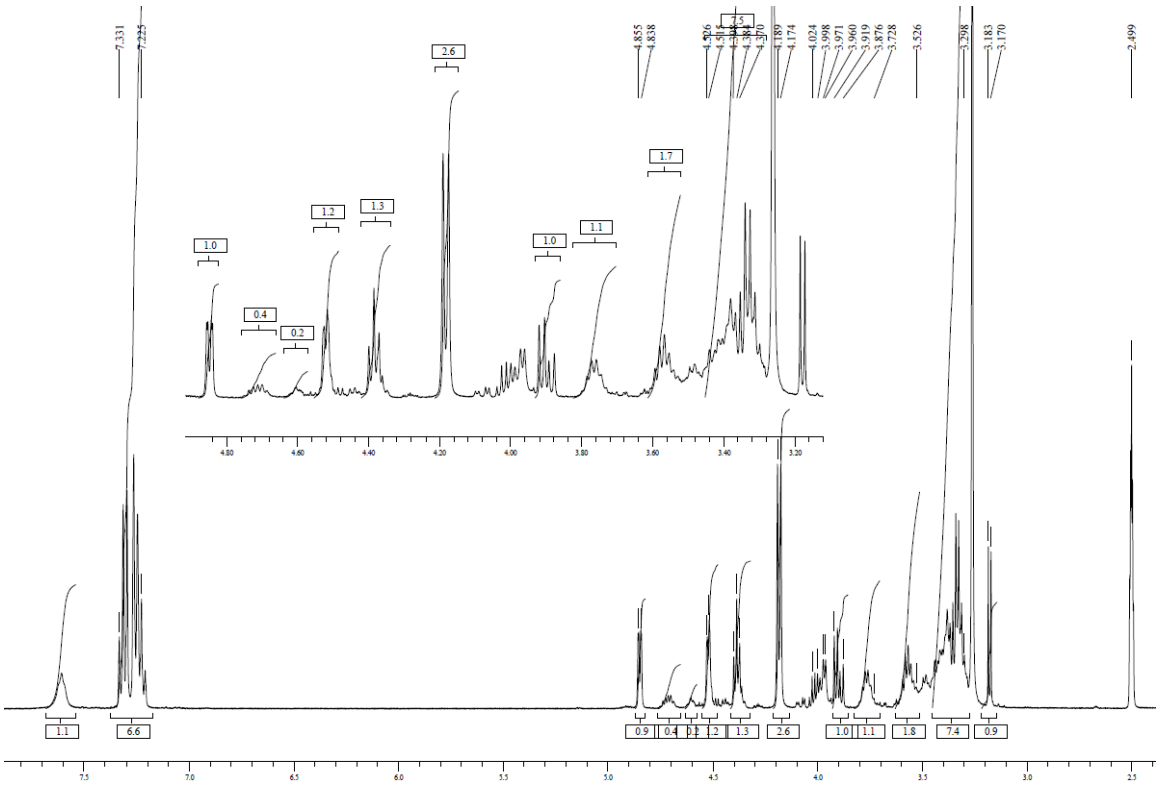
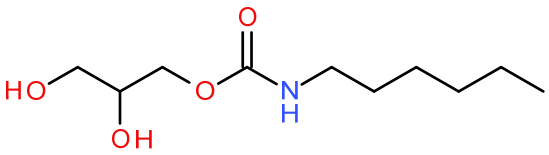
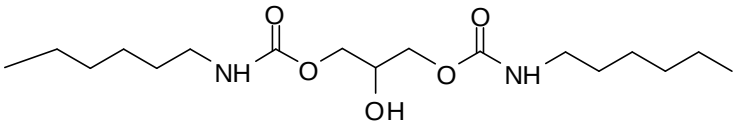


Figure 3.17 – ^{1}H-NMR spectrum [3-(2,3-dihydroxypropoxy)-2-hydroxy-propyl] N-benzylcarbamate.

Reaction of n-hexylamine with glycerol and DEC. In a 100 ml round bottom flask glycerol (0.01086 mol), diethyl carbonate (0.01086 mol), hexylamine (0.01086 mol) and K_2CO_3 (0.0003 mol) were taken and the mixture heated under stirring on oil bath at 50°C for 6 hours. The progress of the reaction was monitored by ^{1}H-NMR and TLC analysis. After completion, excess of DEC and ethanol produced in the reaction were distilled out under vacuum and the reaction mixture obtained analyzed by mass spectrometry.

2,3-dihydroxypropyl N-hexylcarbamate. White solid mp 44-45°C; MS-EISI m/z 258 (M[219] + 39), Exact Mass: found 219.1481, calcd. 219.1470 Anal. Found: C, 54.70; H, 9.74; N, 6.29. $C_{10}H_{21}NO_4$ requires C, 54.77; H, 9.65; N, 6.39%.





[3-(hexylcarbamoyloxy)-2-hydroxy-propyl] N-hexylcarbamate. White solid m.p. 44-45°C; MS-EISI m/z 385 (M[346] + 39), Exact Mass: found 346.2480, calcd. 346.2468 Anal. Found: C, 58.84; H, 9.78; N, 7.99. $C_{17}H_{34}N_2O_5$ requires C, 58.93; H, 9.89; N, 8.09%. ^{1}H-NMR (MeOD): δ in ppm = 4.69 (m, 1H, –CHOCO), 4.06 (m, 2H,–CH_2OCO), 3.78 (quint, 1H, –CHOH), 3.66 (m, 4H, –CH_2OH), 3.54 (m, 2H, –CH_2OH), 3.08 (m, 4H, –CH_2NH), 1.48 (m, 4H, –CH_2–CH_2–CH_3), 1.3 (m, 12H, –CH_2–CH_2–CH_2–CH_2–CH_3), 0.90 (t, 6H, –CH_3). ^{13}C-NMR (MeOD): δ in ppm = 159.18 (a C=O), 158.88 (b C=O), 77.06 (–CHOCO), 71.69 (–CHOH), 66.94 (–CH_2OCO), 62.12 (b, –CH_2OH), 64.21 (a, –CH_2OH), 41.96 (–CH_2NH), 33.10 (–CH_2—CH_2–CH_2–CH_2–CH_2–CH_3), 30.58 (–CH_2—CH_2–CH_2–CH_2–CH_2–CH_3), 31.03 (–CH_2–CH_2–CH_2–CH_3), 23.84 (–CH_2–CH_2–CH_3), 14.54 (–CH_3). IR (KBr) cm^{-1}: 3.342 (t-OH), 1.697 (t –OC(=O)NH–), 1.543 (–OC=ONH-R).

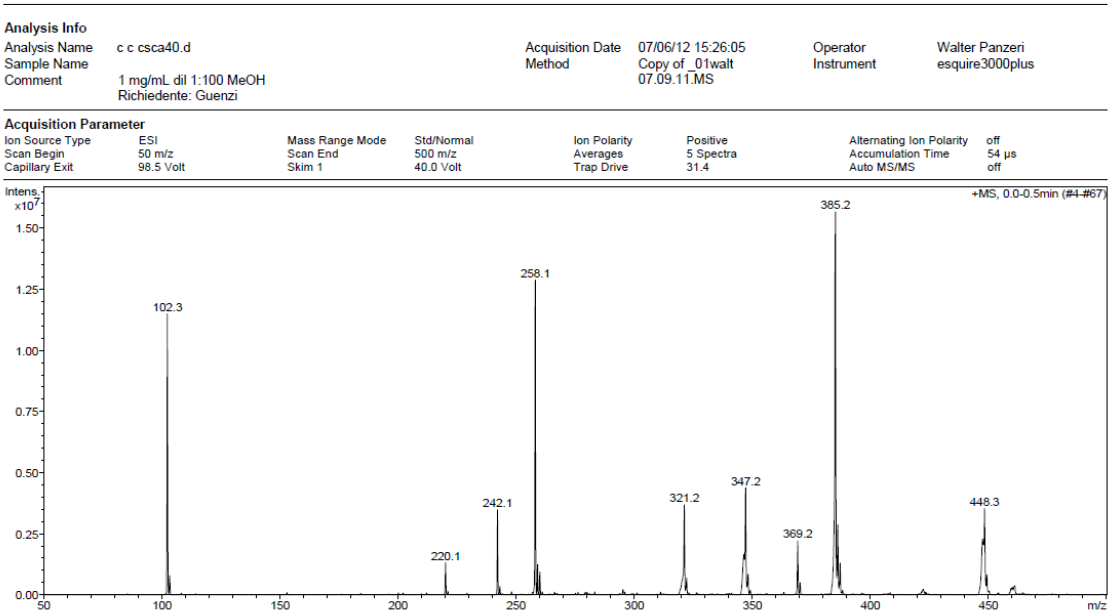
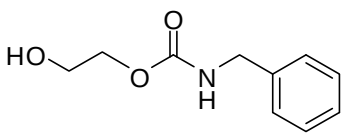


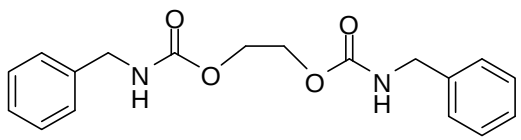
Figure 3.17 – Mass spectrum of crude reaction mixture of n-hexylamine with glycerol and DEC

Sintesi del 2-etilesilMAG. In a two necked 500 ml round bottom flask equipped with a dropping funnel were charged crude glicerolcarbonate (103 g) and the system heated at 70 °C. 2-Ethylhexylamine (56 g, 0.99 eq.) was added drop wise during 2 hours. The mixture was left under stirring for 48 h at 70 °C. The resulting mixture was washed with water (100 ml) and extracted with ethyl acetate (2 x 150 ml), recovering crude MAG (97 g). Gas-chromatographic analysis indicates a distribution of product of MAG (90%) and DAG (5%).

Reaction of benzylamine with ethylene glycol and DEC. In a 100 ml round bottom flask ethylene glycol (0.01612 mol), diethyl carbonate (0.01612 mol), benzylamine (0.01612 mol) and K_2CO_3 (0.0004 mol) were taken and stirred the reaction mixture on oil bath at 50°C for 24 hours. The progress of the reaction was monitored by ^{1}H-NMR and TLC analysis. After completion of reaction, excess of DEC and ethanol produced in the reaction were distilled out under vacuum and the reaction mixture obtained was analyzed by mass analysis.

2-hydroxyethyl N-benzylcarbamate. White solid m.p. 44-45°C; MS-EISI m/z 234 (M[195] + 39), Exact Mass: found 195.0890, calcd. 195.0895 Anal. Found: C, 61.46; H, 6.78; N, 7.25. $C_{10}H_{13}NO_3$ requires C, 61.53; H, 6.71; N, 7.18%.





2-(benzylcarbamoyloxy)ethyl N-benzylcarbamate. White solid m.p. 151-152°C; MS-EISI m/z 367 (M[328] + 39), Exact Mass: found 328.1431, calcd. 328.1423 Anal. Found: C, 65.91; H, 6.48; N, 8.60. $C_{18}H_{20}N_2O_4$ requires C, 65.84; H, 8.53; N, 8.53%.

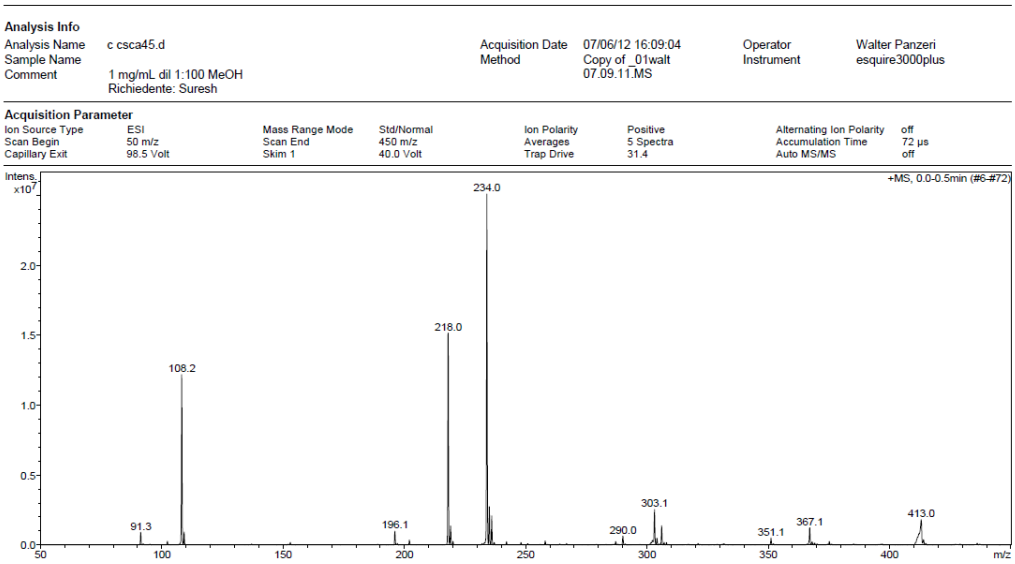
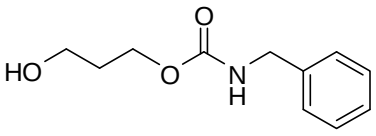
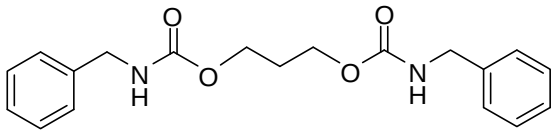


Figure 3.18 – Mass spectrum of crude reaction mixture of benzylamine with ethylenglycol and DEC

Reaction of benzylamine with 1,3-propanediol and DEC. In a 100 ml round bottom flask 1,3-propanediol (0.01315 mol), diethyl carbonate (0.01315 mol), benzylamine (0.01315 mol) and potassium *t*-butoxide (0.00039 mol) were taken and the reaction mixture was heated under stirring in an oil bath at 100°C for 8 hours. The reaction has been studied following distribution of products via ^{1}H-NMR and TLC analyses. After completion (12 hr), DEC in excess and ethanol were distilled out under vacuum and the reaction mixture obtained analyzed by mass spectroscopy.

3-hydroxypropyl N-benzylcarbamate. MS-EISI m/z 248 (M[209] + 39), Exact Mass: found 342.1575, calcd. 342,1580. Anal. Found: C, 63.21; H, 7.28; N, 6.72. $C_{19}H_{22}N_2O2_4$ requires C, 63.14; H, 7.23; N, 6.69%.





3-(benzylcarbamoyloxy)propyl N-benzylcarbamate. MS-EISI m/z 381 (M[342] + 39); exact mass: found 342.1575, calcd. 342,1580. Anal. Found: C, 66.57; H, 6.38; N, 8.21%. $C_{19}H_{22}N_2O2_4$ requires C, 66.65; H, 6.48; N, 8.18%.

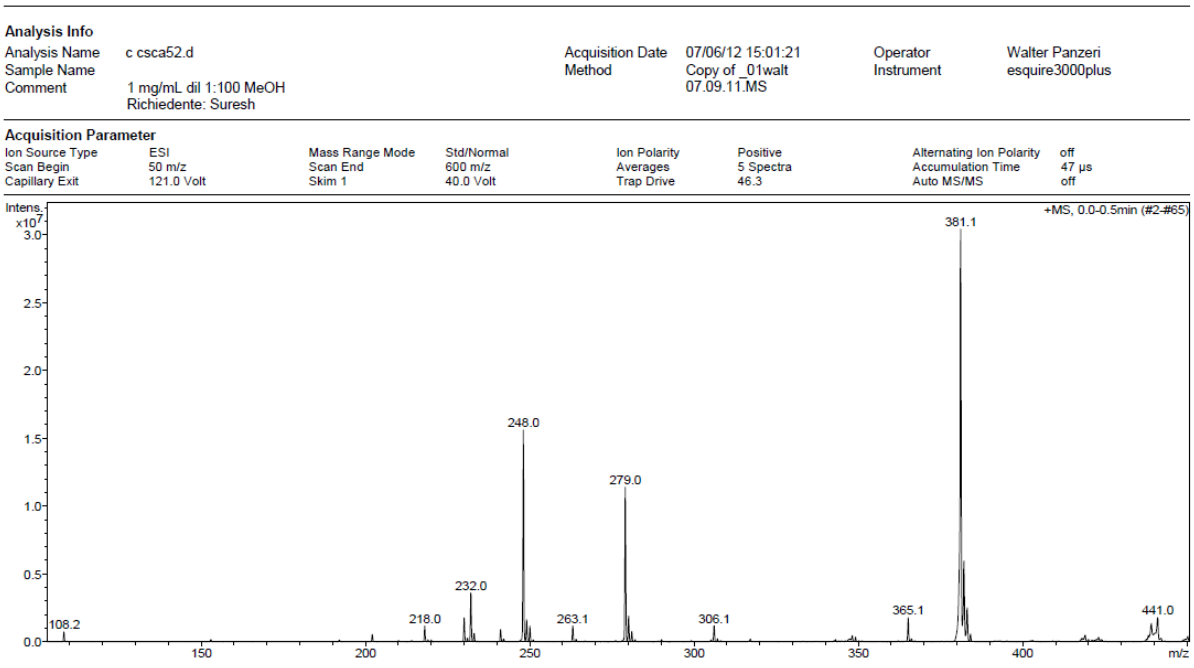
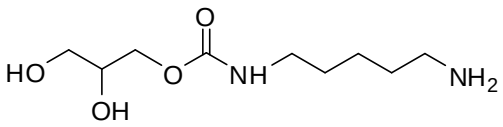


Figure 3.19 – Mass spectrum of crude reaction mixture of benzylamine with 1,3 propanediol and DEC

Synthesis of hexamethylenediamineglycerol carbamates.

A) Reaction of hexamethylenediamine with glycerol and DEC (molar ratio 1:1:1). In a 100 ml round bottom flask glycerol (0.01086 mol), hexamethylenediamine (0.01086 mol), diethyl carbonate (0.01086 mol), and potassium tertiary butoxide (0.0003 mol) were taken and stirred the reaction mixture on oil bath at 50°C temperature for 6 hours. The reaction was monitored by ^{1}H-NMR. After completion of reaction, excess of DEC and ethanol produced in the reaction were distilled out under vacuum and the crude reaction mixture was analyzed by mass spectroscopy for product distribution. The residue was liquid at room temperature having particular sweet smell, it was soluble at r.t. in methanol and water. From water some crystals were obtained but not from methanol. The residue dissolved in ethyl acetate afforded a cloudy solution, which becomes clear after heating and allows to crystallize when cooled at room temperature some solid. Mass spectrometric analysis evidences that only the monosubstituted glycerolcarbamate product was present with very minor amounts of dicarbamates.

2,3-dihydroxypropyl N-(6-aminohexyl)carbamate. MS-EISI m/z 273 (M[234] + 39[K]) and 257 (M[234] + 39[Na]); exact mass: found 234.1571, calcd. 234.1580. Anal. Found: C, 51.31; H, 9.51; N, 11.84%. $C_{10}H_{22}N_2O_4$ requires C, 51.26; H, 9.46; N, 11.96



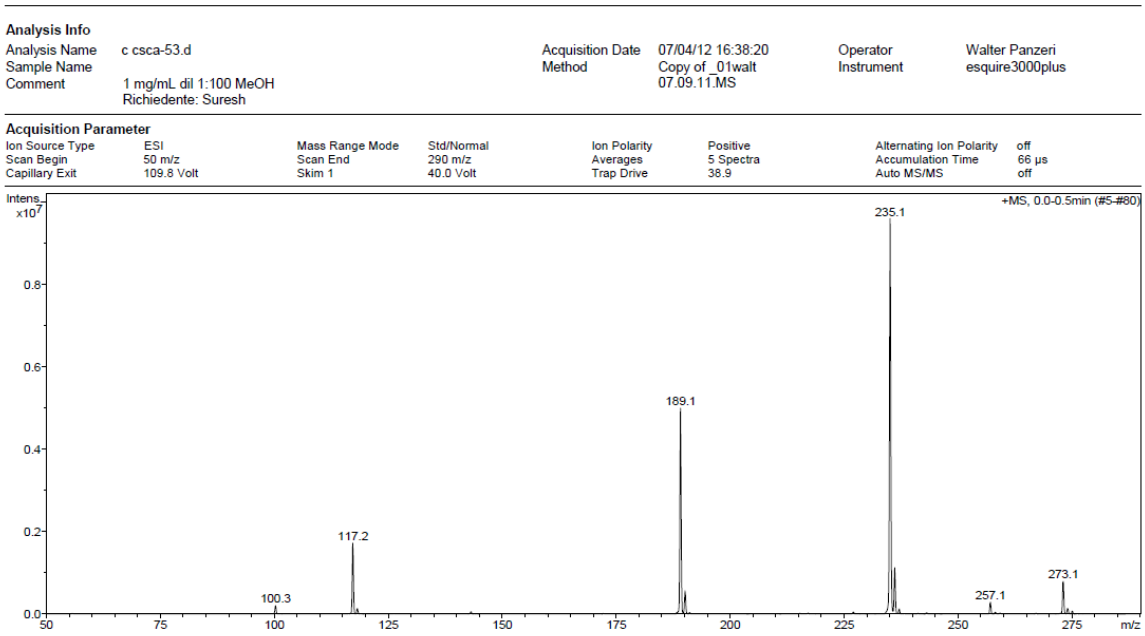
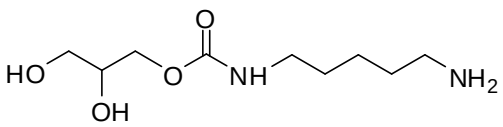


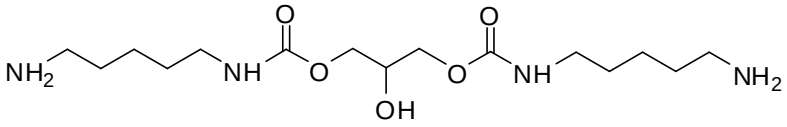
Figure 3.20 – Mass spectrum of reaction mixture of 1,6-hexandiamine with glycerol and DEC (1:1:1)

B) Reaction of hexamethylenediamine with glycerol and DEC (molar ratio 1:2:2). The reaction was carried out as in case A) by using glycerol (0.01086 mol), hexamethylenediamine (0.02172 mol), diethyl carbonate (0.02172 mol), and potassium tertiary butoxide (0.0003 mol). The crude reaction mixture was liquid at room temperature having particular sweet smell. At room temperature reaction mixture was soluble in methanol, water, and ethyl acetate (not crystallized at room temperature). From mass analysis it was deduced that three products were present, one monoubstituted and two disubstituted products.

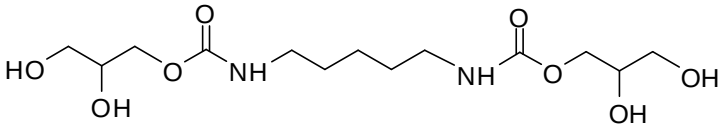
2,3-dihydroxypropyl N-(6-aminohexyl)carbamate. MS-EISI m/z 273 (M[234] + 39[K]) and 257 (M[234] + 39[Na]); exact mass: found 234.1571, calcd. 234.1580. Anal. Found: C, 51.31; H, 9.51; N, 11.84%. $C_{10}H_{22}N_2O_4$ requires C, 51.26; H, 9.46; N, 11.96



2,3-dihydroxypropyl N-[6-(2,3-dihydroxypropoxycarbonylamino)hexyl]carbamate. MS-EISI m/z 399 (M[376] + 23) and 415 (M376 + 39); exact mass: found 376.2697, calcd. 376,2692.



2,3-dihydroxypropyl N-[6-(2,3-dihydroxypropoxycarbonylamino)hexyl]carbamate. MS-EISI m/z 391 (M[352] + 39); exact mass: found 352.1851, calcd. 352,1846.



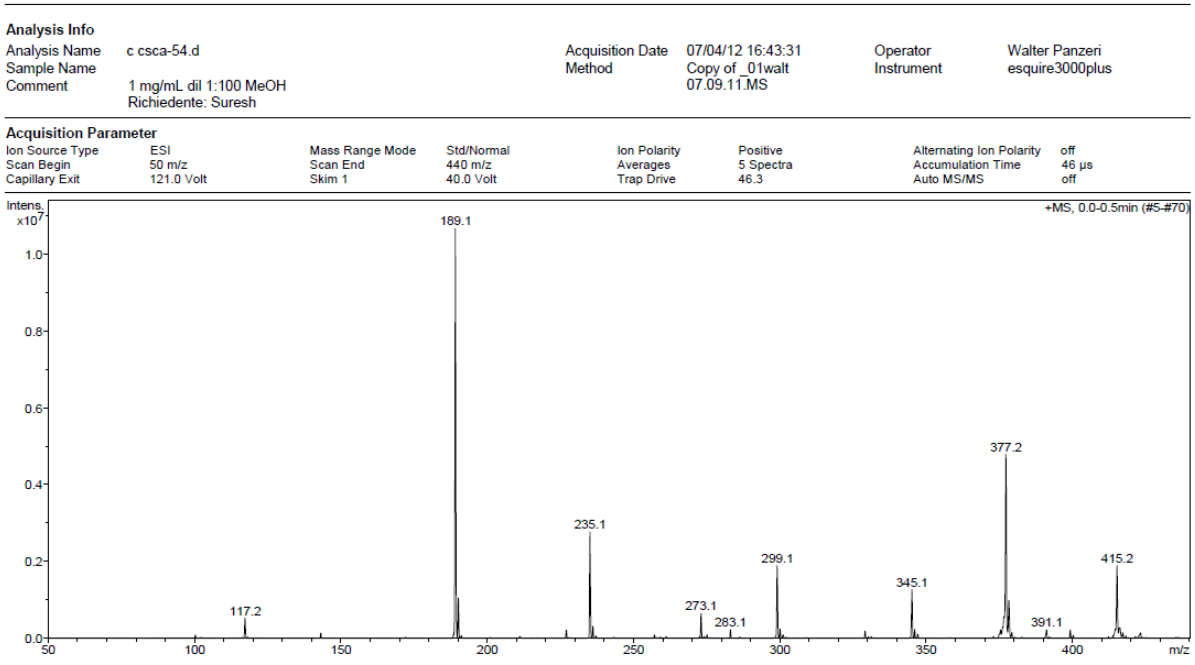
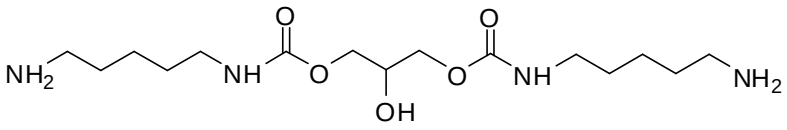


Figure 3.21 – Mass spectrum of crude reaction of 1,6-hexandiamine with glycerol and DEC (1:2:2)

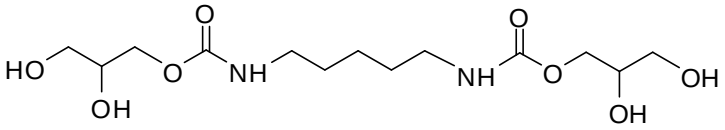
C) Reaction of hexamethylenediamine with glycerol and DEC (molar ratio 2:1:2). The reaction was carried out as in case A) by using glycerol (0.0172 mol), hexamethylenediamine (0.0086 mol), diethyl

carbonate (0.0172 mol), and potassium tertiary butoxide (0.0003 mol). The crude reaction mixture was soluble in methanol at r.t. (but no crystals were obtained by cooling at 0°C), in ethyl acetate and water. In the last case the cloudy system at r.t. becomes transparent on heating and crystals were obtained by cooling at r.t.. Mass analysis of the solid clearly indicates the presence of two products, both disubstituted.

[3-(6-aminohexylcarbamoyloxy)-2-hydroxy-propyl] N-(6-aminohexyl)carbamate. MS-EISI m/z 399 (M[376] + 23) and 415 (M376 + 39); exact mass: found 376.2697, calcd. 376,2686. Anal. Found: C, 54.15; H, 9.80; N, 14.76%. $C_{17}H_{36}N_4O_5$ requires C, 54.23; H, 9.64; N, 14.88%.



2,3-dihydroxypropyl N-[6-(2,3-dihydroxypropoxycarbonylamino)hexyl]carbamate. MS-EISI m/z 391 (M[352] + 39); exact mass: found 352.1853, calcd. 352,1846. Anal. Found: C, 44.85; H, 8.20; N, 7.84%. $C_{14}H_{28}N_2O_8$ requires C, 44.72; H, 8.01; N, 7.95%.



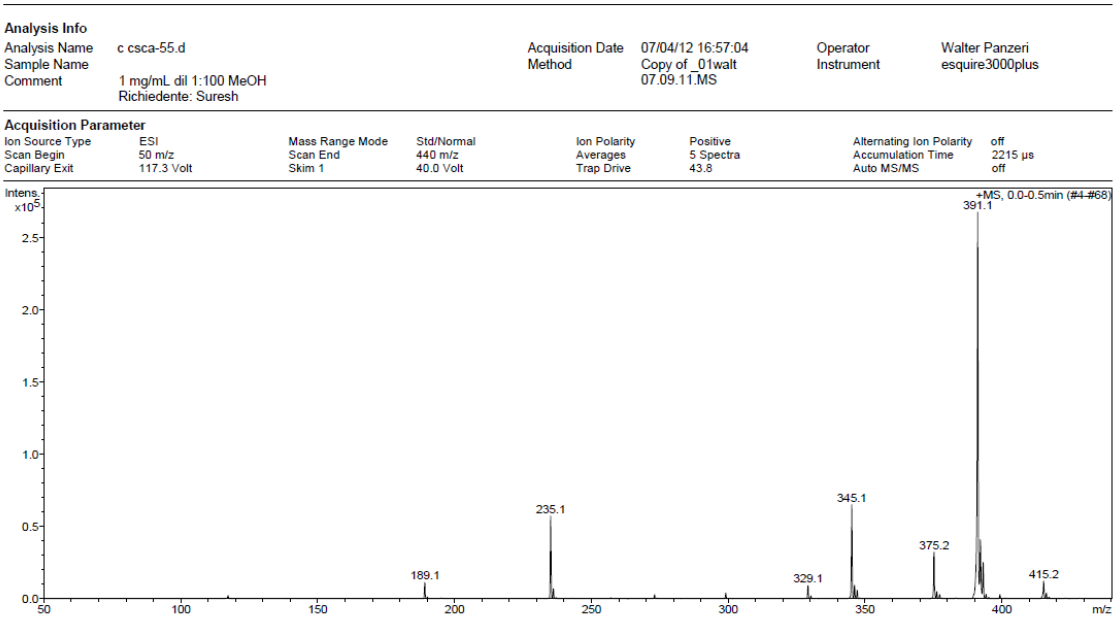


Figure 3.22 – Mass spectrum of crude reaction of 1,6-hexandiamine with glycerol and DEC (2:1:2)

Synthesis of glycerol carbonate. In 50 ml round bottom flash, equipped with a vigreux, distillation head and nitrogen inlet, glycerol (10 g), dimethyl carbonate (14.7 g, 1.5 equivalent based on glycerol) and K_2CO_3 (0.45 g, 3% mol based on glycerol) are mixed. The system is heated under moderate stirring distilling off the formed methanol. Initially are collected 7.65 g of methanol. At the end, using a nitrogen flow, most of the remaining dimethyl carbonate is eliminated, collecting the gas flow in a trap at -70°C. In this way further 2.53 g of liquid is collected, and the residue in the flash is weight (12.45 g). A sample of the reaction mixture is analyzed by ^{1}H-NMR e then, after more nitrogen was flowed for 15 min., further reanalyzed for yield (91%) and conversion (93%) determination. A small amount of glycerol (3%) was again present. In the crude residue glycerol dicarbonate (about 5%) and unidentified epoxides (about 2% by NMR) were identified. Both these products are present in low amount in the second distillate collected at – 70°C. Totally absent from the residue were methanol and dimethyl carbonate. The purity of the crude glycerol carbonate (GC) was 93% against a standard of 98% opurity.

Hydroxymethyl)-1,3-dioxolan-2-one. ^{1}H-NMR (DMSO-d_6, δ): 3.51 (ddd, *2J* = 12.7 Hz, *3J* = 5.6 Hz, *3J* = 3.3 Hz, 1H, H4), 3.67 (ddd, *2J* = 12.7 Hz, *3J* = 5.4 Hz, *3J* = 2.8 Hz, 1H, H4), 4.29 (dd, *2J* = 8.2 Hz, *3J* = 5.8 Hz, 1H, H2), 4.50 (dd, *2J* _ *3J* _ 8.3 Hz, 1H, H2), 4.80 (dddd, *3J* = 8.6 Hz, *3J* = 5.8 Hz, *3J* _ *3J* = 3.0 Hz, 1H, H3), 5.26 (dd, *3J* _ *3J* _ 5.4-5.6 Hz, 1H, OH); ^{13}C-NMR (DMSO-d_6, δ): 60.6 (C4), 65.8 (C2), 77.0 (C3), 155.2 (*C*1). IR (KBr pellet) ν_{max} /cm^{-1} 3404, 2929, 2881, 1786, 1552, 1481, 1402, 1338, 1279, 1178, 1085, 1053, 983, 943, 856, 775, 716, 576: MS m/z (rel. int.) 77.1 (5.1), 87.1 (100), 90.1 (6.4), 94.1 (83.8), 119.1 (M^+.).

Synthesis of methyl *N*-benzyl carbamate and N,N'-dibenzyl urea. The methyl N-benzylcarbamate was prepared mixing benzylamine (4.6728 mmol), dimethyl carbonate (4.6728 mmol) and K_2CO_3 (0.1386 mmol) and heating at 90°C under magnetic stirring in an oil bath for 7 hr, following the reaction by TLC. From NMR analysis it is clear that methyl *N*-benzyl carbamate and N, N'- dibenzyl urea got formed in the reaction. The product formed methyl N-benzylcarbamate and N,N'-dibenzyl urea were isolated from the reaction mixture by column chromatography on SiO_2 with hexane:ethyl acetate 7:3 as eluent.

Methyl *N*-benzylcarbamate. White solid mp 64-65°C (from EtOH); λ_{max} (Nujol)/cm^{-1} 3440–3460, 1730, 1520 and 1230; ^{1}H-NMR (400 MHz, $CDCl_3$) 3.70 (3H, s), 4.37 (2H, d, *J* = 6.1 Hz), 5.01 (1H, s broad), 7.20-7.40 (5H, m); GC-MS *m/z* (rel. int.): 165 (M^+, 70%), 150 ([M - Me]$^+$, 100), 133 ([M - OMe - H]$^+$, 21) 106 ([M - COOMe]$^+$, 51), 91 ([C_7H_7]$^+$, 75), 79 (42), 65 (20), 51 (19); Anal. Found: C, 65.47; H, 6.68; N, 8.47. $C_9H_{11}NO_2$ requires C, 65.45; H, 6.66; N, 8.48%.

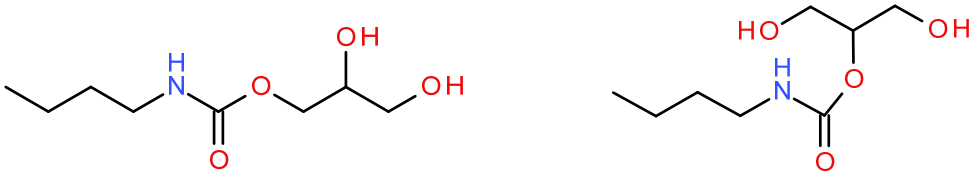
N,N'-Dibenzyl urea. Obtained by separation using silica gel column chromatography, eluting with CH_2Cl_2:MeOH = 10:1. White solid mp 166-167°C; IR ν_{max} /cm^{-1} 1626 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.32-7.20 (m, 10H, 2Ph), 6.39 (t, 2NH), 4.22 (d, 4H, NH-$\underline{CH_2}$-Ph); ^{13}C(100 MHz; $CDCl_3$) δ: 43 ($2CH_2$), 126.7 (CH), 127.1 (4CH), 128.4 (4CH), 141 (2C), 158.3 (C=O); GC-MS, m/z (rel. Int.) 28 (10%), 51 (7), 65 (20), 79 (25), 91 (55), 106 (100), 149 (25), 164 (1), 206 (1), 240 (33).

Synthesis of ethyl *N*-benzylcarbamate. Attempt to synthetize the compound from diethyl carbonate (4.6728 mmol) and benzyl amine (4.6728 mmol) in the presence of K_2CO_3 (0.1386 mmol) at 90°C on oil bath for 7 hrs produce only traces of the expected carbamate. The compound was therefore prepared through the usual alternative procedure starting from ethyl chloroformate. In a 100 ml round bottom flask benzylamine (9.3 mmol), triethylamine (0.0186 mol) and diethyl ether (50-80 ml), were taken and kept stirring for 30 minutes at 0°C in ice bath, then ethyl chloroformate (0.0186 mol) was added dropwise and the resulting heterogeneous reaction mixture was stirred for 4-5 hrs. After completion of reaction 10% aqueous $NaHCO_3$ solution was added to neutralize excess of ethyl chloroformate, the organic layer was separated, dried on sodium sulfate, concentrated, and then purified with the help of column chromatography on flash SiO_2.

Ethyl *N*-benzylcarbamate. mp 47 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.61 (s broad, 1H, NH), 7.34-7.21 (m, 5H, Ph); 4.22-4.20 (d, 2H, J = 6.1 Hz, Ph-$\underline{CH_2}$), 4.05-4.00 (q, 2H, $\underline{CH_2}$-CH_3), 1.18-1.16 (t, 3H, CH_2-$\underline{CH_3}$).

Synthesis of glycerol N-n-butylcarbamates. In a 250 ml round bottom flash were charged glycerolcarbonate (54 g) and the system cooled under nitrogen at 0°C and, controlling the temperature with a cooler, n-butylamine (36.5 g, 0.99 eq.) was added under magnetic stirring. The mixture was left at r.t. for a day. ^{1}H-NMR analysis of the crude reaction mixture shows the presence of 1-N-butylglycerol carbamate and 2-N-butylglycerol carbamate (1:1, yield 75%), unreacted glycerolcarbonate (3%), 1,3-N-butil-glycerol dicarbamate (5%), the absence of n-butylamine and N-n-butylglycerol carbamate-carbonate (< 2%) and glycerol (17 %). Ten grams of the mixture was chromatographed on SiO_2 using a gradient of ethyl acetate/ethanol as eluent and several fraction were recovered, from which were identified the mono carbamate isomers, the dicarbamate, and the carbamate-carbonate.

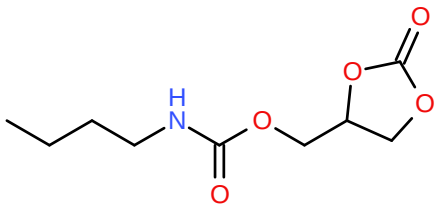
2,3-dihydroxypropyl N-*n*-butylcarbamate. Oil; ^{1}H-NMR (400 MHz, DMSO-d_6) δ (D_2O exchanged): 4.11 (m, 2H, CH_2OCO), 3.85 (q, 1H, $\underline{CH}$-OH), 3,11 (m, 4H, CH_2N), 3.60 (m, 2H, -CH_2OH) 3,10 (m, 2H, N-CH_2), 1.45 (m, 2H), 1,31 (m, 2H), 0.93 (t, 3H, CH_2-$\underline{CH_3}$). ^{13}C NMR (DMSO-d_6) δ: 157.0 (C=O), 75.0 (–CHOH), 68.0 (–$\underline{C}H_2OCO$), 45.0 (–$\underline{C}H_2N$), 34.0 (–$\underline{C}H_2$–CH_2–CH_3), 21.5 (–$\underline{C}H_2$–CH_3), 14.2 (–$\underline{C}H_3$). IR (KBr) cm^{-1}: 3,342 (t-OH), 1,697, (t –OC(=O)NH–), 1,543 (–OC=ONH-R); MS-EISI m/z 230 (M[191] + 39) 214 (M[191] + 23[Na]); exact mass: found 191.1150, $C_8H_{18}NO_4$ requires 191.1158.



[2-hydroxy-1-(hydroxymethyl)ethyl] N-*n*-butylcarbamate. mp 47 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 4.63 (q, 1H, *J* = 7.1 Hz, O-CH), 3.70 (d, 4H, CH_2-O), 3,12 (t, 2H, N-CH_2), 1,44 (m, 2H), 1,30 (m, 2H), 0.93 (t, 3H, CH_2-CH_3). ^{13}C NMR (DMSO-d_6) δ: 157.0 (C=O), 79.2 (–CHOCO), 65.0 (–CH_2OH), 47.0 (–CH_2N), 34.2 (–CH_2–CH_2–CH_3), 21.6 (–CH_2–CH_3), 14.2 (–CH_3). MS-EISI m/z 230 (M[191] + 39) 214 (M[191] + 23[Na]); exact mass: found 191.1147, $C_8H_{18}NO_4$ requires 191.1158

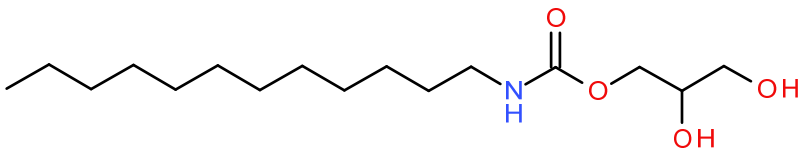
Synthesis of glycerol N-n-butylcarbamate-carbonate. The crude mixture of a reaction carried out as the above (58 g) dimethyl carbonate (35.8 ml, 1.4 eq.) and triethylamine (12.6 ml, 0.3 eq.) were added. The mixture was heated at 90°C for 5 h under nitrogen. The reaction was monitored by ^{1}H-NMR showing that after 2.5 h N-n-butylglycerol carbamate-carbonate was present in 50% yield whereas after 5 hours the product is present in 83% yield and methanol was absent. The cooled crude reaction mixture was chromatographed to isolate the carbonate-carbamate product. Small amount of isomeric oxazolidinone derivatives were identified.

(2-oxo-1,3-dioxolan-4-yl)methyl N-*n*-butylcarbamate. MS-EISI m/z 256 (M[217] + 39) 240 (M[217] + 23[Na]); exact mass: found 217.09538, calcd. 217.0950. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.0 (1H NH), 4.83 (m, 1H, O-CH), 4.41 (dd, 1H, OCH), 4.20-4.35 (m, 2H, CH_2-O), 4,04 (dd, 1H) 3,25 (t, 2H, N-CH_2), 1.59 (m, 2H), 1,36 (m, 2H), 0.93 (t, 3H, CH_2-CH_3).

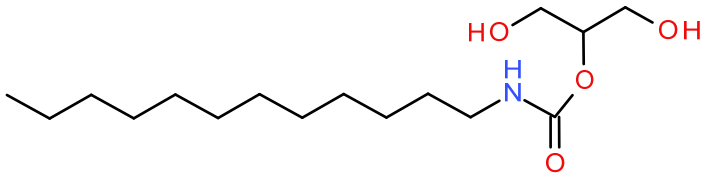


Synthesis of glycerol N-n-dodecylcarbamates. In a 250 ml round bottom flash were charged glycerolcarbonate (5.0 g) and n-dodecylamine (7.7 g, 0.99 eq.) and the mixture was magnetically stirred at r.t. for a day. The system becomes solid and a sample analyzed by ^{1}H-NMR indicates the presence of relevant ampount of monocarbamates (80% in ratio 58:42) and small amount of dicarbamates (estimated 8%). The crude reaction mixture was dissolved in ethyl acetate and water (1:1, 50 ml) and the water separated and ri-extracted with the same solvent (2x 25 ml). The combined extracts were dried on Na_2SO_4 and evaporated at rotary evaporator. A solid residue (11.9 g) of carbamates was obtained which was separated by column chromatography on SiO_2 using hexane/ethyl acetate 8:2 as eluent.

2,3-dihydroxypropyl N-*n*-dodecylcarbamate. White solid mp 54-55°C; MS-EISI m/z 342 (M[303] + 39) 326 (M[303] + 23[Na]); exact mass: found 303.2405, calcd. 303,2410. Anal. Found: C, 63.18; H, 11.03; N, 4.68%. $C_{16}H_{33}NO_4$ requires C, 63.33; H, 10.96; N, 4.62%.

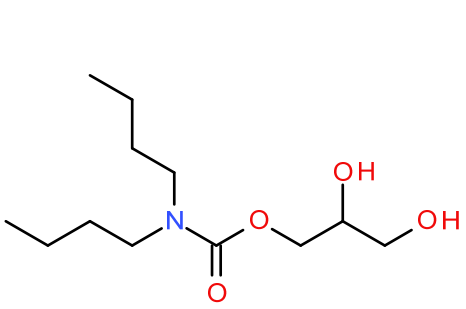


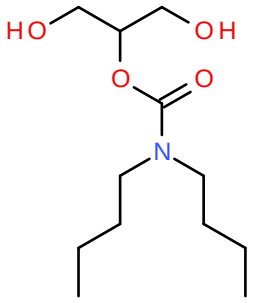
[2-hydroxy-1-(hydroxymethyl)ethyl] N-dodecylcarbamate. White solid mp 65-67; MS-EISI m/z 342 (M[303] + 39) 326 (M[303] + 23[Na]); exact mass: found 303.2416, calcd. 303,2410. Anal. Found: C, 63.38; H, 10.88; N, 4.74%. $C_{16}H_{33}NO_4$ requires C, 63.33; H, 10.96; N, 4.62%.



Sintesi del glycerol N,N-dibutylcarbamate. In a 250 ml round bottom flash glycerolcarbonate (10.0 g) was charged and the system heated at 90 °C. Dibutylamine (5.6 g, 1 eq.) was drpped fron a funnel in 45 min. A two phase system is initially formed. The system was allowed under stirring at 90 °C for 35 hours. When cooled the system becomes again heterogeneous. From the bottom phase 3.3 g of a viscous liquid were recovered. The upper phase was treated with water and extracted with ethyl acetate (2 x 50 ml). After drying and concentration a crude glycerol N,N-dibutylcarbamate (8.8 g) were recovered. Gas-chromatographic analysis shows a yield of 60% of two isomeric mono carbamates and 20% for di carbamate.

2,3-dihydroxypropyl N,N-dibutylcarbamate. Low melting compound mp 17-19°C; MS-EISI m/z 286 (M[247] + 39[K]) 270 (M[247] + 23[Na]); exact mass: found 247.1790, calcd. 247,1784. Anal. Found: C, 58.39; H, 10.27; N, 5.64%. $C_{16}H_{33}NO_4$ requires C, 58.27; H, 10.19; N, 5.66%.





[2-hydroxy-1-(hydroxymethyl)ethyl] N,N-dibutylcarbamate. Low melting compound mp 24-26°C; MS-EISI m/z 286 (M[247] + 39[K]) 270 (M[247] + 23[Na]); exact mass: found 247.1778, calcd. 247,1784. Anal. Found: C, 58.35; H, 10.09; N, 5.68%. $C_{16}H_{33}NO_4$ requires C, 58.27; H, 10.19; N, 5.66%.

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Chapter – 4

Synthesis, Characterization and Biological Activity Study of Novel Ferrocenylglycerol Derivatives.

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Organometallic chemistry and biochemistry have been merged in the last two decades into a new field: bioorganometallic chemistry. This new research area was devoted to the synthesis of new organometallic compounds and their biological and medical effects against some types of diseases, such as cancer and malaria. For several years, the use of ferrocene in bioorganometallic chemistry has been growing rapidly, and several promising applications have been developed since ferrocene is a stable, nontoxic compound and has good redox properties. This area has attracted many researchers due to the promising results of some ferrocene compounds in the medicinal applications. Often these compounds show bioactivity, precisely because of the presence of the ferrocene units in the molecules. In this thesis we will focus on the novel ferrocenylglycerol derivatives synthesized, which have been biologically evaluated against certain fungi. The results obtained were fully comparable with the ones reported in literature: in our opinion this result is important because these simple and cheap compounds shown same biological activity like other much more complex and expensive ferrocenyl derivatives. This information can be useful to test the bioactivity of these cheap compounds on others and more relevant biological systems.

4.1 Bio-organometallic pharmaceuticals

Over the past 50 years organometallic chemistry has developed into wide and important area linking organic and inorganic chemistry. Applications of organometallic compounds are varied and numerous. They include catalysts for industrial syntheses, anti-knocking agents for fuel, in organic synthesis and in bio-organometallic pharmaceuticals.

In bio-organometallic Chemistry, now a day organometallic pharmaceutical is larger part of this field. This broad field incorporates the use of organometallic compounds in biologically relevant functions, including synthesis of biological compounds, organometallic immunoassays, and use of organometallic compounds as direct therapeutic or diagnostic agents for biosensors, bioimagning, bioprobes, molecular recognition in aqueous medium, environmental toxicology, catalysis of biological reactions, and also used in the other different fields.

4.2 Development of organometallic compounds as important medicinal agents

In last few decades, the interest in metal complexes in a biological sense was initiated by the success of *cis*-platin against various types of cancer[1] organometallic compounds containing transition metals, such as Co, Cu, Fe, Ga, Ge, Mo, Pt, Sn, Rh, Ru, Ti, and V are known to have anti-proliferative (in vitro) and anti-neoplastic (in vivo) activities. Platinum coordination compounds, such as *cis*-platin, carboplatin and other derivatives are used in the treatment of a variety of tumors[2]. Now a day's bioorganometallic chemistry is developing and devoted more attention of researchers to the synthesis and study of organometallic compounds of biological and medicinal interest. Notably, the field of medicinal chemistry has benefited considerably from the incorporation of organometallic moieties into potential drug molecules. Some of the most promising novel biologically active compounds are emerging from the field of bioorganometallic chemistry.

In recent years the organometallic compound specially ferrocene and ferrocenyl derivatives have been extensively studied and shown a broad range of biological activity, and including non-biological applications[3], This is because of properties of ferrocene such as it's small size, high stability in aqueous and aerobic media, the low or moderate toxicity, relative lipophilicity, easily membrane-permeability, the central iron atom is easily oxidized from Fe(II) to Fe(III) and it can also be easily derivatized, that is easily attaching ferrocene to molecules of biological interest such as Amino acids, Proteins, DNA, RNA, Carbohydrates and Drug molecules etc. The medicinal application of ferrocene is currently, an active area of research with many reports showing its activity in vivo and in vitro. Detailed reviews on the bio-organometallic chemistry of ferrocene compounds have been reported[4]. Studies of their interaction with biomolecules[5] and for the development of novel drugs are explained[6]. Ferrocene itself exhibits interesting properties such as antianemic, antiseptic, or cytotoxic agent and its derivatives shown significant activity as antifungal, antimalerial, anticancer, antimicrobial, anti-HIV-1, antioxidant, and insecticidal, PDE4 inhibitory activities.

4.3 Ferrocene occurrence, properties and applications in different fields

4.3.1 Introduction

Ferrocene (Figure 4.1) was discovered for the first time unexpectedly by T. J. Kealy and P. L. Pauson in the early 1950's, when they were trying to synthesize fulvene from cyclopentadienyl magnesium bromide and iron (III) chloride. The mechanism is that Fe^{3+} is firstly reduced by Grignard reagent and then reacts with C_5H_5MgBr to give ferrocene. Almost at the same time, Miller and co-workers have also obtained ferrocene

through reactions of Fe with cyclopentadiene under high or normal atmosphere[7]. In 1952, Wilkinson and Woodward[8] have elucidated from measurements of IR, magnetic susceptibility and dipole moment the structure of ferrocene, which was confirmed by X-ray crystallography afterward. The special structure, bonding and aromaticity of ferrocene defied conventional bonding descriptions, thus stirred up the imagination of chemists consumedly. The discovery and characterization of the structure of ferrocene opened up a new area of chemistry, leading to an explosion of interest in d-block metal carbon bonds and bringing about development and the now flourishing study of organometallic chemistry.

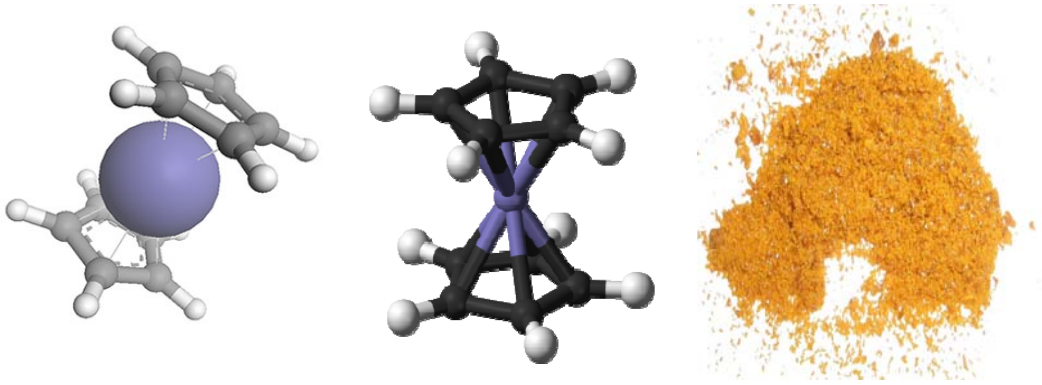


Figure 4.1 Ferrocene structures

The research for the synthesis, structures and properties of ferrocene derivatives has been continually active during the last several decades. Many ferrocene derivatives have been synthesized and their properties and applications have been thoroughly explored, which has promoted the development of the theory of chemical bond and the structural chemistry. During recent years, based on development in electrochemical technologies, great progress has been made in the research of basic electrochemical behaviors of ferrocene and its derivatives, their applications in intermolecular electron transfer research, electrocatalysis, electroanalysis, molecular recognition, etc.

4.3.2 The ferrocene molecule-structure and electronic properties

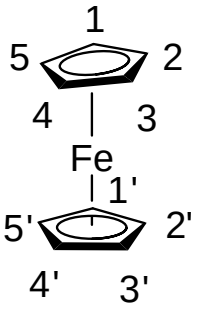


Figure 4.2 Structure of di(η^5-cyclopentadienyl)iron(II) (ferrocene) and carbon atom numbering.

In the ferrocene molecule, with inter-ring distance ~3.32 Å, the two cyclopentadienyl ring ligands, while substantially free to rotate, prefer the eclipsed (D_{5h}) equilibrium conformation both in the gas phase and in the crystal below the k point transition at 164 K. At room temperature, the crystal is characterized by rotational disorder, permitting neither D_{5d} nor D_{5h} symmetry assignment[9]. Although in earlier publications the D_{5d} symmetry with staggered rings was commonly accepted for structural representation[10], we follow the more recent trend of depicting the ferrocene structure with eclipsed rings as shown. The carbon positions are conventionally numbered as in Figure 4.2. Although readily subliming at temperatures exceeding 100°C and more slowly so at ambient temperature, the compound is remarkably heat-resistant. The electrical resistance is in the range of 10^{13}–10^{14} Ω cm. Spectroscopic data indicate the central metal atom to be unable to transmit inter-ring electronic effects,

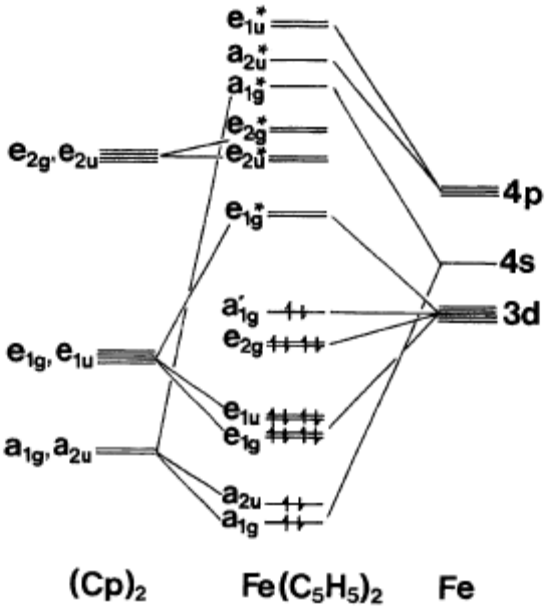


Figure 4.3 MO Diagram of ferrocene (D_{5d} symmetry assignments).

Whereas some intra-ring (notably between positions 1 and 3) transmission of such effects has been observed. This leads us to the topic of electronic structure, proficiently dealt with in Rosenblum's text[10] (although based there on the older D_{5d} symmetry assumption). Without delving into details at this point, we refer to the semi-quantitative molecular orbital diagram (Figure 4.3). The energy levels on the left hand side of the diagram belong to the pair of free cyclopentadienyl rings, and those on the right-hand side pertain to the free iron atom in the appropriate symmetry classifications. The centered energy levels consequently represent the orbitals of the molecule's metal-ring construct. Inspection of the relative energy levels and

electronic occupation permits the following conclusions: (1) All valence-shell electrons are paired; hence, the compound is diamagnetic. (2) Of the total of 18 electrons available for bonding, 12 reside in strongly bonding orbitals, leaving six electrons in the essentially non-bonding a'_1 and e_2 orbitals. This configuration is crucial as the presence of non-bonding electrons in these high-energy orbitals determines the compound's redox behavior and many of its chemical properties. It is from these orbitals that an electron can smoothly be removed, generating the cationic ferricenium species. Possessing an unpaired electron, the cation represents a typical free-radical (**Figure 4.4**).

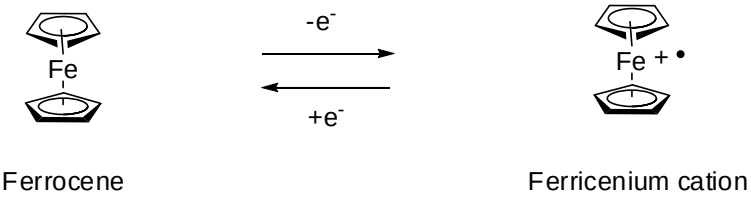


Figure 4.4 One-electron transfer in the ferrocene/ferricenium system.

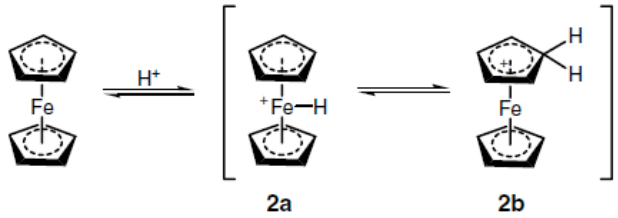
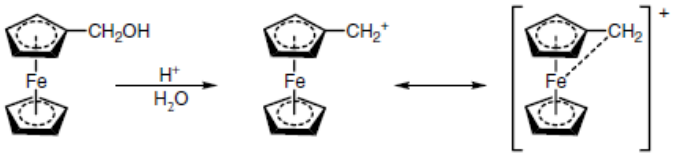


Figure 4.5 Ferrocene protonation.



3

Figure 4.6 Ferrocenylcarbinyl cation formation from ferrocenylmethanol.

(3) With the occupied non-bonding orbitals essentially located on the iron atom, substantial electron density resides around the metal center. This in turn facilitates iron protonation in an acidic environment (2a) and, in

consequence of this unusual configuration, a proton shift resulting in ring protonation as in the sigma complex 2b equilibrating with 2a (**Figure 4.5**). The loosely bound cationic ring in 2b is readily eliminated, leading to destruction of the complex in the presence of strong acids, and this deleterious reaction must be considered in experimental practice.

(4) The electron density on the metal center also accounts for the observed stability of the α-ferrocenyl carbenium ion, in which metal electron participation in the α-carbon electron shells through anchimeric assistance (**Figure 4.6**) leads to reduction of positive charge on that C atom with consequent lower activation energy in transitory states[11].

(5) The energy differential between the a'_{1g} and e_{1g}* orbitals of the rings and those of the metal causes some electronic charge to be drawn to the rings. This accounts for the observed residual p-electron density and resultant aromatic character of the ferrocene rings, facilitating electrophilic substitution, such as Lewis acid-catalyzed alkylation and acylation. The chemical consequences of the ring p-electron density have been amply addressed by Rosenblum[10] and elsewhere[12].

4.3.3 Redox properties of ferrocene

The electron transfer-reactive oxygen species-oxidative stress theory (ET-ROS-OS) has been implicated in the mechanism of action of a wide variety of biologically active compounds, for example nitroaromatics and quinones. Therefore the development of drugs that enhance Reactive Oxygen Species (ROS) has increased in importance. Also the fact that cancer tissue is known to be in a state of oxidative stress further increases the need for new drugs that can exploit this fact[13]. Increasing the concentration of ROS may overwhelm the cancer cells but leave normal cells unaffected. Elevated levels of ROS are also known to induce apoptosis. Current attention is concentrated on increasing concentration of ROS to lethal levels in cells, interfering with anti-oxidant enzymes and the promotion of catalysts that enhance the toxicity of the ROS. The loss of an electron from a high energy, non-bonding orbital to yield the ferricenium cation, (Fc - Fc^+), is an important aspect of the chemistry of ferrocene and is often implicated in its cytotoxicity[14]. This reversible one electron oxidation of ferrocene to yield the ferricenium ion is shown in **Figure 4.7.**

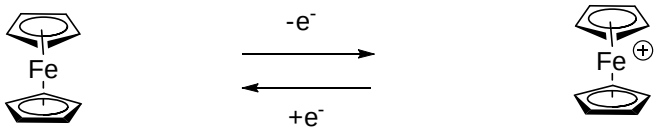


Figure 4.7 Reversible one electron oxidation of ferrocene to yield the ferricenium ion.

In biological systems ferrocene can be oxidized by hydrogen peroxide in the presence of horseradish peroxidase. The hydroxyl radicals formed from Fc^+ under physiological conditions are proposed to act as DNA damaging agents for biologically active ferrocene derivatives. The ferricenium cation has been shown to form charge transfer complexes with donor groups in proteins. The reverse reaction, (Fc^+ - Fc), is known to proceed through oxidation of metalloproteins, in the presence of glutathione forming hydroxyl radicals and through oxidation of NADH to NAD^+ [14]. The last oxidation is a good indicator of the ferricenium cations capacity for interfering with biologically important, enzyme controlled electron-transfer reactions. The redox status of a given biological system is vitally important as numerous processes in living cells are mediated by redox reactions. For example, cellular respiration whereby ATP is formed involves a series of reactions including the reduction of NAD^+ and oxygen and the oxidation of sugars. Redox activation of otherwise inactive prodrugs coupled with further chemical modification e.g. hydrolysis, can lead to highly reactive electrophilic compounds. A suitable bio-redox prodrug should have minimal toxicity to healthy cells, stability to metabolism in aerobic cells and suitable bioavailability and pharmacological properties.

Redox potential of ferrocene derivatives depends on the substituent on the cyclopentadienyl rings of ferrocene[15]. Electron withdrawing substituent increases the oxidation potential while electron donating substituent decreases the oxidation potential of ferrocene[16]. Thus, with a suitable substituent it should be possible to have a ferrocene derivative that can be applied in selective oxidative coupling or oxygenation reactions in the presence of other functional groups.

4.3.4 Basic electrochemical behaviors

A number of the ferrocene derivatives have been synthesized and used as electronic and optical materials because the cyclopentadienyl (Cp) ligand of ferrocene is readily functionalized by nucleophilic organic reagents and because of electrochemical properties of the Ferrocene fragment can be tuned by selecting the substituent's introduced on the Cp ligand. The oxidation between the neutral Fe(II) state and cationic Fe(III) state, involving fast and reversible electron-transfer, is the important property of the ferrocene derivatives. Introduction of electrochemically active organic groups on the ligand of ferrocene leads to molecules containing both organometallic and organic redox-active centers, which can be used as electrochemical materials in various applications.

4.3.5 Cytotoxicity of ferrocene

Although the anticancer potential of ferrocene had first been detected in the late 1970s, this field of investigation truly started after 1984, when Köpf-Meyer and Neuse disclosed the cytotoxicity or anti-tumour activity of ferrocenium salts (Fc^+)[17]. It has been proposed that ferrocenyl derivatives could be metabolically

oxidized in the cell to ferrocenium salts, and that medicines bearing either Fc or Fc^+ could be responsible for anti-proliferative effects[18]. The Fenton pathway and DNA involvement have been suggested for their mechanism of action[19]. After the facile oxidation of ferrocene by the metabolism or ROS to the ferrocenium radical cation (Fenton reaction), the iron compound can catalyze the formation of $HO^{\cdot}$ (Haber-Weiss reaction). It has been shown that these radicals influence the apoptosis of cells and can damage the DNA[20].

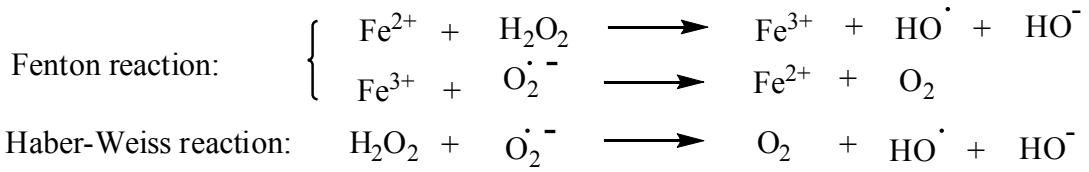


Figure 4.8 Fenton reaction and Haber-Weiss reaction.

4.3.6 Application of ferrocene in different fields

4.3.6.1 Ferrocene in organic synthesis

The use of ferrocenyl derivatives in organic synthesis for catalysis is becoming common; they are used in homogeneous catalysis[21] and in chiral catalysis, a review on chiral catalysis by ferrocene is published[22] which includes asymmetric hydrogenation of alkenes, ketones, and imines, asymmetric addition of hydrogen-heteroatom and heteroatom–heteroatom bonds to alkenes, asymmetric metal-catalyzed coupling reactions and related processes, asymmetric metal-mediated additions to carbonyl compounds and imines, asymmetric cycloaddition and other pericyclic reactions, asymmetric nucleophilic catalysis.

Derivative of ferrocene that is ferrocenyl phosphines have been employed in a variety of organic transformations. 1,1'-Bis(diphenylphosphino)ferrocene (abbreviated as dppf) (**Figure 4.9**) has been widely employed in various catalytic processes[23]. Although it has not only become a "ligand of choice" among diphosphines, its wide acceptance has also inspired the development of other derivatives[23]. The most widely used ferrocenyl phosphines in catalysis are shown in Figure below. The use of ferrocenyl phosphines in catalysis has the following advantages: Stable and easily handled, Readily tunable by variation of electronic and steric properties via chemical modification, Able to form complexes with a variety of transition metals in various oxidation states and coordination geometries, Ability to combine the planar chirality of the constituent ferrocene moiety with the chirality of other centers in the ligand backbone[24].

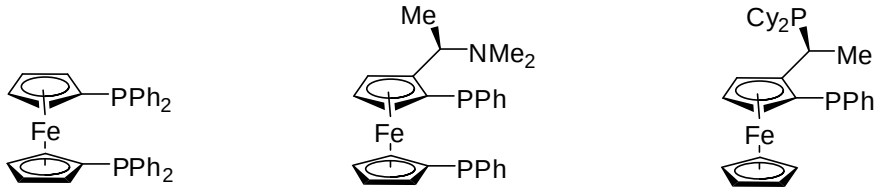


Figure 4.9 Examples of ferrocenyl diphosphino ligands.

The examples where the use of dppf has resulted in increased activity include, Suzuki-Miyuara cross-coupling reaction between organoboronic acids and halides is successfully supported by dppf. Kumuda-Hayashi[25], Heck[26], and Stille coupling reactions[27] involving rhodium, palladium and nickel complexes.

The dppf supported system has shown high activity and selectivity in the coupling between bromobenzene and the activated 4-bromoacetophenone with phenyl boronic acid[27]. The high performance of dppf is attributed to the large bite angle of the ligand that promotes interaction between the organic substituent thus driving the reductive elimination step[23].

Apart from C-C coupling, dppf has been successfully used as a ligand in a number of organic transformations such as hydroformylation[28], hydrogenation[29], hydroamination[30].

4.3.6.2 Material science

Ferrocene is a famous organometallic compound used for variety of applications due to its useful redox property and stability. This stability property has been utilized for sensors, surfactants, conducting electronic materials, and even molecular machines[31]. In addition, the accumulation of the redox center has been investigated in relation to multi electron-transfer, magnetic, and nonlinear optical devices[32]. While ferrocene is easily oxidized into ferricenium, which acts as a 1-electron acceptor, its non covalent sensitivity for various anions based on the hydrogen-bonding, electrostatic attraction, and topological effect has been investigated in previous studies of the ferrocenyl dendrimers[33].

4.3.6.3 Fuel additive

Ferrocene in particular, have been used rather extensively in the combustion area especially as fuel-additive. The properties of ferrocene which make it efficient fuel-additive are its solubility in conventional liquid fuels, as well as its thermal stability and vapor pressure. Ferrocene is soluble in a wide variety of organic

solvents, albeit to a varying degree depending upon the particular solvent selected[34], Its solubility is greatest in aromatic liquids. Since conventional jet fuels all have some aromatic character, ferrocene is soluble in them as well, which enhances the feasibility of ferrocene use to suppress soot in practical, large scale combustion devices.

Ferrocene is a small, strongly bound ligand. Very low pressure pyrolysis data have shown that ferrocene decomposition occurs only at temperatures of 1120*K and above[35]. Which is above the b.p. of the almost fuels, so the ligands stability is not a problem. The vapor pressure of ferrocene is high even at very modest temperatures[36]. This is a property crucial to the success of the experiment reported here since without it there would be no hope of observing an additive induced perturbation of the emitted soot.

Some of the important uses of ferrocene as a fuel-additive are. As a smoke inhibitor in jet and domestic burners, flow reactor acetylene pyrolysis, diesel combustion of petroleum hydrocarbons, aircrafts and utility gas turbine engines, poly (vinyl chloride) combustion, laboratory diffusion flames, and also used as gasoline antiknock agent, solid propellant burning rate enhancer, soot ignition temperature reducer

Figure 4.10 Burning crude oil (source- sintef Institute-Trondehim, Norway).

4.3.6.4 Bioconjugates of ferrocene

Ferrocene can be easily reacted with different biological molecules such as amino acids, peptides, proteins, DNA, RNA, PNA, carbohydrates, hormones etc. Ferrocene is covalently bonded to the biomolecule or it is also used in the form of salt in several applications. Ferrocene bioconjugates serves for biological purposes, for example, as an electron mediator between enzymes and an electrode, it serves as biosensor also ferrocene bioconjugates are applied in medicinal field. Neuse and co-workers found greatly enhanced

activity of cytotoxic metal compounds including ferrocene when these were bound to polymers as prodrug. Conjugates of ferrocene with well-known drugs were reported, for example, with antibiotics such as penicillins and cephalosporins, ferrocenyl aspirin, the anti-malarial drugs ferroquine, quinine, mefloquine, and artemisinin, and the anti-cancer drug ferrocifen.

Schlogl reported the first ferrocenyl amino acids[37], Bergs, Severin, and Beck have published a fairly comprehensive article on bioorganometallic derivatives of amino acids and peptides[38]. Ryabov has reviewed the interaction of organometallic compounds with enzymes and proteins[39]. Very recently, Salmain and Jaouen published a review on the covalent labeling of proteins with organometallic complexes[40]. Two older reviews on the biological chemistry of metallocenes have appeared[41]. More specialized reviews cover related aspects of ferrocene chemistry, such as, for instance, applications of the compound in glucose biosensors and bioelectronics[42]. An excellent Russian review on ferrocene-containing nucleic acids[43] and Very recently, a nice review on bioorganometallic chemistry of ferrocene[44] have been published

4.3.6.5 Bio-analysis

A) Ferrocenyl derivatives in DNA detection

One of the recent fields of research in organometallic chemistry is the synthesis and development of DNA detection sensing systems. Such systems (chips) enable quick, simple, sensitive and low-cost gene diagnosis by the electrochemical detection method. To construct such a system, it is important to develop a reproducible method to immobilize a capture DNA probe on the gold surface. Electrochemical systems for DNA detection are potentially cheaper and more reliable than the conventional fluorescence spectroscopy. Ferrocene and its derivatives are often used in such devices because of their favorable electrochemical properties. Several reviews have been published recently covering this topic[45].

B) Scanning electrochemical microscopy of HeLa cells[46]

The viability and activity of HeLa cells were probed using scanning electrochem microscopy (SECM). The feedback generated by HeLa cells during scanning depends on the electrochem. mediator. Living HeLa cells generated pos. feedback when ferrocene methanol (FcMeOH) was oxidized at the tip, showing that the cells reduced $FcMeOH^+$. The pos. feedback with FcMeOH changed to neg. feedback when the HeLa cells were exposed to toxic treatments, i.e. CN- or UVC radiation, suggesting that $FcMeOH^+$ reduction can be used to monitor cell activity. Living HeLa cells also accumulate FcMeOH after exposure times of a few hours, but the presence of mM concns. of FcMeOH has no apparent effect on the cell viability.

4.3.6.6 Organometallic polymers

Organometallic polymers have attracted attentions in recent years due to the fact that polymers containing metals might be expected to possess properties different from those of conventional organic polymers[47]. The prospective for the defined introduction of metal-containing components into structures with controlled hierarchical order is particularly fascinating and, if achieved, would make a significant input to one of the major areas of synthetic challenge in the 21st century[48]. They can be used in a wide range of applications including resins for ion and electron exchange, radiation-resistant polymers, flame-retardant polymers, catalysts, organic semi-conductors, photoconductors, Ferro magnets, and biosensors[49]. Outstanding properties of ferrocene-containing polymers including air, heat, and photochemical stability make them suitable for a variety of applications including thermally stable lubricants and thermally stable elastomers[50]. The continuous interest in ferrocene is in part due to the rich chemistry of iron (II) center and the broad range of synthetic methods available for functionalizing the cyclopentadienyl ligands[51].

4.3.6.7 Ferrocene in medicinal chemistry

Ferrocene is becoming a popular substituent in medicinal chemistry, and in favorable cases, it can potentiate the biological activity of the parent compound. Since Kopfmaier and his colleagues[52] first discovered the antiproliferative efficiency of ferrocene compounds by the example of ferricenium salts, a number of detailed reviews committed to the bio-organometallic chemistry of ferrocene compounds have been published[53]. Incorporation of ferrocene fragment into the molecule of an organic compound often leads to unexpected biological activity, which is due to their different membrane permeation properties and anomalous metabolism[54]. Moreover, ferrocene as a redox mediator might involve in metabolism in organism[55]. Hence, ferrocene and its derivatives could be considered as a potential agent and applied to medicine.

Several reviews have been directed to the chemistry of ferrocene: Dyson et al. focused their review on the properties of organometallic compounds that make them suitable for pharmaceutical applications[56]; Neuse devoted his review to the macromolecules containing ferrocene in the cancer research[57]; and Metzler-Nolte et al.[58] and also Fish et al.[59] directed their reviews to the bioorganometallic chemistry of ferrocene. Therefore, medicinal application of ferrocene is an active research area and many reports have shown that ferrocene derivatives have a highly promising activity in vitro and in vivo against several diseases. Review focusing on the promising results of the ferrocene derivatives including their effect against certain diseases in the last decade is published[60].

Ferrocene itself exhibits interesting properties such as antianemic[61], antiseptic[62], or cytotoxic agent and its derivatives shown significant activity as antifungal, antimalerial, anticancer, antimicrobial[63], anti-HIV-1[64], antioxidant[65], and insecticidal, PDE4 inhibitory activities[66].

4.3.6.6.1 Antibacterial compounds

Pioneering work on organometallic complexes with organic ligands of known antibacterial properties began with the work of E I Edwards in the 1970s. Utilizing the ferrocenyl group as the relevant organometallic centre, this work outlines derivatization of one Cp ring with penicillin, cephalosporin, or hybrids including both of these b-lactam antibiotics.

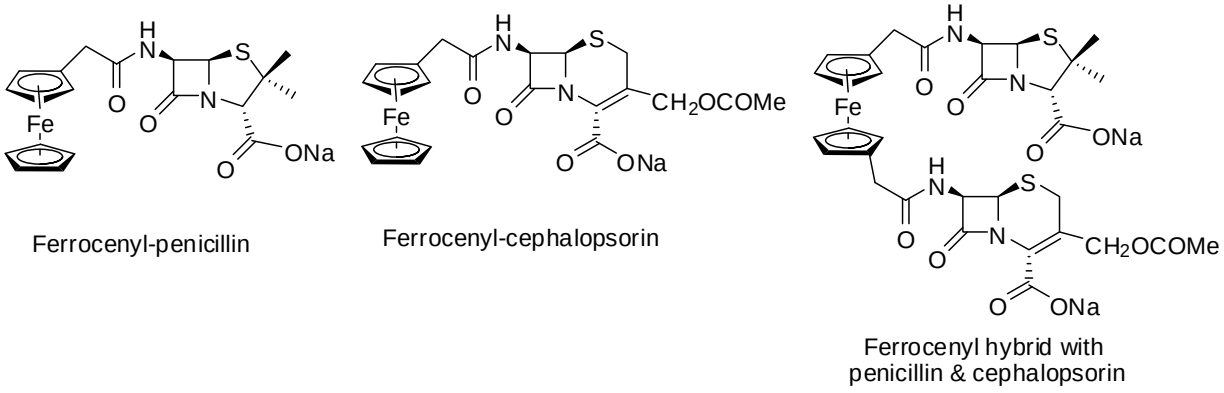


Figure 4.11 antibacterial compounds containing ferrocene unit.

The impetus in this work is undoubtedly to combat acquired antibiotic resistance by the general population. These compounds act as b-lactamase inhibitors, restricting the activity of this enzyme in the cleavage of the four-membered b-lactam ring.

4.3.6.6.2 Anticancer Treatment

In 1984 Kopf-Maier et al. published the results of antitumor activity of ferricenium salts[67]. It was established that the ferrocene compounds should be positively charged in order to display antitumor activity. However, later the antitumor activity of uncharged ferrocene compounds – ferrocenylalkyl azoles[68], ferrocene-modified complexes of platinum(II)[69] macromolecular ferrocene bioconjugates[70] and

ferroceneconjugates of polyaspartatamides[71] was shown. It is belived that[72] these originally uncharged compounds may acquire the charges during their transportation in biological systems (via oxidation to ferricenium salts or protonation of nitrogen containing heterocyclic moieties). The ferrocifens (i.e. ferrocene-modified tamoxifens), which exhibit strong antiproliferative effects not only in hormone dependent but also in hormone-independent breast cancer cells and also polyphenolic ferrocenyl derivatives have shown same activity.

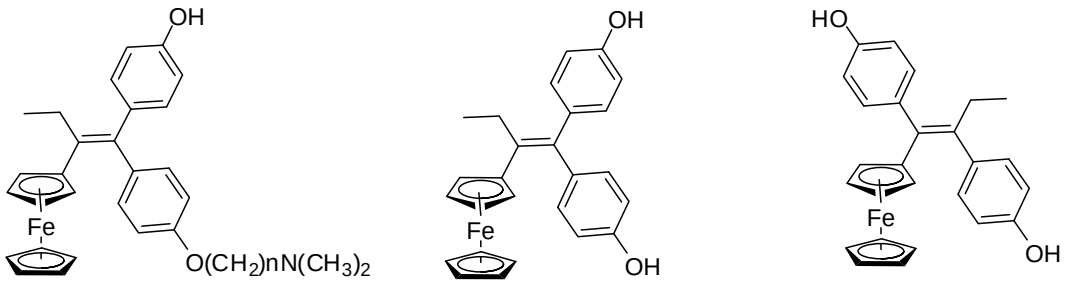
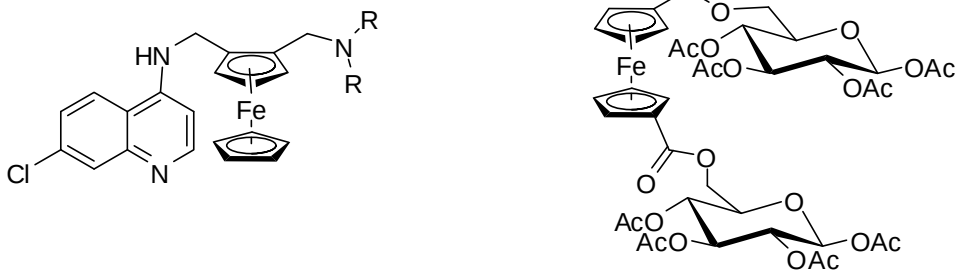


Figure 4.12 ferrocefen and polyphenolic ferrocenyl derivatives as anticancer.

4.3.6.6.3 Antimalerial

Out of four parasite species of malaria, Plasmodium falciparum is becoming resistant to the traditional drugs like chloroquine (CQ), mefloquine and quinine. Ferroquine derivatives are novel antimalarial compounds designed to overcome the CQ resistance. Ferroquine is a combination of ferrocene and chloroquine. Along with this some derivatives of ferrocene shown good antimalerial activity like ferrocene chalcones and ferrocene derivatized carbohydrate compounds, in ferrocene carbohydrate as antimalerial drug the elevated glucose consumption by infected erythrocytes is a good strategy of specific targeting infected cells.



Ferroquine

Ferrocenyl carbohydrate conjugate

Figure 4.13 Ferroquine and ferrocenyl carbohydrate conjugate.

4.3.6.6.4 Activity of ferrocenyl derivatives against AIDS (HIV)

The Champdore et al[73]. Prepared some adducts by incorporating the ferrocene methyl moiety into a heterocyclic base, which were evaluated against HIV-1, HBV, YFV, BVDV and several bacteria. Only compounds bearing thymine showed significant cytotoxicity against MT-4 cells. The ferrocenyl derivatives of 3-deoxy-3-aazidothymidine were the sole compounds active against HIV-1.

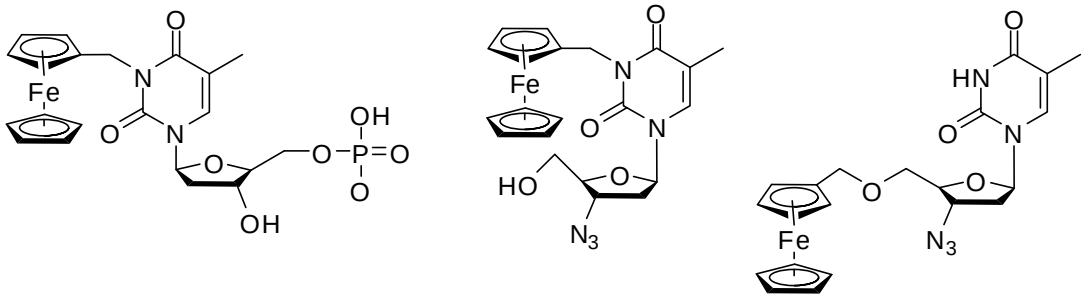


Figure 4.14 ferrocenyl compounds showing activity against AIDS (HIV).

4.3.6.6.5 Antifungal compounds

Until now several ferrocene derivatives were prepared and tested as antifungal agents such as, ferrocene fluconazole[74], ferrocene 1H-1,2,4-triazole alcohols[75], 2-ferrocenyl benzimidazoles[76], ferrocene-triadimefon[77], ferrocene triadimefon and triadimenol[78], ferrocene dithiothione and dithioketone[79], ferrocene carbohydrates[80], 1,1-bis(aroyl)ferrocenes and their derivatives[81], ferrocenyl-substituted azaheterocycle compounds[82].

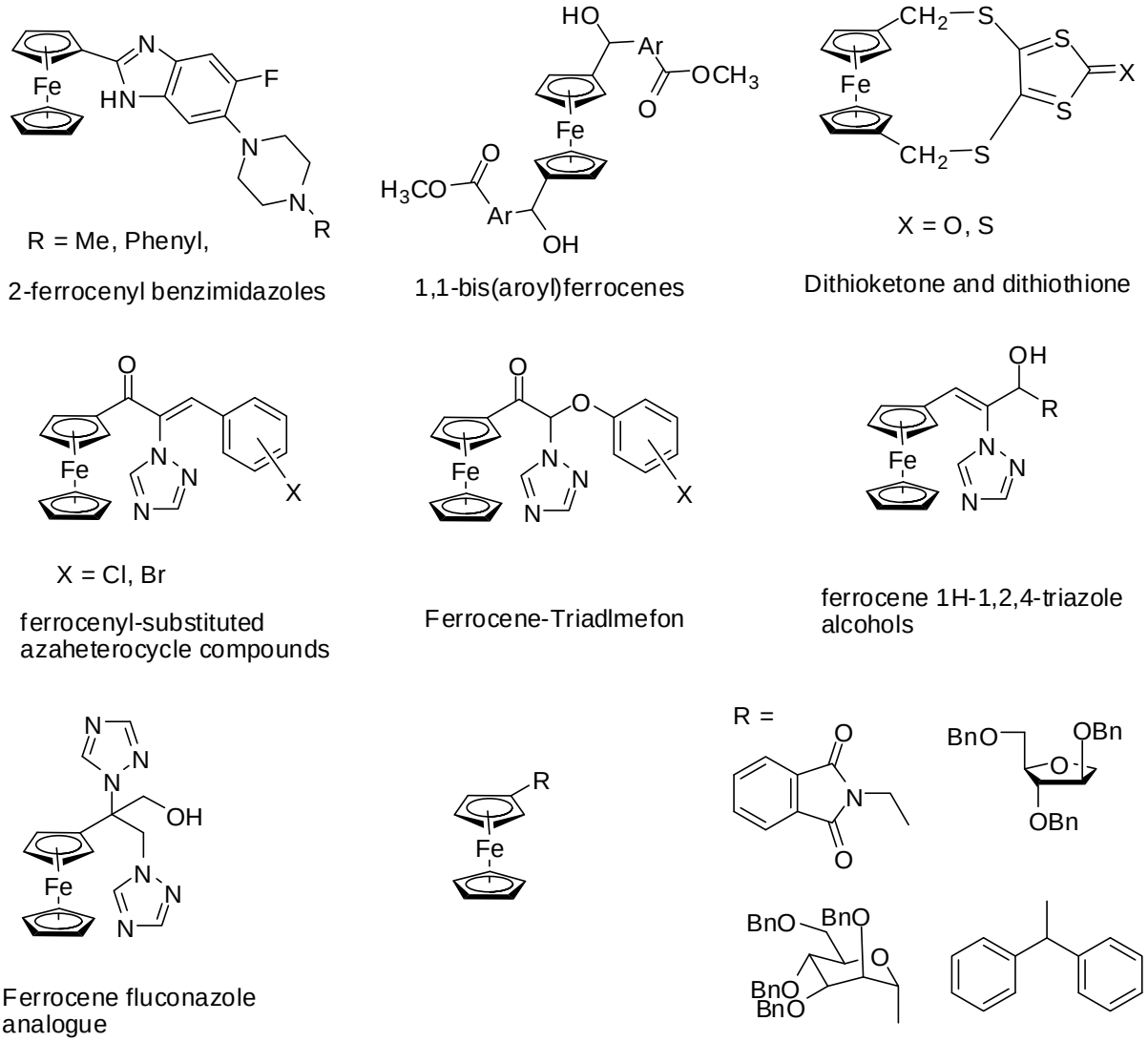


Figure 4.15 Ferrocene compounds showing antifungal activity.

4.4 Introduction (synthesis and discussion)

In search of simple ferrocenyl-substituted potential biologically active molecules, to synthesize in easy and cheap way, a series of novel ferrocene glycerol derivatives were prepared and their antifungal activity was tested. These novel organometallic compounds were synthesized by etherification reaction, taking advantage of the ferrocenemethanol spontaneous solvolysis that occur in glycerol derivatives, which allow working without solvent and acid catalyst, in high yield and with good selectivity. These reactions can be promoted by carbon dioxide catalysis, but effectively only in the reactions with substrate having vicinal hydroxyl groups. Because of clean reactions and the biocompatibility of glycerol and glycerol derivatives, for particular applications crude reaction mixtures can be directly applied without work-up by diluting reaction mixture, for example in some biological activity testing's. In addition, the novel ferrocenyl derivatives synthesized are multifunctional compounds suitable for further functionalization to give molecules, including polymers, with high potentiality to be used in the manifold fields, where ferrocene derivatives found several applications.

All the derivatives synthesized here are resulting from the direct etherification of ferrocenemethanol with glycerol and its derivatives. Though synthesis of ethers, looks very simple synthetic route on the paper, by direct condensation of alcohols, but often practically, this reaction need acid, base or even heavy metal as a catalyst and care to shift the unfavorable equilibrium to the products and some times halogenated solvents.

From the literature it is already known that the acid promoted condensation of ferrocenemethanol with alcohols to give the corresponding ethers, by S_N1 reactions, involving ferrocenylmethyl cations. The reactivity in presence of Lewis or Brønsted acids, such as acetic acid[83a], TFA[b], sulphuric acid[c], Ytterbium triflate[d], Indium Tribromide[e], cerium ammonium nitrate (CAN)[f], and the comparative reactivity of different acid catalyst like CAN, $InBr_3$, $Zn(OTf)_2$, AgOTf, $Yb(OTf)_3$, $Bi(OTf)_3$, $Al(OTf)_3$ and (TfOH) with alcohols, are reported[g]. In these reactions, ferrocenemethanol proved to be efficient starting material, when used mainly in halogenated solvents[h].

However, as recently reiterated by E. Elmer et *al*[84], several S_N1-type reactions can be performed under more safe, economical and green conditions just by appropriate combinations of the reactants, so as to take advantage of their intrinsic electrophilic and nucleophilic properties. On these bases we decided to perform direct nucleophilic substitution S_N1-type reaction with appropriate alcohols that is glycerol derivatives, in the absence of solvent and acid catalyst, taking advantage of the peculiar high degree of stability and unusual reactivity of ferrocenylmethyl cation which has been reported in literature.

In 1959, it was reported that ferrocenylmethyl acetate undergoes S_N1 solvolysis at a similar rate to triphenylmethyl acetate[85], the 1,2-rearrangement of tertiary 2-ferrocenylethyl cation[86], cyclopropylferrocenylmethyl cation[87], and stability comparable to the trityl cation[88]is reported. The ^{13}C-NMR spectra of ferrocenylmethanol in sulfuric acid[89], indicate that ferrocenylmethyl cation is stable specie and the ferrocenyl group strongly delocalizes the positive charge of adjacent carbenium ion[90]. X-ray diffraction studies of diferrocenylmethyl tetrafluoroborate, have shown that exocyclic carbon atom deviates from the plane of the adjacent cyclopentadienyl ring and bends towards the iron atom by an angle of 17-20

degree, therefore confirming a weak, but existing, Fe-CHR^+ bonding interaction, as already hypothesized in 1968 by Hill and Wiesner[91], (see **Figure 4.16**).

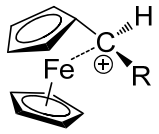


Figure 4.16 Fe-CHR^+ bonding interaction.

Several works reported in literature shows that ferrocene unit, attached to complex biological molecules, has shown good biological activity. By emphasizing on this point we decided to synthesize simpler ferrocene derivatives with glycerol unit, which is a fundamental widespread molecule in biological systems, for example in the form of phospholipids and fats as energy storage. Moreover, its involvement in several metabolic processes makes glycerol derivatives relatively safe, biodegradable.

Furthermore, the ferrocenyl methyl ethers and its derivatives are easy to synthesis and their characteristic free chemical functions still available opens to a versatile chemistry, such as for the synthesis of polymers and functional materials containing ferrocene unit, which can found widespread applications in the numerous fields[92] where ferrocene derivatives are largely utilized.

4.4.1 Synthesis of Novel 1-Ferrocenylmethylglycerol derivatives

Synthesis of novel 1-ferrocenylmethylglycerol ethers was carried out by reacting ferrocenylmethanol with the glycerol and glycerol derivatives such as diglycerol, glycerol carbonate, glycidol, glycerol formal and cyclohexanone glycerol ketal in very short time, at room temperature(30-90°C), in mild conditions, and in the absence of solvent and acid catalyst or CO_2 was used as an catalyst, S_N1 induced dissociation of ferrocenylmethanol to ferrocenylmethyl carbocation is promoted by polarity and intrinsic acidity of glycerol derivatives. Reactions were selective with primary (terminal) alcoholic(-OH) group and selectively mono substituted products were obtained, Glycidol and simple aliphatic primary alcohols does not react under these conditions but ferrocenylmethyl ethers can be prepared by using acid catalysis.

Thanks to the low cost and availability of the glycerol and glycerol derivatives, the reactions can be performed in large excess of substrate, with all the advantage that this opportunity provides. So the reactions here reported were conducted with a molar ratio substrate/ferrocenemethanol 10/1, 5/1 and 1/1 ratio, When reactions were carried out with limited amount of substrate that is with high concentration, the reactions results faster but less selective, when more than one reactive hydroxyl group was present in the substrate disubstituted products obtained in small quantity. Also it is interesting to observe that working at lower ratio, the formation of diferrocenylmethyl ether ($FcCH_2OCH_2Fc$) occurs(**Figure 4.17)**, but at 90°C this compound behaves as a reactive intermediate that is converted quantitatively to **3**. For example, in the case of the glycerol carbonate reaction, performed at 90°C with ratio 1/1 substrate/ferrocenemethanol, the formation of diferrocenylmethyl ether is evident just after few minutes, but in 15–20' minutes it is fully converted to the derivative **3a** (**see Table 4.1**).

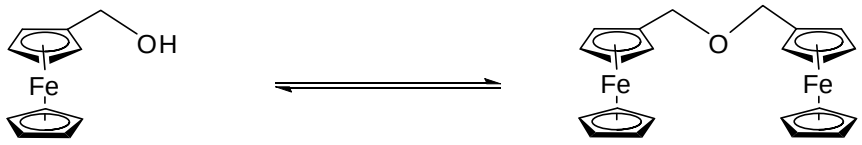
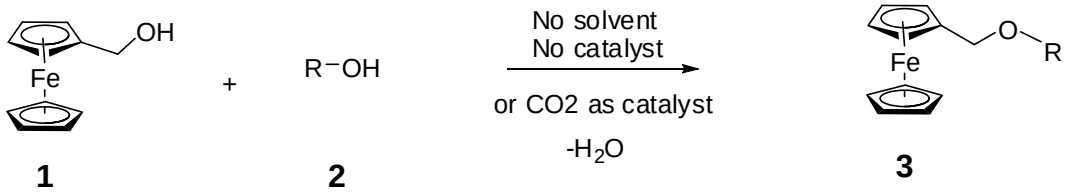


Figure 4.17 Reversible reaction of formation of diferrocenylmethyl ether.

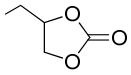
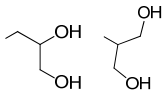
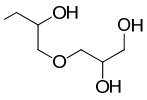
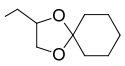
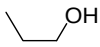
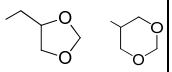
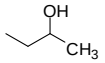
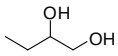
Following is a concise description of the reactions which were investigated, at different concentrations and reaction conditions, with the more significant substrates, starting from the most reactive substrate first. Some considerations about the different chemical reactivity of the substrates studied are commented at the end of this section.

General reaction

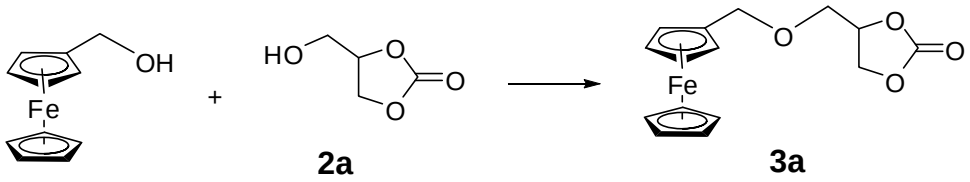


Scheme 4.1 General reaction of Ferrocenemethanol with glycerol derivatives.

Table 4.1 The ferrocenylmethyl derivatives 3a-i synthesized in different operative conditions.

	R 2,3	Molecular Dipole Moment (D)		Cat.	T°C	Time	1/2 molar ratio	1 Conv. (%)	3 Yield (%)
		Exp.	Calc.						
a		5.50	4.49	no TFA	50 50	15' 2-3'	1/10 1/10	100 100	97 95
b	 1 2	2.56	3.10	no CO_2 no no TFA	60 60 90 90 60	22 h 4.5 h 3 h 2 h 10-15'	1/10 1/10 1/10 1/5 1/10	98 98 98 100 95	88, 10 89, 09 87, 10 72, 24 63, 22
c		-	2.88	no CO_2 No TFA	60 60 90 60	42 h 18 h 18 h 15-20'	1/10 1/10 1/10 1/10	92 96 99 99	54 62 66 50
d		-	2.0	no no no	25 60 90	72 h 21 h 15 h	1/10 1/10 1/10	99 58 99	92 57 98
e		2.41	2.44	no CO_2 no	60 60 60	48 h 24 h 120 h	1/10 1/10 1/10	95 75 77	80 73 75
f	 1 2	- (1) 2.64(2)	2.42(1) 2.63(2)	no no	60 90	114 h 48 h	1/10 1/10	32 100	22, 09 60, 40
g		1.44	1.8	no TFA	60 25	2 h 1 h	1/10 1/10	0.0 98	0.0 65, 30
h		-	-	No Acetic acid	60 60	14h 5h	1/10 1/10	20 99	≈ 4 93
i		2.56	3.10	no	60	16h	1/10	100	40:40:20

4.4.2 Reaction of ferrocenemethanol with glycerol carbonates (2a)



Scheme 4.2 Reaction of ferrocenemethanol with glycerol carbonates.

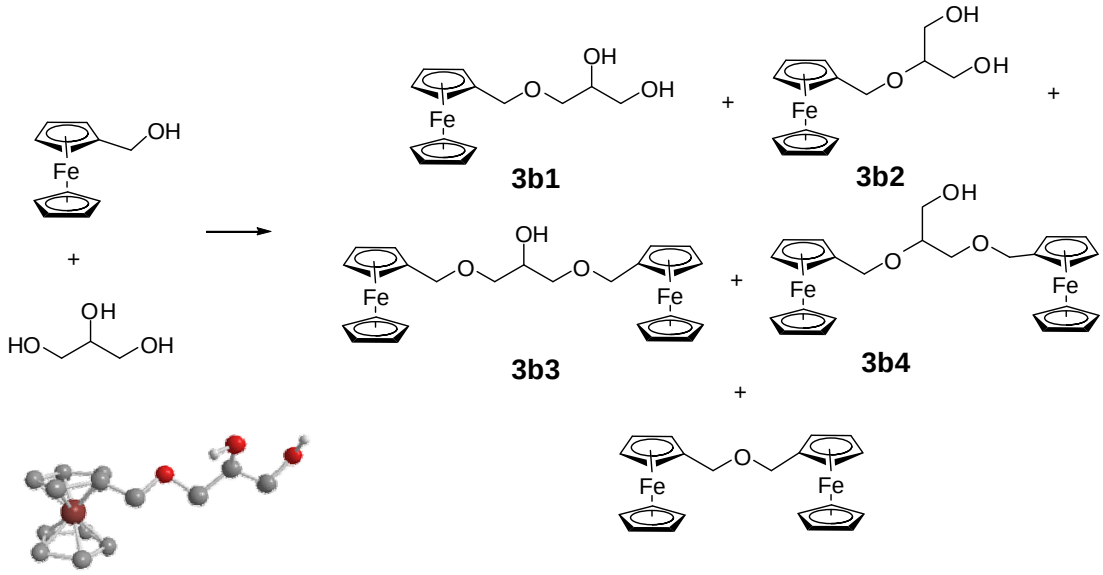
The glycerol carbonate react very quickly with ferrocenemethanol at 60°C and in absence of acid catalyst, to give the corresponding ether **3a**. In 30 minutes the reaction is almost complete to give a single product, easily recovered from the reaction mixture as yellow solid. When reaction was carried out at lower molar ratio of substrate/$FcCH_2OH$ from 10/1, 5/1 to 1/1 ratio, the reaction results faster and clean. When reaction was carried out with catalytic amount of trifluoroacetic acid reaction was very fast, complete in 2-3 minutes (The carbonyl group of glycerol carbonate is stable in presence of acid ex. sulfuric acid). We have also noticed that under CO_2 atmosphere, the kinetic of the reaction is not improved at all. Working in pseudo first order conditions (120/1 molar ratio substrate/$FcCH_2OH$), at 60°C a kinetic constant of $k_{oss} = 1.17 \cdot 10^{-1}$ min.$^{-1}$ is measured. This product **3a** was characterized by IR, NMR, mass and all data is reported in experimental part.

4.4.3 Reaction of ferrocenemethanol with glycerol (2b)

glycerol was selected as a model substrate for reaction, and the etherification of this substrate in various conditions was studied. Ferrocenemethanol react with glycerol very selectively, glycerol has two primary and one secondary hydroxyl group, reaction is possible with all three hydroxyl groups, mono substituted products were obtained in major quantity. Where as ferrocenemethanol shown very selective reactivity towards primary hydroxyl group giving major product(**3b1**), where as with Secondary hydroxyl group reacted less giving minor product (**3b2**), where as disubstituted products (**3b3** and **3b4**) were obtained in trace amount. But when reaction was carried out by using acid as a catalyst the amount of disubstituted products found to be increased.

The reaction ferrocenemethanol with glycerol working at 60°C (glycerol/ferrocenemethanol ratio = 10/1), gives the derivative **3b1** in good yield and selectivity, the isomer **3b2** is formed only in the 9% yield (ratio of **3b1**/**3b2** = 8.8). In these conditions the reaction is complete in less than 24 hours. The same

reaction with the same selectivity can be performed in 3 hours just by working at 90°C temperature. The reaction is faster using a glycerol/ferrocenemethanol ratio = 5/1: in this case the starting material is fully converted in 2 hr but with less selectivity.



Scheme 4.3 Possible products by the reaction of ferrocenemethanol with glycerol.

The same reaction at 60°C can be significantly speed up by CO_2 catalysis just by working in atmosphere of carbon dioxide, the reaction is completed in around 4 hr with the same selectivity found in absence of catalyst.

When the same reaction was carried out with the help of TFA as catalyst reaction got completes in 10-15 min. and in polar solvent like DMSO at 148°c in 6 hr without catalyst.

The pseudo first order kinetic constant observed for glycerol/ferrocenemethanol reaction at different concentration ratio at 60°C was (under CO_2 atmosphere for10/1) 10/1 and 120/1 $k_{oss} = 1.44 \cdot 10^{-2}$ min.$^{-1}$ and $k_{oss} = 3.50 \cdot 10^{-3}$ min.$^{-1}$ respectively.

Have to be underlined that ferrocenemethanol reacts with the same efficiency also using crude glycerol coming directly from biodiesel synthesis plant, without further purification (glycerol 85% the analysis data is presented in **Table 4.2**).

Table 4.2 Analysis of Impure glycerol directly coming from biodiesel plant.

	Impurities	percentage
1	Glycerol	85 %
2	Water	7.9 %
3	MeOH	0.08 %
4	Ashes	6.0 %
5	MONG	0.72 %
6	P^H	5.6
7	Color	Dark thick oily

The product shown good solubility in water, Solubility measured at different conditions 1) In water excess of compound was added and at 80°C the solution was heated up to saturation then solid filtered and remaining solution was concentrated and obtained solubility 340mg/58 ml (5.862 g/liter). 2) 100mg of compound was taken and dissolve in water at room temperature (20-22°C) by adding water portion wise and found 100mg/20 ml (5.0 g/liter)

These products **3b1, 3b2, 3b3, 3b4** were characterized by IR, NMR, mass and all the data is reported in experimental part.

Reaction of ferrocenemethanol and glycerol in presence of different Acid catalyst

The reaction of ferrocene methanol and glycerol was carried out at 50-60°C temperature, with different acid catalyst such as trifluoroacetic acid (TFA), methylsulfonic acid (MSA), Acetic acid, or in solvent such as THF, or without catalyst in neat at higher temperature 90°C and also in presence of water (5% mol) and results obtained are summarized in the table below. The reaction in presence of acid is very fast it completes in few minutes but with the loss of selectivity.

Table 4.3 Different Acid catalyst for the reaction of ferrocenemethanol and glycerol.

Rea. no	solvents	Catalyst in %	Temp (°C)	Time (min)	Ferrocenyl methanol	Yield %	selectivity
1	neat	TFA(4% wt)	50	10-15	0.0	80	75
2	neat	MSA(1.3%)	50	60	0.08	75	90
3	neat	AcOH (5%)	60	135	0.05	66	82
4	THF(1:1)	MSA (3%)	50	70	0.2	80	75
5	neat	-	90	70	1.1	88	95
6	5% H_2O	-	90	85	1.2	90	92

Table 4.4 Reactions of ferrocenemethanol with pure glycerol with different concentration.

Ferrocene methanol : pure glycerol	Temperature °C and time	Ferrocene methanol	Diferrocenyl methyl ether	1,2 and 1,3 disubstituted	Ferrocenyl methyl glycerol ether
1 : 10	60 after 20 hr	10.7 %	10 %	0.7 % : 1.5 %	74.9 %
	90 after 1 hr	0.4 %	3.6 %	1.5 % : 2.2 %	88.2 %
	90 after 20 hr	0.0 %	0.0 %	> 3 %	95.2 %
1 : 5	60 after 20 hr	27 %	21.8 %	1.5 % : 3.8 %	44.3 %
	90 after 1 hr	4.5 %	12.5 %	1.5 % : 4.2 %	77.2 %
	90 after 20 hr	0.09 %	-	7.2 : 11.6	80.0 %

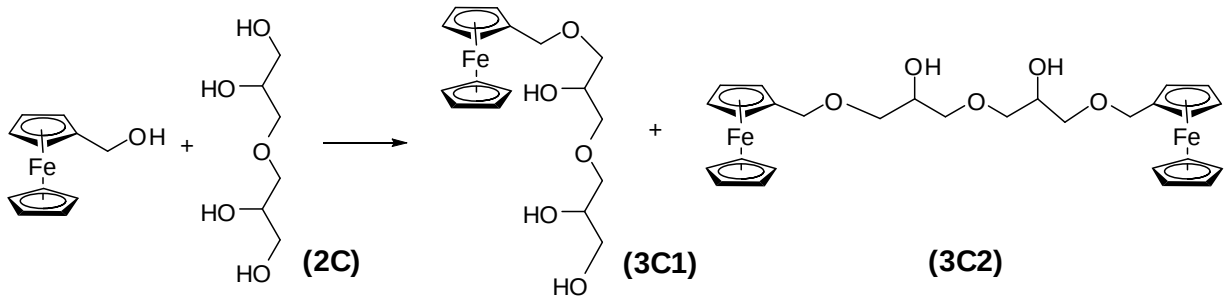
We carried out some reactions of ferrocenemethanol and pure glycerol purchased from Aldrich Company and also with impure glycerol directly obtained from biodiesel plant without further purification at different temperature and concentration as mentioned in the tables 4.4, all reactions with time interval were analyzed with the help of HPLC and result obtained are also reported in the tables 4.4.

Table 4.5 Reactions of ferrocenemethanol with crude Glycerol (**Table 4.2**) with different concentration

Ferrocene methanol : glycerol	**Temperature °C and time In min**	**Ferrocene methanol**	**Diferrocenyl methyl ether**	**1,2 and 1,3 disubstituted**	**Ferrocenyl methyl glycerol ether**
1 : 10	90 after 40	33.30 %	1.83 %	-	64.32 %
	90 after 90	25.92 %	2.8 %	-	70.65 %
	90 after 150	00.19 %	1.7 %	-	97.19 %
1 : 5	90 after 40	63.86 %	4.8 %	-	31.12 %
	90 after 90	37.85 %	4.8 %	-	57.00 %
	90 after 180	34.58 %	5.9 %	-	63.05 %
	90 after 214	17.00 %	6.6 %	-	70.00 %
1 : 1	90 after 40	15 %	6.1 %	-	78.75 %
	90 after 90	9 %	5.64 %	-	85.34 %

4.4.4 Reaction of ferrocenemethanol with α,α'-Diglycerol (2c)

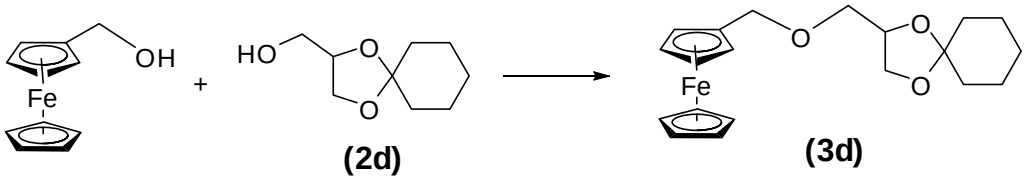
α,α'-Diglycerol reacts slowly than glycerol in the same conditions reason might be the viscosity of diglycerol with this substrate, the reactions at 60°C and 90°C are completed in 42 and 18 hours respectively. Again, it is evident that the reaction time is reduced from 42 to 18 hours at 60°C when carbon dioxide is used as catalyst. The commercial α,α'-diglycerol used is a mixture of at least three isomers; so, the crude reaction mixture consists of several ferrocenylmethyl derivatives with preference for the α,α'-compound **3c1**, isolated by flash column chromatography in 60 % yield. With this substrate, CO_2 and temperature have moderate effect on the selectivity of the derivative **3c1:** at 60°C the yield is 54% but in the presence of CO_2 is improved to 62%**,** whereas in absence of CO_2 at 90°C the yield of **3c1** is 66% (see **Table 1**). These products **3c1 and 3c2** were characterized by IR, NMR, mass and all data is reported in experimental part.



Scheme 4.4 Reaction of ferrocenemethanol with α,α'-Diglycerol.

4.4.5 Reaction of ferrocenemethanol with cyclohexanone glycerol ketal (2d)

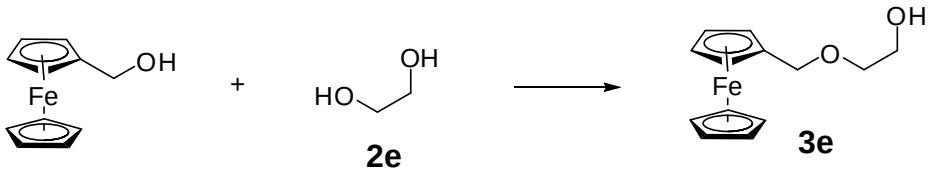
Reaction of cyclohexanone glycerol ketal with ferrocenemethanol is little bit fast than diglycerol at 60°C, while at 90°C is more reactive. At room temperature reaction is possible, it got complete in 3 days, at 60°C temperature reaction completes in 4-5 hr and at 90°C in 2 hr. Note that also in this case the carbon dioxide does not improve the reaction rate. This product **3d** was characterized by NMR & mass and all the data is reported in experimental part.



Scheme 4.5 Reaction of ferrocenemethanol with cyclohexanone glycerol ketal.

4.4.6 Reaction of ferrocenemethanol with ethylene glycol (2e)

Ethylene glycol is not a glycerol derivative but its reaction with ferrocenemethanol was investigated to compare its reactivity with glycerol and diglycerol, considering the structural and functional analogies between these compounds. When ferrocene methanol/ethylene glycol ratio is 1/10 at 60°C temperature reaction got complete in 48 hr and when ratio is 1/120 the reactivity of ethylene glycol with ferrocenemethanol is very slow: after 48 hr the conversion of the starting material to give the corresponding hydroxyl ether, is only 75% but, again, significant improvement of the reaction rate was observed in presence of CO_2 (in 24 hours yield was 73%). This product **3e** was characterized by IR, NMR, mass and all the data is reported in experimental part.

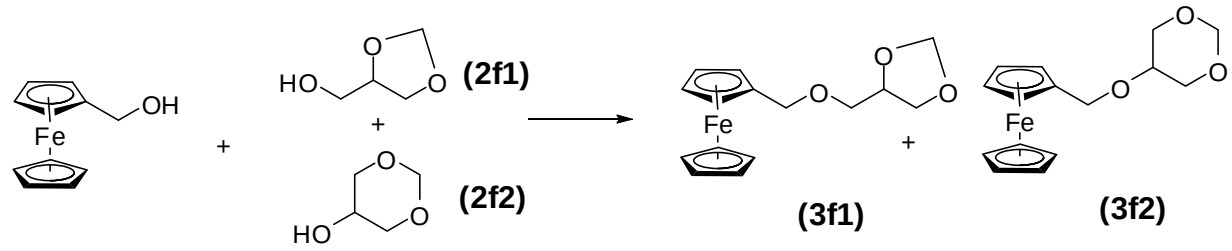


Scheme 4.6 Reaction of ferrocenemethanol with ethylene glycol.

4.4.7 Reaction of ferrocenemethanol with Glycerol formal (2f1 + 2f2)

Glycerol formal reacts very slowly with ferrocenemethanol, at room temperature it is not reacting at all but, at 60°C both in the absence and presence of CO_2 it reacts but very slowly. In these two cases after 4 days, the conversion of the starting material is found to be lower than 40%, and also CO_2 does not improve the rate of reaction. At 90°C reaction got complete in 48 hr. However, it must be taken into account that the glycerol formal is a mixture of two isomers in the ratio **2f1/2f2:** 40/60**, where 2f1** is a primary alcohol five member ring derivative and **2f2** is a secondary alcohol six member ring derivative. From the reaction products distribution (see **Table 1**), it is evident that the primary alcohol **2f1** reacts faster than **2f2**. So,

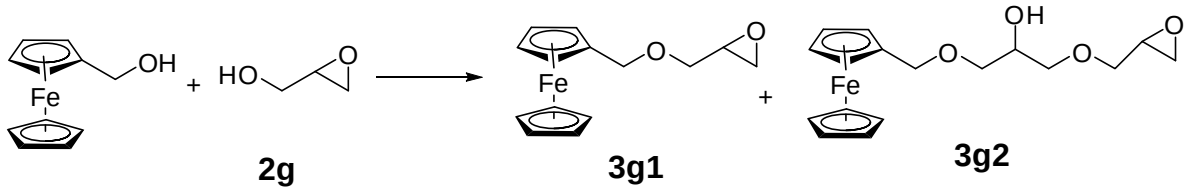
taking in account that the more reactive isomer **2f1** is present in lower concentration, the reactivity of the ferrocenemethanol with this primary alcohol have to be consider higher than the apparent rate observed on the base of the ferrocenemethanol disappearance. Better results, in terms of reaction rate, were obtained working at 90°C and with a molar ratio substrate/ferrocenemethanol = 10/1. In this case, full conversion of the starting material occurs in 48 hours but, as expected, with some loss of selectivity (ratio of **3f1/3f2** passes from 2.4 to 1.5 from low temperature to higher temperature and concentration). These products **3f1 and 3f2** were characterized by NMR & mass and all data is reported in experimental part.



Scheme 4.7 Reaction of ferrocenemethanol with Glycerol formal.

4.4.8 Reaction of ferrocenemethanol with glycidol (2g)

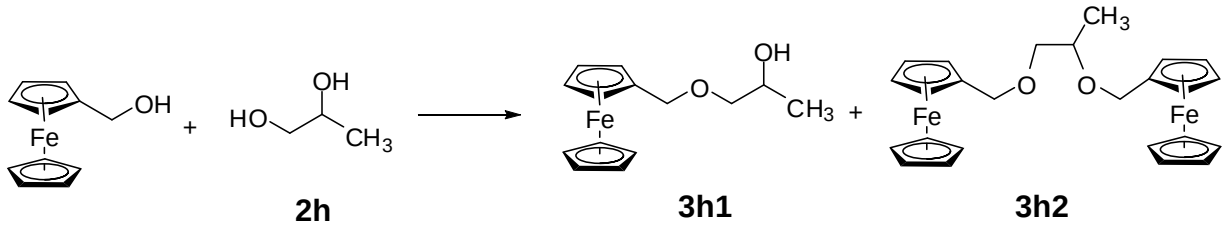
The reactivity of glycidol with ferrocenemethanol is so low that a conventional acidic catalyst must be used to carry out the reaction, but just a 0.02 % (v/v) of TFA is enough to complete the reaction in less than one hour at 25°C. These products **3g1 and 3g2** were purified with the flash silica gel column chromatography, obtained yield 65% and 30% respectively, compounds were characterized by IR, NMR & mass, and all data is reported in experimental part.



Scheme 4.8 Reaction of ferrocenemethanol with glycidol.

4.4.9 Reaction of ferrocenemethanol with 1,2-Propanediol (2h)

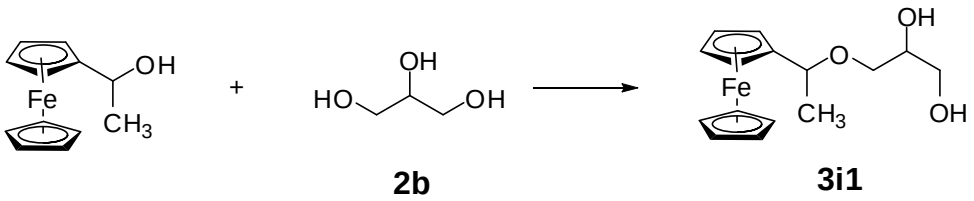
The reaction of 1,2-propanediol with ferrocenemethanol was found to be similar like ethylene glycol. At 60°C the reaction of 1,2-propanediol with ferrocenemethanol with ratio 10/1 was carried out for 14 hours but only trace (2-4%) amount of product was found whereas, when the same reaction was carried out with catalytic amount of acetic acid (5% wt) at 60°C, the reaction got completes in 5 hr with mono and disubstituted products. This product **3h1** was characterized by NMR & mass and all data is reported in experimental part.



Scheme 4.9 Reaction of ferrocenemethanol with 1,2-Propanediol.

4.4.10 Reaction of ferrocenylethanol with glycerol (2b)

At 60°C the reaction of glycerol with ferrocenylethanol (glycerol/ferrocenylethanol ratio = 10/1) is found to be faster than ferrocenemethanol. The reaction is complete in 16 hr instead of 24 hr but with lower selectivity. In this reaction 3 products were found these are primary monosubstituted: secondary monosubstituted: (1,2 +1,3) -disubstituted in the ratio approximately 40 : 40 : 20, respectively this data was analyzed from ^{1}H-NMR of reaction mixture. This product **3i1** was purified with the flash silica gel column chromatography and characterized by NMR & mass and all data is reported in experimental part.

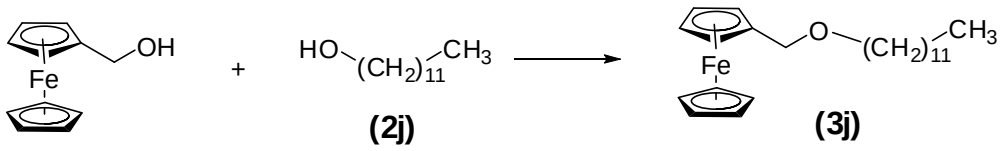


Scheme 4.10 Reaction of ferrocenylethanol with glycerol.

4.4.11 Reaction of ferrocenemethanol with non glycerol derivatives

4.4.12 Reaction of ferrocenemethanol with dodecanol (2j)

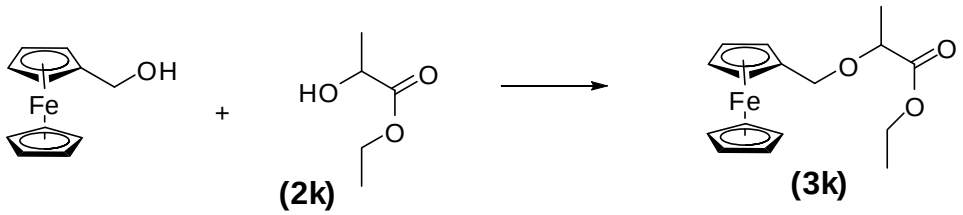
Reactions of ferrocenemethanol with aliphatic alcohols are not possible without acidic catalyst even at high temperature; we have carried out reaction of dodecanol with ferrocenemethanol in presence of trifluoroacetic acid (4% mol). This product was characterized by IR, NMR & mass and all data is reported in experimental part.



Scheme 4.11 Reaction of ferrocenemethanol and dodecanol.

4.4.13 Reaction of ferrocenemethanol with ethyl lactate (2k)

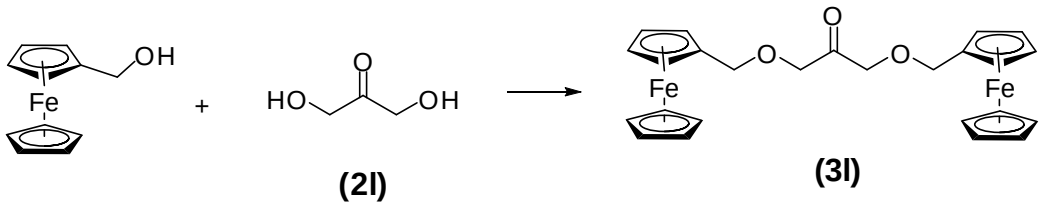
Reaction of ferrocenemethanol with ethyl lactate was carried out at 50°C temperature with catalytic amount (40 μL) of trifluoroacetic acid for 15-20 minutes, reaction was not clean, we got complex reaction mixture and we have got following product in very less yield (15-20 %) which was characterized with the help of H-NMR and MASS.



Scheme 4.12 Reaction of ferrocenemethanol with ethyl lactate.

4.4.14 Reaction of ferrocenemethanol with 2,3-dihydroxy acetone(2l)

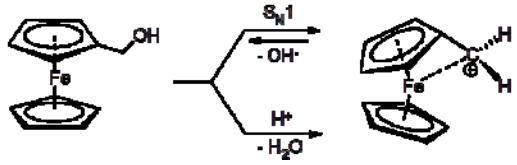
2,3-dihydroxy acetone is unstable compound and commercially available in dimer form. We have done reaction of this dimer with ferrocenemethanol at 80°C temperature, reaction was complete in 1 hr, but reaction mixture was found complex, we purified the disubstituted product (**3l**) as shown in figure in small quantity 10% and characterized by mass spectroscopy.

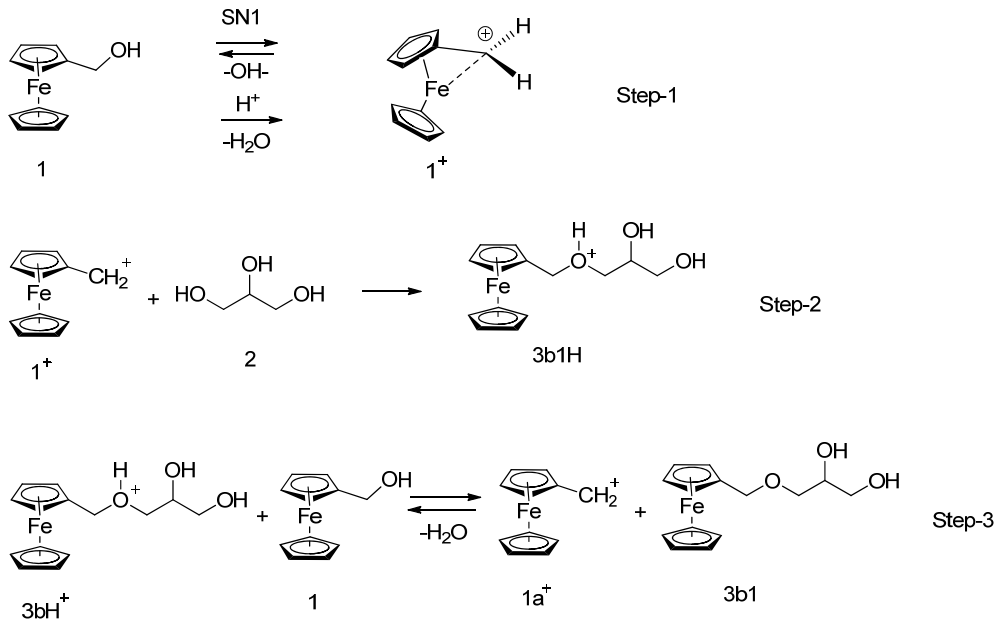


Scheme 4.13 Reaction of ferrocenemethanol with 2,3-dihydroxy acetone.

4.5 Mechanism of the reaction

Mechanism of the reaction is summarized the in the **Scheme 14**. The first step of the reaction consist of generation of the ferrocenylmethyl carbocation by spontaneous solvolysis of ferrocenemethanol in glycerol derivatives and in steps 2 and 3 lead to the final product formation by the attack of nucleophile OH of glycerol derivative on carbocation followed by loss of proton, and it can justify the high selectivity observed in the case where more than one isomer can be formed.





Scheme 14 – Mechanism for the synthesis of ferrocenylmethylglycerol by spontaneous solvolysis of ferrocenemethanol in glycerol.

The first step of the reaction reported in the **Scheme 1** is the solvolysis of ferrocenemethanol: on the basis of ferrocenemethanol chemistry known, it is considered to be the key step for the process. The solvolysis reaction can be in principle, promoted by two physicochemical factors of the substrate, which is used as reaction medium in this reaction: 1) the polarity of the molecule and 2) the intrinsic acid/base properties of the O-H functions in the autoprotolysis reaction. Unfortunately, only the dipolar moment values of these compounds are available in literature as experimental data. So it is not possible to perform satisfactory correlations between these two parameters and the chemical reactivity observed. However, some qualitative considerations can be given on the base of the results collected: 1) the number and the nature of the oxygen atoms present (that is hydroxyl, carbonyl or ether group) in the molecules studied are clearly in connections with the two above cited parameters and a qualitative trend with the molecular dipole moment can be ascertained (see values in **Table 1**). So, S_N1 solvolysis of ferrocenemethanol in the very polar glycerol carbonate is favored than in the less polar glycidol (4.49 D vs. 1.8 D) and other simple aliphatic alcohols, because of the mechanism pass through a polar transition state.

But only this parameter is no longer sufficient to explain the reactivity observed in the others cases studied. In absence of autoprotolysis constants values of the substrates used, we try to consider the acidity in water (pK_a), but this parameter does not help very much. For example glycerol and ethylene glycol have the same pK_a value (~14) but they show a significant difference in reactivity not related to the small difference in polarity (3.10 and 2.44 D, respectively). A third relevant aspect that it can be involved in the reactivity observed, strongly connected with the chemical structure/functions of the substrate investigated, is the stabilization of the transition state due to the hydrogen bonding in the rate determining step. So, analyzing

the data of Table 1, it is evident that the presence of two vicinal hydroxy groups is important to favor the reaction, and the inductive effects of two oxygen in ketal function (**2d** and **2f** substrates) improves the reaction more than the single ethereal oxygen in glycidol (1.8 D).

Carbon dioxide catalysis

Almost all glycerol derivatives studied here reacted conveniently without catalyst. The effect of the CO_2 on the reaction rate was investigated: the reactions were performed just under CO_2 atmosphere at atmospheric pressure. The choice of CO_2 as a peculiar catalyst, is justified considering the potential large scale application of these processes: the carbon dioxide in fact offers several advantages in term of safety, economy, low corrosion effect, strong limitation of side products formation, easily removed and recycled from the reaction mixture and so on, which make this "inert reactant" very attractive to use.

From the studies here performed, it is evident that the carbon dioxide does not react just as a simple weak acidic catalyst. In fact this molecule clearly effective in increasing the rate of condensation process, when the substrate having 1,2-diol (**2b, 2c, 2e**), while in the others case (**2a**, **2g** and **2f)**, the presence of CO_2 not only found to be ineffective, but also a weak inhibiting effect on the reaction rate was observed. This behavior of carbon dioxide with the ferrocenylmethanol in presence of the reactants used, was not further investigated in this project, but deserves attention.

4.6 Antifungal activity

In literature studies, it is often reported that the molecules containing ferrocene unit shown biological activity, mainly attributed to the peculiar redox properties of the metal organic center. Often, the compounds tested are complex derivatives, synthesized by elaborate pathway, where the ferrocene unit is functionalized with biomolecule fragments (polypeptides or nucleic bases etc.) or multifunctional radicals or fluorinated derivatives etc., On the contrary the novel ferrocenylmethylglycerol derivatives synthesized here are, simple molecules, easy and cheap to synthesize having potential biological activity that we have verified by screening their ability to inhibit fungal growth.

Antifungal activity testing was performed at **Biotecnologie BT Srl** c/o Parco tecnologico Agroalimentare dell Umabria, Fraz. Pantalla 06050, Todi (Pg) Italy. The aim of this investigation is the in vitro antifungal activity evaluation of the ferrocene derivatives by surface treatment. The antifungal activity of the ferrocene derivatives was tasted in vitro on 3 different plant fungi, *Fusarium spp., Botrytis cinerea, Penicillium spp,*. The fungal stocks *Fusarium* (ISPAVE 383), *Botrytis* (ISPAVE 1717) and *Penicillum* used were from Oxon Italia SPA biotechnology department collection. Growth medium was potato dextrose agar (PDA) sterilized in autoclave, Composition: 4.0 g/L potato extract, 20.0 g/L, dextrose, 15.0 g/L Agar, were purchased by OXOID S.p.A. Rodano – Italy.

Five ferrocene derivatives were tested performing two sets of *in-vitro* growth inhibition experiments on the three fungus stocks *Fusarium spp*., *Botrytis cinerea* and *Penicillium spp*.: in the first case the effects of the compounds are studied by applying them on the surface of the solidified cultural growth medium (surface treatment) whereas, in the second case, the products were dissolved in the cultural growth medium before of the solidification (inclusion treatment).

In vitro antifungal experiments

In vitro antifungal activity of ferrocene derivatives synthesized are tested against three fungal species by two methods, surface treatment and inclusion treatment of the growth medium.

Surface treatment: general procedure

50 μL of the ferrocenyl derivative solution, at the proper concentration, was uniformly distributed on the surface of the solid growth medium, which were taken in Petri dishes and kept at 25°C for 48 hr. After this time, fungus was inoculated putting a piece of agar, containing the appropriated fungi, at the center of the Petri dish. After 5 days at 25°C, the diameter of the fungal growth was measured (generally having circular shape). Finally the FGI% was calculated according to following equation:

FGI% = 100 – diameter of fungi colony treated / diameter of fungi colony non treated x 100

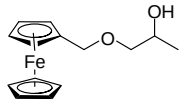
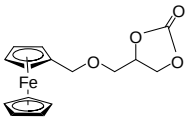
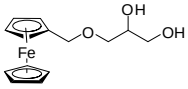
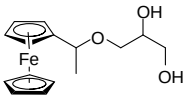
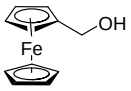
All the experiments were carried out three times and the data reported in table 2 are their average.

Inclusion treatment: general procedure

20 mL of a proper solution of ferrocenyl derivative in the growth medium was added in the Petri dish and kept at 25°C for 48 hr. After this time, fungus was inoculated putting a piece of agar, containing the appropriate fungi, at the center of the Petri dish. After 5 days at 25°C, the diameter of the fungal growth was measured (generally having circular shape). Finally the FGI% was calculated according to following equation:

FGI% = 100 – diameter of fungi colony treated / diameter of fungi colony non treated x 100

Table 4.6 Fungal growth inhibition values (FGI%) of all the ferrocene derivatives tested.

Samples or Compounds		Fungal Growth Inhibition (FGI %)					
		Penicillium spp.		Fusarium spp.		Botrytis Cinerea ssp.	
		Surface	Inclusion	Surface	Inclusion	Surface	Inclusion
3h		77.0(100) 46.2(100) 74.6(1)	84.2(100) 58.2(100) 46.8(1)	23.4(100) 7.4(100) 817.8(1)	2.0(7) 0.6(6) 12437(22)	68.1(100) 35.3(100) 117.1(1)	62(100) 30.1(100) 153(1)
3i		72.2(93.8) 40.2(87) 96.1(1.3)	72.6(86) 40.2(69) 96.9(2.1)	22(94) 6.8(92) 884.5(1.1)	0.4(1) 0.2(2) 62437(109)	44.1(65) 17.2(49) 316(2.7)	39.0(63) 14.0(47) 390(2.6)
3b (1+2)		53.9(70) 23.2(50) 213.8(2.9)	56.0(66) 24.6(42) 196.4(4.2)	15.8(67) 4.5(61) 1332(1.6)	12.06(40) 4.0(43) 1734(3)	59.1(87) 27.2(77) 173(1.5)	57.6(93) 25.7(85) 184(1.2)
3i (1+2)		50.6(65) 21.0(45) 244.1(3.3)	59.6(71) 27.3(47) 169.5(3.6)	11.2(48) 3.2(43) 1982(2.4)	19.8(66) 6.2(68) 1012(1.8)	66.5(98) 33.8(96) 125(1.1)	38.2(62) 14.7(49) 404(1.1)
1		61.1(79) 27.8(60) 159.2(2.1)	54.2(64) 22.6(39) 221.2(4.7)	22.4(95) 6.6(89) 866(1.1)	30.0(100) 9.2(100) 572.3(1)	59.6(87) 26.3(75) 169(1.4)	61.3(99) 29.4(98) 157(1.0)

For any experiment are reported three data: FGI% at [sample] = 250 mg/mL, FGI% at [sample] = 62.5 mg/mL; and IC_{50} (mg/mL). The numbers in brackets are the corresponding normalized values, respect to the best values in the column.

All the experiments were carried out three times and the data reported in table 2 is their average. All the ferrocenyl derivatives here tested are stable in the growth medium for five days at the experimental conditions.

The fungal growth inhibition values (FGI%) of all the ferrocene derivatives tested are mentioned in **Table 4.6** In the table, three values are reported for each compound and for both treatment. First two values are the FGI% values measured by using two different concentrations of ferrocene derivatives that are 250 μg/mL and 62.5 μg/mL. The third value is CI_{50} value (in μg/mL), which is calculated by the Michaelis - Menten equations[93]. Along with these values, in the bracket, are reported respectively, the % inhibition normalized values and the CI_{50} values normalized on the best inhibitor compound.

From the analysis of the data in **Table 2**, it is clear that the compound **3h** is found to be the most effective for the growth inhibition in all the three fungi, by surface treatment and, in almost all the cases by inclusion treatment, with a significant activity toward the *Penicillium fungi*, followed by the *Botrytis cinerea*. Whereas only in the case of the inclusion experiments on the stock *Fusarium*, this compound shown a very low biological activity. The compounds **3a** and **1** are the subsequently active for growth inhibition, followed by the compounds **3b** and **3i** but, in some specific cases, this order is found reverse. In all the cases *Fusarium* fungi found to be most resistant to all these compounds tested, since the FGI % values measured result from 1/2 to 1/3 than the *Penicillium* fungi case, which is the fungus more sensible to the products here tested.

4.7 EXPERIMENTAL

Reagents and chemicals

All organic reagents were commercially available and used without further purification: ferrocenemethanol, 1-ferrocenylethanol, ethylene glycol, 1,2-propanediol, glycerol, 2,3-epoxy-1-propanol were from Sigma Aldrich, diglycerol (92% purity) and glycerol formal (mixture of 4-hydroxymethyl-1,3-dioxolane 40% and 5-hydroxymethyl-1,3-dioxolane 60%) from Fluka, glycerol carbonate from Huntsman and solvents like acetonitrile, methanol, hexane, ethyl acetate are from Carlo Erba. 2,2-Bis-pentamethylene-1,3-dioxolane-4-methanol was synthesized according to the reported procedure[94]. Reaction was performed also with crude glycerol directly coming from biodiesel synthesis (Oxon Italia SPA). Chromatographic separations were performed using Merck Kieselgel 60 silica gel.

General procedure

As the general procedure, ferrocenemethanol was added to glycerol derivatives **1a-l** in a round bottom flask and the mixture was heated under stirring at 60-90°C (as reported in Table 1). The reaction was monitored by TLC, HPLC or capillary electrophoresis when reaction was complete, pure compounds were obtained (**3a-l** as reported in **Table 1**) by flash silica gel column chromatography.

Methods used

A) Capillary electrophoresis analyses were performed by a HP 3DCE equipped with an UV-Vis diode-array detector. Fused silica capillaries 50 μm I.D. were purchased from Composite Metal Service LTD (UK). Total capillary length was 45 cm, effective length to the detector was 37.5 cm. All the new capillaries were pretreated by washing for 5 minutes with 1 M sodium hydroxide and 5 minutes with BGE (SDS 20 mM in sodium tetraborate buffer 25 mM at pH9). All the capillary flushing was performed at high pressure (4.5 bar). Typical electrophoresis conditions: temperature cassette 25°C, voltage +28 kV, injection: sample 20 mbar x 2" + BGE 10 mbar x 3". Preconditioning step: BGE washing (4.5 bar) x 1'. Sample preparation: 20 μL of crude reaction mixture is added to 20 μL of MeCN. To the solution were added 300 μL of BGE. The mixture was well shaken and then injected.

B) HPLC analyses were performed on Varian 9010 equipped with a diode array detector. using a column Purospher Star RP-18 end capped column (125 mm × 2.0 mm, particle size 5 μm) preceded by a C18 guard column (4 × 4.5 μm), both supplied by Merck (Darmstadt, Germany) using a gradient mixture of acetonitrile/methanol (1:1-1:0, v/v, 10 min)

C) ESI-MS spectra were performed with an Esquire 3000 plus ion-trap mass spectrometer equipped with an ESI source.

D) NMR spectra were determined on a Bruker 400 MHz instrument. Chemical shifts were reported in ppm with the solvent residual peak as internal standard (DMSO-d6: δH= 2.50 ppm, δC = 39.52 ppm and in $CDCl_3$ δH= 7.27 ppm,).

E) IR spectra were registered with a Perkin Elmer 2000 FTIR instrument.

F) Melting points were determined with a Buchi 535 instrument and were uncorrected.

Reaction of ferrocenemethanol with glycerol carbonates (2a):-

In a round bottom flask ferrocene methanol (2.314 mol), glycerin carbonate (266.11 mol) were taken and stirred at 50°C temperature for 15-20 minutes, reaction was monitored by TLC and electrophoresis, after the completion of reaction, pure compound was obtained by flash column chromatography. When reaction was carried out with acidic catalyst such as trifluoroacetic acid (4% mol) reaction was complete in 2-3 minutes.

4-[(Ferrocenylmethyl)oxymethyl]-1,3-dioxolan-2-one (3a):-

Yellow crystals, soluble in water, m.p. 124-125°C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.88-4.95(m, 1, CH), 4.53 (t, 1, J = 8.6 and 17.1 Hz, $\underline{CH_2}$-O-CO), 4.32 (s broad, 2, Cp-$\underline{CH_2}$), 4.25 (s broad, 2, subst. Cp ring), 4.25 (q, 1, $\underline{CH_2}$-O-CO), 4.16 (s broad, 7, 5H Cp ring and 2H subst. Cp ring), 3.71-3.57 (m, 2, $\underline{CH_2}$-O-CH_2-Cp). ESI mass spectra, m/z (rel. int. %) (MeOH): 339 ([M+Na^+], 100 %), 316 ([M^+], 63 %); mass-mass spectra of 339: m/z (rel. int. %): 101(38), 179 (11), 199 (11), 314 (11), 316 (63), 339 (100). IR (KBr, ν_{max}, cm^{-1}): 3086 (m), 2991 (w), 2903, 2861, 1782 (s), 1548, 1478, 1398, 1345, 1241, 1176 (s), 1125, 1104, 1057, 1026, 968, 834, 813, 775, 713, 640, 577, 504,487.

Reaction of ferrocenemethanol with glycerol (2b):-

In a round bottom flask ferrocene methanol (0.23148 mol) and glycerin (2.3148 mol) were taken and stirred at 60°C temperature for 22hr, (at 90°C reaction got complete in 2-3 hr) reaction was monitored by TLC, HPLC or electrophoresis, after the completion of reaction, the isomers were separated by flash column chromatography with ethyl acetate as eluent and quantitatively determined by capillary electrophoresis and HPLC. When reaction was carried out with acidic catalyst such as trifluoroacetic acid (4% mol) reaction was complete in 10-15 minutes and trace amount of disubstituted products were obtained in mixture form.

Yellow crystals, m.p. 46-47°C (mixture of isomers **3b1** and **3b2** in ratio 9:1). Solubility in water at 20°C : 5 g/l, TLC (AcOEt/hexane 7:3).

3-[(Ferrocenylmethyl)oxy]propan-1,2-diol (3b1):-

m.p. 50°C. ^{1}H NMR (400 MHz, DMSO-d6): δ 4.50 (d, 1, OH), 4.36-4.39 (t, 1, OH), 4.22-4.23 (m, 4, 2H subst. Cp ring and 2H Cp-CH_2), 4.13-4.14 (m, 7, 2H subst. Cp ring and 5H-Cp ring), 3.50-3.55 (m, 1, CH-OH), 3.33-3.40 (m, 4, CH_2-O). ESI mass spectra (rel. int. %) (MeOH): 313 ([M+Na$^+$], 80 %), 290 ([M$^+$], 100 %); mass-mass spectra of m/z 313 (rel. int. %): 128(10), 138 (80), 146 (40), 152 (10), 164 (15), 177 (5), 194 (70), 212 (20), 224 (100), 290 (70). IR (KBr, ν_{max}, cm^{-1}): 3377 (s), 3095 (w), 2996, 2868, 1675, 1459, 1405, 1372, 1348, 1235, 1099 (s), 1044, 999, 816 (s), 750, 668, 485 (s).

2-[(Ferrocenylmethyl)oxy]propan-1,3-diol (3b2):-

m.p. 59°C. ^{1}H NMR (400 MHz, DMSO-d6): δ 4.32 (t, 2, two OH), 4.22-4.23(m, 4, 2H subst. Cp ring and 2H Cp-CH_2), 4.13-4.14 (m, 7, 2H, subst. Cp ring and 5H-Cp ring), 3.35-3.48 (m, 1, CH), 3.33-3.40 (m, 4, CH_2-CH-CH_2). ESI mass spectra (rel. int. %) (MeOH): 313 ([M+Na$^+$], 80 %), 290 ([M$^+$], 100 %); mass-mass spectra of m/z 313 (rel. int. %): 128 (10), 138 (80), 146 (40), 152 (10), 164 (15), 177 (5), 194 (70), 212 (20), 224 (100), 290 (70). IR (KBr, ν_{max}, cm^{-1}): 3377 (s), 3095 (w), 2996, 2868, 1675, 1459, 1405, 1372, 1348, 1235, 1099 (s), 1044, 999, 816 (s), 750, 668, 485 (s).

1,3-[Bis(Ferrocenylmethyl)oxy]propan-2-ol (3b3):-

The mixture of 1, 2 and 1, 3 disubstituted products which was obtained from column was brown sticky liquid we was not further abale to purify because of they have same Rf value, so we have characterized this mixture with the help of mass and H^1-NMR and assigned proton signals.

^{1}H NMR (DMSO-d6, 400 MHz) δ (ppm) 4.63-4.64 (1 H, d, OH), 4.22(4 H, br m, 2H subst. Cp ring and 2 H Cp-CH_2), 4.13 (7 H, br m, 2H subst. Cp ring and 5 H-Cp ring), 3.60-3.67 (1 H, m, CH), 3.24-3.39(4 H m, 2 CH_2). m/z (ESI, MeOH) 511 ([M+Na$^+$], 100 %), 488 ([M$^+$], 97 %), mass-mass m/z (rel. int. %) 511(100), 488 (97), 286(20), 411(12), 305(10), 239(21), 216 (25), 199(12).

2,3-[Bis(Ferrocenylmethyl)oxy]propan-1-ol (3b4):-

^{1}H NMR (DMSO-d6, 400 MHz) δ (ppm) 4.45-4.48 (1 H, t, OH), 4.22(4 H, br m, 2H subst. Cp ring and 2 H Cp-CH_2), 4.13 (7 H, br m, 2H subst. Cp ring and 5 H-Cp ring), 3.44-3.50 (1 H, m, CH), 3.24-3.39(4 H m, 2 CH_2). m/z (ESI, MeOH) 511 ([M+Na$^+$], 100 %), 488 ([M$^+$], 97 %), mass-mass m/z (rel. int.%) 511(100), 488(97), 286(20), 411(12), 305(10), 239(21), 216(25), 199(12).

Reaction of ferrocenemethanol with α,α'-Diglycerol (2c):-

In a round bottom flask ferrocene methanol (0.23148 mol) and diglycerine (26.611mol) were taken and stirred at 60°C temperature, reaction was complete in 42 hr(at 90°C in 18 hr), The reaction was monitored by capillary electrophoresis, after the completion of reaction, the pure compound was obtained by flash column chromatography. When catalytic amount of trifluoroacetic acid (4% mol) was used at 60°C temperature reaction got complete in 15-20 minutes and trace amount of disubstituted product was obtained, with CO_2 as catalyst reaction got complete in 18 hr. TLC (AcOEt/ MeOH 9/1), column was done by using solvents methanol and DCM, (**3c1** and **3c1** were eluted from column at the concentration of methanol + DCM, 5% + 95% and 10% + 90%, respectively.)

3-[2-hydroxy-3-(ferrocenylmethyloxy)propoxy]propane-1,2-diol (3c1) (primary mono substituted):-

Viscous liquid, soluble in water, purity > 96 %. ^{1}H NMR (400 MHz, DMSO-d6): δ 4.67 (d, 1, OH), 4.51 (d, 1, OH), 4.39 (t, 1, OH), 4.23 (s, 2, Cp-CH_2), 4.22 (t, 2, subst. Cp ring), 4.14 (s, 5, Cp ring), 4.13 (t, 2, subst. Cp ring), 3.70-3.63 (m, 1, CH-O), 3.59-3.52 (m, 1, CH-O), 3.41-3.31 (m, 8, CH_2). ESI mass spectra (rel. int. %) (MeOH): 387 ([M+Na^+], 45 %), 364 ([M^+], 20 %); mass-mass spectra of m/z 387 (rel. int. %): 187 (17), 199 (100), 243 (16), 387 (22). IR (neat, ν_{max}, cm^{-1}): 3428 (s, br, O-H), 3090 (s), 2996 (m), 2866, 1647, 1468, 1410, 1345, 1239, 1028, 1099 (s), 1000, 908, 827 (s), 754, 488 (s).

3,3'-oxybis[(1-ferrocenylmethyl)oxy]propan-2-ol (3c2):-

Viscous liquid, purity 95%. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.05 (d, 1, OH), 6.784(d, 1, OH), 4.197-3.907 (m, 11, Fc and Cp-CH_2), 3.76-3.66 (m, 1, CH-O), 3.66-3.57 (m, 1, CH-O), 3.53-3.26 (m, 8, CH_2-O). ESI mass spectra (rel. int. %) (MeOH): 585 ([M+Na^+], 51 %), 562 ([M^+], 11 ; mass-mass spectra of m/z 585 (rel. int. %): 107 (20), 242 (18), 362 (5), 387 (100), 443 (35), 517 (12), 562 (11), 585 (50),

Reaction of ferrocenemethanol with cyclohexanone glycerol ketal (2d):-

In a round bottom flask ferrocene methanol (0.2314 mmol), cyclohexanone glycerol ketal (1.1574 mmol) were taken and stirred at 90°C temperature for 2 hr, reaction was monitored by TLC and electrophoresis, after the completion of reaction, pure compound was obtained by flash column chromatography. TLC (AcOEt/hexane 5:5).

2-[(Ferrocenylmethyl)oxymethyl]-1,4-dioxaspiro[4,5]decane (3d):-

Viscous liquid. ^{1}H NMR (400 MHz, DMSO-d6): δ 4.27 (s, 2, Cp-CH_2), 4.23 (m, 2, subst. Cp ring), 4.14 (m, 7, 2H subst. Cp ring and 5H-Cp ring), 4.12-4.14 (m, 1, CH-O), 3.93-3.96 (q, 1 CH_2-O), 3.54-3.58 (q, 1 CH_2-O), 3.27-3.45 (dd, 2 , CH_2-O), 1.49-1.51 (m, 8, CH_2-O), 1.33 (m, 2, CH_2-O). ESI mass spectra (rel. int.

%) (MeOH): 409 ([M+ K^+], 35%), 370 ([M^+] 100%); mass-mass spectra of m/z 409 (rel. int. %): 157 (12), 195 (18), 213 (10), 237 (30), 255 (5), 312 (100), 380 (8), 409 (35).

Reaction of ferrocenemethanol with ethylene glycol (2e):-

In a round bottom flask ferrocene methanol(0.23148 mmol) and ethylene glycol (1.1574 mmol) were taken and stirred at 60°C temperature, reaction was complete in 48 hr and after completion of reaction, compound was purified by flash column chromatography. When catalytic amount of trifluoroacetic acid (4% mol) was used reaction got complete in 10 minutes in this case disubstituted product was not obtained at all.

2-[(Ferrocenylmethyl)oxy]ethan-1-ol (3e):-

Viscous liquid. ^{1}H NMR (400 MHz, DMSO-d6): δ 4.52 (t, 1, OH), 4.24 (s broad, 2, Cp-CH_2), 4.23 (t, 2, subst. Cp ring), 4.14 (broad s, 5, Cp ring), 4.13 (t, 2, subst. Cp ring), 3.46 (q, 2, $\underline{CH_2}$-OH), 3.38 (t, 2, O-$\underline{CH_2}$-CH_2-OH). ESI mass spectra (rel. int. %) (MeOH): (283 [M+ K^+], 10%), 260 ([M^+], 100%); mass-mass spectra of m/z 260 (rel. int. %): 134 (5), 152 (10), 164 (20), 182 (20), 194 (10), 258 (35), 260 (100). IR (neat, ν_{max}, cm^{-1}): 3394 (s, broad, OH), 3092 (m), 2996, 2861, 2251, 2124, 1649, 1459, 1409, 1347, 1277, 1235, 1103 (s), 1028 (s), 1004, 929, 891, 823 (s), 760, 448.

Reaction of ferrocenemethanol with glycerol formal (2f1 + 2f2):-

In a round bottom flask ferrocene methanol(0.23148 mmol) and glycerol formal (1.1574 mmol) were taken and stirred at 90°C temperature, reaction was complete in 48 hr and after completion of reaction, compound was purified by flash column chromatography. TLC (AcOEt/hexane 4:6).

4-[(Ferrocenylmethyl)oxymethyl]-1,3-dioxolane (3f1):-
Viscous liquid. ^{1}H NMR (400 MHz, DMSO-d6): δ 4.87 (s, 1, -O-CH_2-O-), 4.77 (s, 1, -O-CH_2-O-), 4.28 (s, 2, Cp-CH_2), 4.23 (m, 2, subst. Cp ring), 4.15 (m, 7, 2H subst. Cp ring and 5 H-Cp ring) 4.06-4.11 (m, 1, CH-O), 3.85-3.89 (t, 1, -O-C$\underline{H}$-CH_2-O-), 3.48-3.51 (q, 1, -O-CH-$\underline{CH_2}$-O-), 3.38-3.47 (dd, 2, -O-$\underline{CH_2}$-CH-).

5-[(Ferrocenylmethyl)oxy]-1,3-dioxane (3f2):-

Viscous liquid. ^{1}H NMR (400 MHz, DMSO-d6): δ 4.75-4.77 (d, 1, -O-CH_2-O-), 4.56-4.58 (d, 1, -O-CH_2-O-), 4.31 (s, 2, Cp-CH_2), 4.23 (m, 2, subst. Cp ring), 4.15 (m, 7, 2H subst. Cp ring and 5 H-Cp ring), 3.93-3.96 (2d, 2, -O-$\underline{CH_2}$-CH-), 3.38-3.51 (m, 1, CH-O), 3.34-3.46 (q, 2, -O-CH-$\underline{CH_2}$-O-). ESI mass spectra (rel. int.%) (MeOH): 325 ([M+ Na^+], 55%), 302 ([M^+] 100%); mass-mass spectra of m/z 302 (rel. int. %): 122 (15), 134 (17), 150 (14), 164 (100), 177 (13), 191 (12), 199 (27), 206 (13), 216 (10), 224 (45), 236 (22), 302

(25). The isomers **3f1** & **3f2** were separated by flash column chromatography with hexane/ethyl acetate 8:2-1:1 as eluent and quantitatively determined by CE.

Reaction of ferrocenemethanol with glycidol (2g):-

In a round bottom flask ferrocene methanol (0.23148 mmol), 2,3-epoxy-1-propanol (2.3148 mmol) and catalytic amount of trifluoroacetic acid (2% mol) were taken and stirred at 50°C temperature, reaction was complete in 15-20 minutes, reaction was monitored by TLC and after completion of reaction, compounds **3g1** and **3g2** (65% and 30% respectively) were purified by flash column chromatography, TLC (AcOEt/hexane 8:2).

2-(Ferrocenylmethyl)oxymethyl)oxirane (3g1) and (3g2):-

Yellow crystals, m.p. 35-36°C. ^{1}H NMR (400 MHz, DMSO-d6): δ 4.27(broad s, 2, Cp-CH_2), 4.24 (s, 2, subst. Cp ring), 4.15 (m, 7, 5H-Cp ring and 2H subst. Cp ring), 3.65 (dd, 1, J = 11.48 and 2.84 Hz), 3.23 (dd, 1, J = 11.48 and 6.35 Hz) 3.05 (m, 1, CH-epoxide) 2.71-2.68 (dd, 1, J = 5.13 and 4.32 Hz, CH_2-epoxide) 2.51 (dd, 1 H, J = 5.27 and 2.70 Hz, CH_2-epoxide). ESI mass spectra(rel. int. %) (MeOH): 295 ([M+ Na+], 51%), 272 ([M+] 100%); mass-mass spectra of m/z 272 (rel. int. %): 122 (16), 134 (17), 152 (23), 164 (100), 182 (15), 199 (16), 270 (82), 272 (47). IR (KBr, λ_{max} cm^{-1}): 3429, 3097, 2996, 2870, 2824, 2247, 1772, 1678, 1644, 1516, 1475, 1405, 1326, 1243, 1093, 1000, 910, 854, 746, 520, 490.

3g2:- ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm) 4.76-4.75(1 H, d, -OH), 4.23(2 H, br s, Cp-CH_2), 4.22(2 H, br t, subst. Cp ring), 4.14(5 H br s, -Cp ring), 4.13(2 H, br t, subst. Cp ring), 3.69-3.66(1 H, dd, *J* = 11.478, 2.836 Hz), 3.44-3.34(2 H, 2 dd, CH_2-O- CH_2-Cp), 3.26-3.22(1 H, dd, *J* = 11.478, 6.347 Hz), 3.07-3.03(1 H, m, CH-epoxide), 2.99-2.95 (1 H, m, CH-OH), 2.71-2.69(1 H, dd, *J* = 5.131, 4.321 Hz CH_2-epoxide), 2.68-2.66(1H, CH_2-O-CH_2-epoxide) 2.53-2.50(2 H, m, 1 H, CH_2-epoxide and 1 H, CH_2-O- CH_2-epoxide). m/z (ESI, MeOH) 369 ([M+ Na^+], 100%), 346 ([M^+] 46%), mass-mass m/z (rel. int. %) 369(100), 346(46), 101(16).

Reaction of ferrocenylethanol with glycerol (2b):-

In a round bottom flask ferrocenylethanol (0.23148 mmol) and glycerol (2.3148 mmol) were taken and stirred at 60°C temperature, reaction was complete in 16 hr, reaction was monitored by TLC and after completion of reaction, The reaction mixture was found very complex and we were abale to purify only one

compound by flash column chromatography. This compound was analyzed by NMR and Mass spectroscopy. The reaction is complete in 16 hours instead of 24 hours (as in ferrocene methanol) but with less selectivity. In this reaction 3 products found were primary monosubstituted: secondary monosubstituted: 1,2-disubstituted in the ratio approximately 40 : 40 : 20 respectively this ratio was analyzed from NMR. TLC (AcOEt/hexane 9:1).

3-[(1-Ferrocenylethyl)oxy]propane-1,2-diol (3i) (primary mono substituted)**:-**

^{1}H NMR (400 MHz, DMSO-d6): δ 4.48 (d, 1, OH), 4.42-4.39 (t, 1, OH), 4.22-4.23(br m, 4, 2H subst. Cp ring and 1 H Cp-CH), 4.13-4.14 (br m, 7, 2H subst. Cp ring and 5 H-Cp ring), 3.46-3.53 (m, 1, CH), 3.38-3.25(m, 4, $\underline{CH_2}$-CH-$\underline{CH_2}$), 1.44-1.43(d, 3, CH_3). ESI mass spectra (rel. int. %) (MeOH): 327 ([M+Na^+], 100 %), 304 ([M^+], 25 %); mass-mass spectra of m/z 304 (rel. int. %): 103(3), 28(15), 138(100), 146(30), 156(3), 164(15), 180(3), 194(40), 212(70), 239(5), 304(12).

Reaction of ferrocenemethanol with 1,2-propane diol (2h):-

In a round bottom flask ferrocene methanol(0.23148 mol) and 1,2-propanediol (2.3148 mol) were taken and stirred with catalytic amount of acetic acid (5% wt) at 60°C temperature, reaction was complete in 5 hr and after completion of reaction, primary mono and di substituted products were purified by flash column chromatography. TLC (AcOEt/Hexane 3:7)

3-[(Ferrocenylmethyl,)oxy]propane-2-ol (3h) (Primary mono substituted)**:-**

^{1}H NMR (400 MHz, DMSO-d6): δ 4.25(s br, 2, subst. Cp ring), 4.15(s br, 2, subst. Cp ring), 4.08(s br, 2, Cp-$\underline{CH_2}$), 4.06(s br, 5, Cp ring), 3.92(m, 1, CH), 3.44-3.42, 3.23-3.19(2 dd, 2, CH_2), 2.21(s br, 1, OH), 1.05(d, 3, CH_3). ESI mass spectra (rel. int. %) (MeOH): 297 [M+ Na^+], 274 ([M^+] 95%); mass-mass spectra of m/z 274 (rel. int. %): 108(2), 122(8), 138(47), 150(100), 166(38), 178(62), 194(45), 208(60), 241(2), 272(40), 274(10).

3,2-[Bis(Ferrocenylmethyl,)oxy]propane (3h)di substituted:

^{1}H NMR (400 MHz, **$CDCl_3$**): δ 4.31(s br, 4, two subst. Cp ring), 4.29(s br, 4, two subst. Cp ring), 4.24(s br, 4, two Cp-CH_2), 4.14(s br, 10, two Cp ring), 3.64(m, 1, CH), 3.44-3.41, 3.34-3.30 (2 dd, 2, CH_2), 1.09(d, 3, CH_3). ESI mass spectra (rel. int. %) (MeOH): 495 [M+ Na^+], 472 ([M^+] 30%); mass-mass spectra of m/z 472 (rel. int. %):199(30), 276(30), 331(18), 396(20), 407(9), 472(100).

Reaction of ferrocenemethanol with dodecanol (2j):-

In a round bottom flask ferrocene methanol (2.314 mol), dodecanol (1.1574 mol) and catalytic amount (4% wt) of trifluoroacetic acid were taken and stirred for 15-20 minutes and after completion of reaction compound was purified by flash column chromatography. TLC (AcOEt/hexane 5:5).

1-[(Ferrocenylmethyl,)oxy]dodecane (2j):- ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.345(2 H t, subst. Cp ring) 4.274(2 H, br s, subst. Cp ring) 4.215(2 H, br s, Cp-CH2) 4.172(5 H, br s, Cp ring) 3.384(2 H, t, O-CH_2- CH_2) 1.512(4 H, m, CH_2- CH_2) 1.254(16 H, m) 0.884(3 H, t, CH_3). m/z (ESI, MeOH) 384 (M^+), mass-mass m/z 384(25 %) 382(15) 284 270(100) 238(55) 200(98) 182(19) 168(30) 154(35) 140(24) 126(20) 110(18) IR absorptions (neat) 2926 s 2855 1785 1685 1461 1349 1222 1163 1098s 1008 819s 728 492

Reaction of ferrocenemethanol and ethyl lactate (2k):-

In a round bottom flask ferrocene methanol (0.4628 mol), Ethyl lactate (23.1481 mol) and catalytic amount (4% wt) of trifluoroacetic acid were taken and stirred at 50°C temperature for 15-20 minutes and after completion of reaction, reaction mixture was concentrated on rotavapour and compounds were partially purified by flash column chromatography. Pure compound was obtained by preparative TLC and characterized by NMR and mass spectroscopy. TLC (AcOEt/hexane 5:5).

^{1}H NMR (DMSO-d6, 400 MHz) δ (ppm) 4.210-4.093(13 H m, ferrocene, Cp- CH_2 and 2 H CH_2- CH_3) 4.048-3.998(1 H, q, CH) 1.243-1.226 (3 H, d, J = 6.685 Hz CH_3) 1.229-1.194 (3 H, t, J = 6.975 Hz CH_2-CH_3). m/z (ESI, MeOH) 316 (M^+), mass-mass m/z 316(11) 314(30) 290(13) 250(129 238(100 %) 210(28) 194(16) 166(67) 154(41)

Reaction of ferrocenemethanol and 2,3-dihydroxy acetone(2l):-

2,3-dihydroxy acetone is unstable compound and commercially available in dimer form. We have done reaction of this dimer with ferrocenemethanol. In a round bottom flask ferrocenemethanol (0.2314 mmol) and 2,3dihydroxy acetone (1.157 mmol) were stirred at 80°C temperature for 1hr. Reaction was monitored by TLC, after the completion of reaction, reaction mixture was found to be complex, we purified the disubstituted product (in small quantity 10%) by preparative TLC and characterized by mass spectroscopy. m/z (ESI, MeOH) 486 (M^+) mass-mass m/z 486. TLC (AcOEt/hexane 7:3).

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Chapter – 5

H_2O_2/Ethyl lactate: A New Eco-Friendly Per acids-like System for Oxidation of Organic Substrates.

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H_2O_2/Ethyl lactate: A New Eco-Friendly Per acids-like System for Oxidation of Organic Substrates

5.1 - Introduction

Oxidation is one of the main pathways for the activation of raw materials that are readily available and selective oxidation reactions are widely used in the chemicals industry to provide many useful intermediates including pharmaceuticals, agrochemical, fragrances and flavorings. The success of these reactions depends largely on the use of metal catalysts to promote both reaction rate and selectivity to partial oxidation products. Therefore, a great effort has been devoted to the development of effective metal catalyst that can activate simple readily available and low cost final oxidants under mild conditions and a huge number of commercial oxidation catalysts have been identified. In this context, the most attractive oxidants appear H_2O_2 and O_2 because of their high content of active oxygen species and co-production of only water. This general trend has however, in our opinion, the limit to focus near exclusively to the use of metal catalyst with quite minor attention to activation by organic catalyst. Taking in mind that the goal of green oxidation chemistry is to replace current oxidation technologies, which often use toxic materials, with environmentally safe and sustainable alternatives, this appear a preconception. The ideal system for "green oxidation" is in fact the use of environmentally-friendly oxidants together with recyclable catalysts

in nontoxic solvents. Thus, the use of organic solvents able to dissolve a wide variety of substrates and to activate the terminal oxidant needs at least to be carefully taken into consideration as organic catalyst. With hydrogen peroxide this approach has been in fact just exploited with several organic acids (acetic acid, formic acid, maleic acid, etc.) and the corresponding activated forms (anhydrides, acyl halides, etc.) through the formation of the corresponding peroxy derivative, but the structural role of this activation was sporadically investigated and in our opinion needs more attention. On this basis, we designed a screening to devise new solvents for the activation of hydrogen peroxide and in this context we identify the role of alfa-hydroxy esters of carboxylic acid (and ethyl lactate in particular) as relevant organic catalysts. First attempt in this direction were reported in 2001 but metal catalyst were judged essential for practical applications.[1]

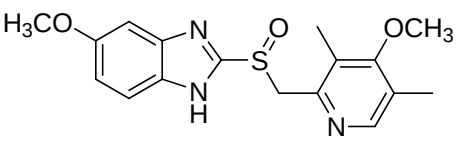
In the following section, the possible use of eco-friendly ethyl lactate/hydrogen peroxide system without metal catalyst for the oxidation of selected classes of organic substrates is described and the limits of its use are devised. The chapter is divided in to three parts: oxidation of sulfides (par. 5.2), oxidation of reduced phosphorous species (par. 5.3) and oxidation of carbonyl compounds (par 5.4). The chapter on oxidation of sulfides is preceded by an overview and a detailed review of oxidation methods of sulfide to sulfoxides, owing the relevance of this reaction in our study on the investigated oxidant system.

5.2 Oxidation of sulfides to sulfoxides

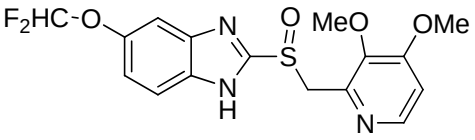
5.2.1 - Summary of oxidation methods of sulfides to sulfoxide

The oxidation of sulfides to sulfoxides is of significant importance in organic chemistry, both for fundamental research and for a wide range of applications such as in the synthesis of chemically useful and biologically active molecules such as drugs, flavors, germicides as well as catabolism regulators and for desulfurization in petroleum.[2] Relevant is the use of chiral sulfoxides as versatile intermediates in drug synthesis. There are several nice reviews[3] on synthesis of sulfoxides and on their biological activity, especially chiral sufoxides, written by Carrenoi[3a] in 1995, Inmaculada Fernandez[3b] in 2003, J. Legros[3c] in 2005, W. Kaczorowska[3d] in 2005, E. Wojaczynska[3e] in 2010, K. A. Stingl[3f] 2010, and Anita R. Magure[3g] in 2011. Organic sulfoxides often play an important role as therapeutic agents such as anti-ulcer (proton pump inhibitor),[4] antibacterial, antifungal, anti-atherosclerotic,[5] anthelmintic,[6] antihypertensive,[7] and cardiotonic agents,[8] as well as psychotropic, psychotonics[9] and vasodilators.[10]

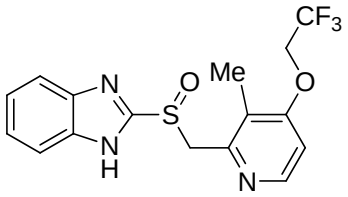
Enantiopure sulfoxides have found use in the pharmaceutical industry due to their important biological activity. Omeprazole, the world's highest selling drug in 1997 ($5 billion U.S.),[11] is a proton pump inhibitor used to treat acid-induced inflammation and ulcers of the stomach and duodenum. A number of other acid secretion inhibitors based on the framework of Omeprazole have also been developed. Esomeprazole, the (S)-form of Omeprazole, was launched in Europe in 2000 and the USA in 2001 under the trade name Nexium™.



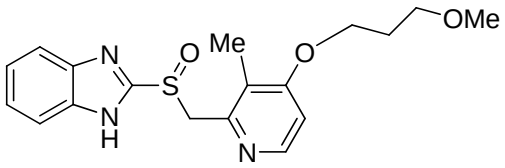
Omeprazole (Astra Zeneca)



Pantaprazole (Byk Guilden)

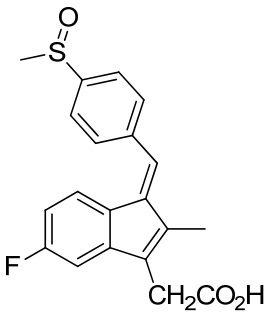


Lansoprazole (Takeda)

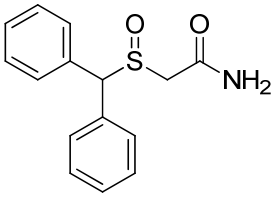


Rabeprazole (Eisai)

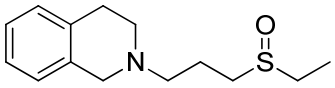
Other biologically active compounds containing the sulfinyl moiety include Modafinil and Sulindac, which have been used to treat narcolepsy and inflammation respectively.[12] A number of reviews outlining the asymmetric synthesis of biologically active sulfoxides have been reported.[13]



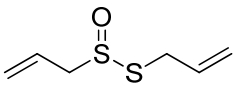
Sulindac



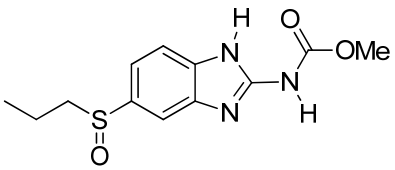
Rac-modafinil
CNS stimulant



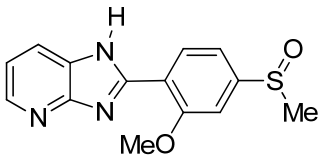
Rac-esproquin
Antihypertensive



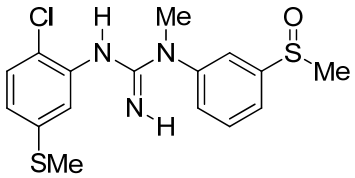
Rac-allicin
Antibiotic
Anti-atherosclerotic



Rac-ricobendazole
Anthelmintic



(+)-Sulmazole
phospodiesterase inhibitor
cardiac agent



(R)-CNS 5788
NMDA ion-channel blocker

Some of the medicinal sulfoxide compounds are obtained by either from natural sources or synthesized by sulfide oxidation; there are many reagents available for the oxidation of sulfides to sulfoxides. The synthesis of sulfoxides was reported for the first time by Marcker in 1865 and, since then, a number of methods have been developed for the conversion of sulfides into sulfoxides and sulfones, for this reason wide variety of oxidants were proposed, developed and commercially made available.[14] Most of the selective oxidation methods for the synthesis of sulfoxide uses, hazardous peroxides and toxic heavy metal or expensive exotic oxidants; therefore, a large effort has been devoted to develop cheaper and more environmentally benign reagents. Hydrogen peroxide has been extensively explored in this direction with some interest for the synthesis of fine chemicals,[15] as well as on the desulfurization of fuels,[16] Hydrogen peroxide is an ideal waste avoiding oxidant and its aqueous solution shows safety in usage, storage and handling, but it reacts generally slowly, so efforts were focused on its catalytic activation.[17] For the selective oxidation of sulfides to sulfoxide mediated by H_2O_2 many transition metals, such as iron,[18] manganese,[19] vanadium,[20] titanium,[21] selenium,[22] tungsten,[23] molybdenum,[24] tellurium[25] and rhenium[26] have been proposed as catalysts. Metal Schiff base complexes in combination with H_2O_2 or other oxidants were found particularly efficient.[27] At the same time, metal-free methods have been reported. Fontana et al. developed a free-radical/electrophilic sulfoxidation in the presence of H_2O_2 and Br_2.[28] Pandit and co-workers developed a ultra-sound accelerated system in which β-cyclodextrin in water increases the selectivity toward the sulfoxide.[29] More recently Fu et al. reported the solvent-free sulfoxidation of sulfides by H_2O_2 without catalysts.[30] Similar oxidations under catalysis of Montmorillonite K10 in methanol proceed without over-oxidation under mild condition, showing many advantages over the existing methodologies.[31] Furthermore, enzymatic catalysis was found effective,[32] but suffers from low operation stability due to facile oxidative degradation of enzymes.

From an analysis of the literature, it is clear that most of the existing methods use sophisticated reagents, complex catalysts, toxic metal reagents or catalysts, or rare oxidizing agents that are difficult to prepare. Also transition metal-catalyzed reactions present some drawback such as the use of acidic or basic conditions (Mn), long reaction times (Fe and Mo), hazardous solvents and/or reagents (Mo, V, Cu, and Mn), low chemoselectivity (Ti, Fe, V, W, and Re), and rare elements in the earth (Re and Au).

Moreover, many of the procedures developed suffer also from poor selectivity or undesirable products, such as aromatic halogenations, C–S bond cleavage and if the sulfur group of substituted sulfides containing other oxidation prone functional groups, such as alcohols, olefins, etc., these last reacts as well producing undesirable by products.

Furthermore, over oxidation of the sulfoxides to sulfones is a common and main problem during the oxidation of sulfides and most proposed reagents involve processes that are not suitable for medium to large scale operations, generating a large volume of toxic wastes. Hence, for a practical conversion of sulfides to sulfoxides, careful selection of the oxidizing agent and the reaction conditions (time, temperature and relative amount of oxidants), are prerequisites. All these aspects indicate that there is still considerable interest in the development of selective oxidants for this transformation and the development of green, environmentally acceptable oxidative methodologies is emerging as an urgent task in this field.

From a Green Chemistry standpoint it is very important to develop a "green" oxidation system for chemical manufacturing. Hydrogen peroxide is considered as an ideal "green" oxidant due to its strength and lack of toxic by-products, it produces water as the only by product, also it is a cheap and is a readily available reagent. Mahamuni and co-workers[33] have reported a novel and green approach for the sulfoxidation of thioanisole with hydrogen peroxide promoted by ultrasound irradiation without any catalyst and organic solvent. However, this method is complicated in the experimental procedure and its applicability extended to other sulfides is not expected.

5.2.2 - Known methods of oxidation of sulfides to sulfoxide

Oxidation of sulfides is a general reaction to produce sulfoxides (R-S(=O)-R), but the generated sulfoxide also gets consumed in a consecutive oxidation to the corresponding sulfones (R-S(=O)$_2$R). The process can be simplified as follow referring to dimethyl sulfide as model example and to XO as the terminal oxidant specie involved.

$$S(CH_3)_2 + XO \rightarrow (CH_3)_2SO + X$$

$$OS(CH_3)_2 + XO \rightarrow (CH_3)_2SO_2 + X$$

A large number of oxidants or oxidant systems have been investigated in context with catalytic liquid-phase oxidations of sulfides and we have summarized in the following paragraph the main results published on the subject. References will be concentrated mainly on preparative aspects; the mechanistic details of these oxidation will be analyzed better along the subsequent discussion.

A) Halogen derivatives

There is detail review on oxidation of sulfides to sulfoxides by using halogen derivatives written by Michel Madexlaire[34] in 1986 and P. Kowalski et al.[35] in 2005. The halogens and their derivatives have been considered as environmentally unfriendly, although their advantages are low price, easy handling, commercial availability, and relatively high stability.

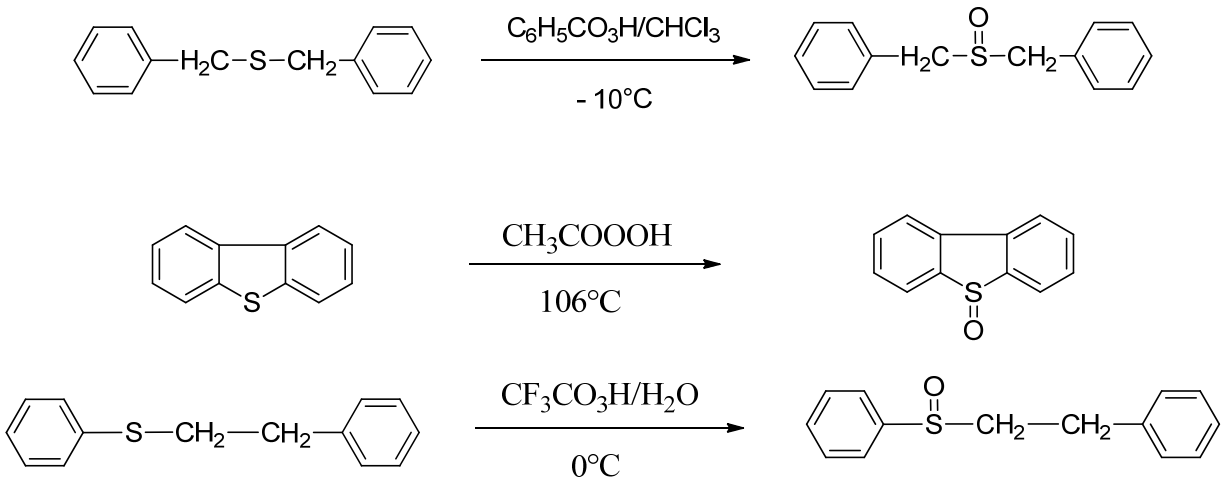
Between the several halogen derivatives used for the oxidation of sulfides, the more investigated were molecular halogens (e.g. hexamethylenetetramine–Br_2 complex (HMTAB), pyridine or 1,4-diazabicyclo[2.2.2] octane Br_2 complex (DABCO-2Br_2), quaternary ammonium polybromides $[QA]^+[Br_3]^-$, e.g. cetyltrimethylammonium tribromide (CTMATB), hypochlorites (e.g. inorganic sodium hypochlorite (NaOCl) and calcium hypochlorites ($Ca(OCl)_2$), but also organic hypochlorites, e.g. t-butyl hypochlorite ($(CH_3)_3COCl$)), chlorites (e.g. sodium chlorite, $NaClO_2$) and bromites (e.g. sodium bromites, $NaBrO_2$), bromates (e.g. $NaBrO_3$–$Mg(HSO_4)_2$), iodo-compounds such as Hypervalent iodine(III) reagents ((C_6H_5I=O), C_6H_5I=O–$(RCO)_2O$, C_6H_5I=O–C_6H_5SeOOH, $C_6H_5I(OTs)OH$, $C_6H_5I(OTs)OCH_3$, C_6H_5I=O–metalloporphyrin, C_6H_5I=O–metallosalen, C_6H_5I=O–clays, C_6H_5I=O–cationic surfactants, and C_6H_5I=O–KBr), Hypervalent iodine(V) reagents (Iodoxybenzene, $C_6H_5IO_2$, 4-tert-Butyl-iodoxybenzene, o-iodoxybenzoic acid, benziodazole oxide (BIO)), periodates (periodic acid HIO_4 and its dihydrate (paraperiodic acid), H_5IO_6,), N-haloamides (N-bromocaprolactam, N-chloronylon-6,6, chloramines,

bromamines, N-halosuccinimides, N-bromoacetamide (NBA), N-chloroacetamide (NCA), N-bromobenzamide (NBB), N-chlorosuccinimide (NCS), N-bromosuccinimide (NBS)), Other halo-derivatives such as N-chlorobenzotriazole and N-bromoamines.

The mechanism of the halogen oxidation of sulfides to sulfoxides is still being developed, especially of those oxidants, which are impregnated on inorganic supports, which work efficiently under solvent-free conditions, and which are effective in asymmetric oxidations.

B) Organic Peroxyacids and Peroxides

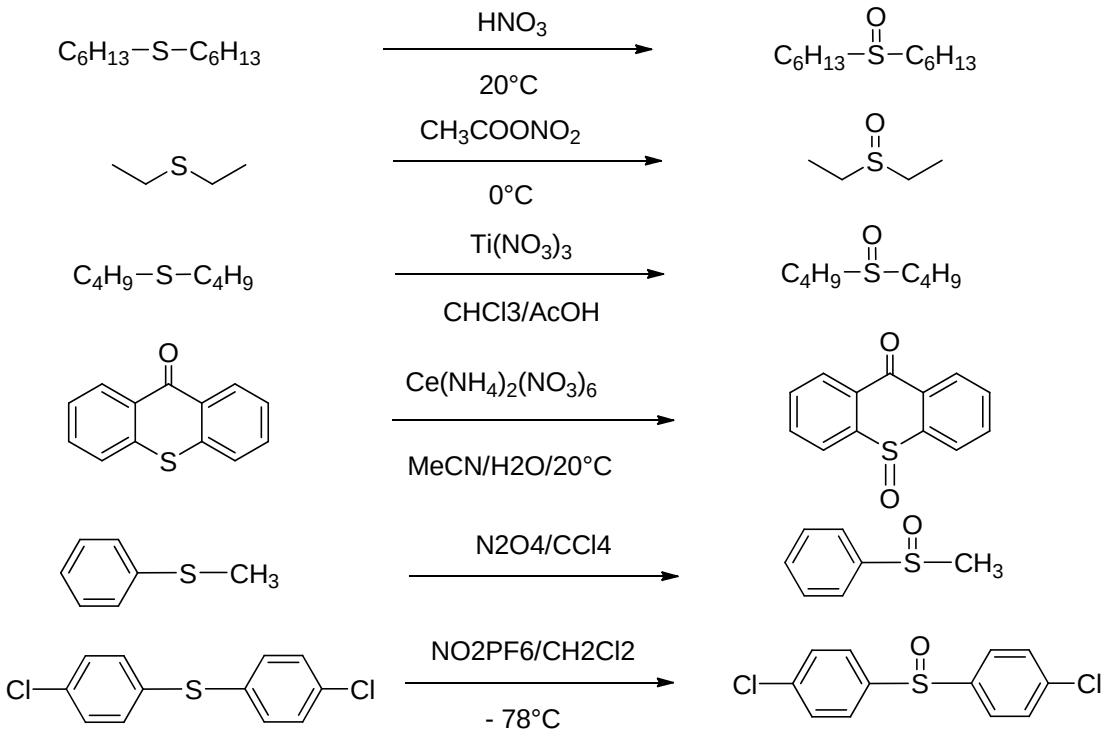
Perbenzoic acid and its derivatives.[34] Lewin was the first to describe (in 1928) the oxidation of sulfides to sulfoxides using perbenzoic acid ($C_6H_5CO_3H$). This method has since been widely used and several peroxyacids were used for oxidation of sulfide to sulfoxides, such as *m*-chloroperbenzoic acid (*m*-$ClC_6H_4CO_3H$), benzoyl peroxide [$(C_6H_5,CO)_2O_2$]. Peracetic acid (CH_3CO_3H), trifluoroperacetic acid (CF_3CO_3H), monoperphthalic acid, permaleic acid and other peroxyacids such as percamphoric acid and alpha-cyclohexyl perpropanoic acids, were extensively used in these reactions even if several drawbacks and lack of selectivity were frequently reported. Some of the more significant examples are collected in the following figure. These reactions were characterized by generally low temperature and halogenated or ethereal solvents.



C) Nitrogen oxide derivatives[34]

Nitric acid was the very first oxidizing agent used to convert sulfides into sulfoxides in 1865 by Marcker.[36] He used this reagent to oxidize dibenzylsulfide to dibenzylsulfoxide. Then other nitrogen oxide

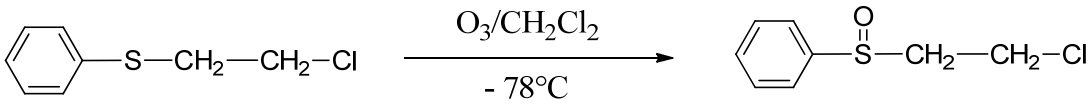
derivatives like, nitrates such as acetyl nitrates, benzoyl nitrates, thallium and cerium ammonium nitrates, dinitrogen tetroxide, nitronium hexafluorophophate(NO_2PF_6), nitrocobalt complex $(Co(NO_2)_6)^{3-}$, etc. were investigated for these oxidations. Representative examples are:



High valent nitrogen oxidants were used mainly at low temperature and in near stoichiometric amounts but frequently lack of selectivity were observed with good results mainly on simple and symmetrical substrates.

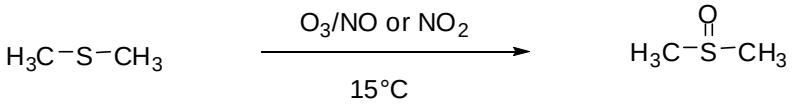
D) Ozone

The oxidation of thioethers to sulfoxides with ozone was first described in 1942 by Btihme and Fische and was subsequently widely used. One procedure involves bubbling ozone through a solution of sulfide in methylene chloride at –78°C. High selectivity is achieved using this reagent at very low temperature and under diluted conditions.

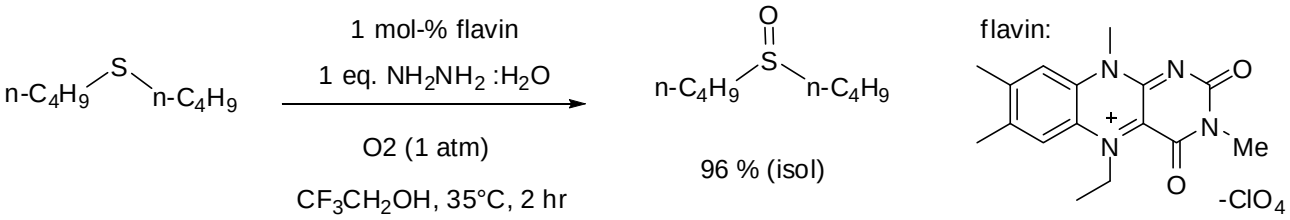


E) Oxygen

Oxygen is the more interesting final oxidant for the conversion of sulfides to sulfoxides, mainly inspired by similar biological conversions and the problem of control odor, toxicity and corrosion problems caused by sulfides in wastewaters. Several attempts to use this gas (or air) for this selective conversion have appeared using a large variety of inorganic and metal catalysts. One method, described by Smedslund and subsequently used by other workers, involves the use of nitric oxide or nitrogen dioxide as catalyst; sulfoxide yields are generally high. Bateman and co-workers studied the oxidation of thioethers using oxygen at temperatures between 45-75°C and in the presence of various catalysts. Further modifications have been made to this method, and recently catalysts such as ruthenium complexes, metal acetylacetonates, phthalocyaninecobalt complexes, and vanadium(V) oxide have been used to obtain highly pure aryl sulfoxides.



In 2003 oxidations of sulfides, with molecular oxygen in the presence of 5-ethyl-3-methyllumiflavinium perchlorate catalyst and hydrazine monohydrate in 2,2,2-trifluoroethanol was carried out in excellent yields.[37]



F) Enantioselective Biological Sulfoxidation

In past few decades promising results were obtained in biological sulfoxidation. Reviews on detailed study were published on these aspects, written by Michpl Madexlaire[34] in **1986**, Herbert Leslie Holland[38] in **1988**, Inmaculada Ferna´ndez and Noureddine Khiar[39] in **2003**. The enantioselective oxidation of sulfide to enantiomerically pure sulfoxides is undoubtedly the most direct and economical method to access these products and both isolated enzymes and whole cells were investigated.[40] From these studies specific enzymatic approaches, as well as chemical reagents that mimicking enzymes, have been developed.

F1) Enzyme-Catalyzed Sulfoxidation[41]

Isolated enzymes were used in the oxidation of prochiral sulfides for the first time by Walsh et al at the beginning of the 1980s.[42] The use of pig liver FAD-dependent mono-oxygenase afforded (R)-ethylp-tolylsulfoxide in 90% enantiomeric excess (ee), while flavin-containing cyclohexanone mono-oxygenase (CMO) from *Acinetobacter* afforded the opposite enantiomer with 64% ee. In a series of papers,

Colonna's group has shown that CMO is the most effective and general enzyme for the enantioselective synthesis of sulfoxides.[43] The stereochemical outcome of the enzymatic reactions has been shown to be highly dependent on the sulfide structure.

Peroxidases are another important class of enzymes that are able to catalyze sulfoxidation. To date, the most versatile one is a chloroperoxidase from *Caldariomyces fumago* (CPO), isolated by Hager,[44] and used by Kobayashi,[45] whereas Wong's group used similar chloroperoxidase-catalyzed oxidations[46]. Moreover, other peroxidase, such as vanadiumcontaining bromoperoxidase (VBrPO) from alga *Corallina officinalis*.[47] heme-containing chloroperoxidase (CPO) from *Caldariomyces fumago*,[48] horseradish peroxidase (HRP),[49] cytochrome c peroxidase (CcP),[50] microsome peroxidase (MP),[51] lactoperoxidase (LPO),[52] and dioxygenase[53] were also investigated and seldom found useful The double mutant Ph-43-His, Leu-29-His and His-64-Leu of the oxygen carrier myoglobin provides similarly an useful enzyme.[54]

F2) Microbiological Sulfoxidation

The great advantage of the utilization of whole cell biocatalysts comes from avoiding the need for enzyme isolation, as well as the provision of cofactors. Thus, even though the enantioselectivities achieved are less spectacular than with isolated enzymes, for preparative scale the production of chiral sulfoxides is more convenient. Biological oxidation of sulfides to sulfoxides using whole cells has employed mainly fungi and bacteria and, to a lesser extent, yeasts.[55]

Among the bacterial strains screened in the oxidation of metallocene sulfides, *Corynebacterium equi* ATCC 21107 gave the best results, allowing the oxidation of the ferrocenyl derivatives to the (RS)-sulfoxides with ee > 95%.[56] *Pseudomonas putida* UV4 and an engineered *Escherichia coli* which expresses the toluene dioxygenase (TDO) enzymes oxidize a wide range of alkylarylsulfides, substituted dithianes, and dithiolanes to sulfoxides.[57]

Strains expressing naphthalene dioxygenase (NDO) activity, such as *P. putida* NCIB8859 and an engineered strain of *E. coli*, oxidize a wide range of prochiral sulfides, leading to sulfoxides with S configuration in high ee's.[58] Holland's group has broadly studied the oxidation of prochiral sulfide by the fungi the fungus species are *Helminthosporium*, *Mortierella isabellina*, and NRRL 4671. The enantioselective oxidation of thiafatty acid[59] was first achieved by Buist[60] using baker's yeast (*Saccharomyces cerevisae* NRC 2335). Roberts,[61] using *S. cerevisae* NCYC 73. Boyd and Dalton by bacterium *P. putida* UV4 and *P. putida* NCIMB 8859.[62]

F3) Antibodies-Catalyzed Sulfoxidation

Schultz reported the synthesis of an antibody[63] directed oxidation of thioethers with sodium periodate. The antibody was raised against the aminophosphonic acid hapten 64. Since the hapten 64 contains a protonated amine at physiological pH, antibodies specific for 64 were expected to stabilize the incipient

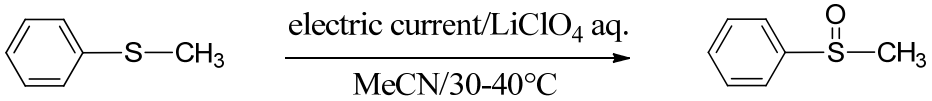
positive charge on sulfur present in the transition state in.[64] The obtained antibody 28B4.2 was shown to accelerate the oxidation of sulfide 65 by a factor of 2.2,[65] validating the synthetic design. The turnover and rate acceleration for antibody 28B4.2 reveal that this antibody is as efficient as numerous monoxygenase enzymes. The X-ray structure of the antibody with and without the hapten has been resolved at 1.9 and 2.2 Å, which has permitted the determination of the structural parameters responsible for the catalysis and the low ee (16%) observed. Recently, Keinan and Nimri reported an interesting antibody-metalloporphyrin that mimics natural oxidation enzyme.[65] On the basis of the catalytic cycle of metalloporphyrin-catalyzed sulfoxidation of thioanisole, the authors designed a hapten with an R-naphthoxy ligand as the transition state analogue.[66]

G) Microwave irradiation

Varma et al.[67] have reported for the first time the use of supported iodobenzene diacetate (IBD) as an oxidant for sulfides; the use of alumina as a support improved the yields remarkably as compared to neat. The solid IBD-alumina system has also been used for the rapid, high yielding and selective oxidation of alkyl, aryl and cyclic sulfides to the corresponding sulfoxides upon MW irradiation.[68] The oxidation of sulfides to sulfoxides and sulfones is achieved in a selective manner using MW irradiation under solvent-free conditions with desired selectivity to either sulfoxides or sulfones over sodium periodate ($NaIO_4$) on silica (20%).[68] A noteworthy feature of the protocol is its applicability to long chain fatty sulfides that are insoluble in most solvents and are consequently difficult to oxidize. An extension of these microwave promoted reactions is expected in the near future.

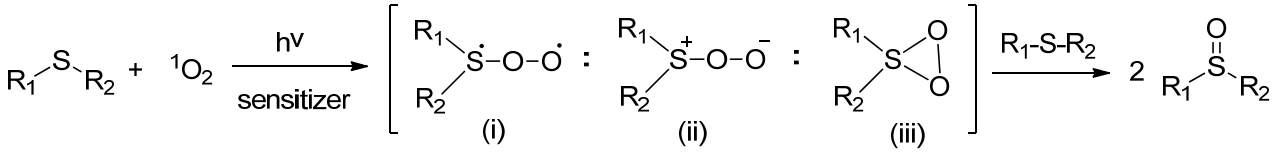
H) Electrochemical oxidation of sulfides

Among the less common methods of oxidation of sulfides is electrolytic oxidation carried out in various electrolyte solutions. In spite of several improvements, this method has remained rather unselective and often yields mixtures of sulfoxides and sulfones.

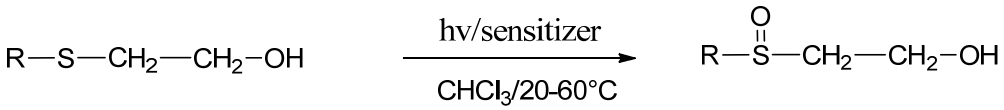


I) Photochemical oxidation of sulfides

Photo-oxidation of sulfides was first described by Schenck and co-workers in 1963. A number of intermediates have been suggested to explain the mechanism of the reaction. Gollnick has proposed an intermediate diradical of type (I) which reacts with a second sulfide molecule giving two sulfoxide molecules. Foote and co-workers have postulated the intermediate formation of a persulfoxide (II) or a highly reactive cyclic peroxide (III).



A very simple method for the photochemical synthesis of aliphatic sulfoxides has been proposed, involving UV irradiation of hexane solutions of sulfides. Other work describes the photooxidation of sulfides with high yields by irradiation with a mercury vapour lamp of thioether solutions containing photosensitizer such as bengal pink or phloxine, methylene blue, 9,10-dinitrile anthracene (DNA), 10-methyl phenothiazine (MPH) and titanium dioxide.



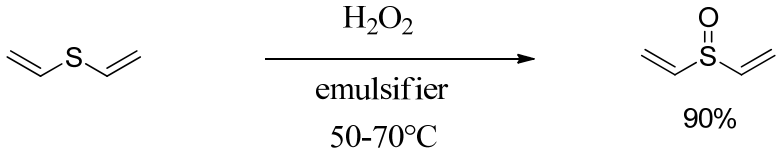
J) Hydrogen peroxide

Introduction

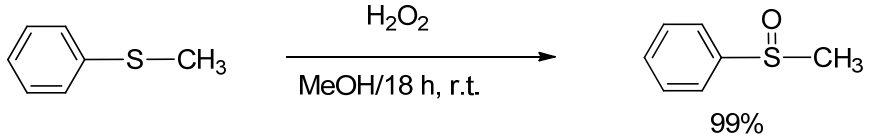
Hydrogen peroxide is the most attractive reagent after oxygen for these oxidation from an environmental viewpoint. It is an ideal waste-avoiding oxidant, since water is the only theoretical by-product, and is very attractive as an oxidant for liquid-phase reactions, thanks to its solubility in water and many organic solvents.[69] Moreover, aqueous hydrogen peroxide solution shows safety in storage, operation and transportation, is easy available on the market and is relatively cheap.[70] Hydrogen peroxide alone, without any organic solvents and catalysts, however, has to be used in a controlled manner, due to the possibility of over-oxidation reactions and accumulation of dangerous peroxide intermediates.[71] The oxidation of sensitive sulfides by hydrogen peroxide usually proceeds under relatively mild conditions and, in many cases, only a small excess of H_2O_2 is required.[72] Hydrogen peroxide, either alone or in the presence of catalysts, in various solvents under neutral, acid or alkaline conditions, is known to oxidize aromatic or aliphatic sulfides to the corresponding sulfoxides with high yields. It is noteworthy that frequently in these reactions dialkyl sulfides are more easily oxidized than diaryl sulfides.[73]

J1) Solvent effect in the oxidation of sulfides by hydrogen peroxide

Gazdar and Smiles did oxidation of sulfides to the corresponding sulfoxides by the use of hydrogen peroxide, in acetone and acetic acid as the solvents. Since that time, many sulfoxides were obtained by the use of their procedure and several papers published.[74] Addition of an emulsifier in the oxidation of unsaturated sulfide gives the corresponding sulfoxide with high yield.[75]



Drabowicz et al. observed that the use of methanol instead of acetone as the solvent in the case of thioanisole (**3**) oxidation by H_2O_2 to give the sulfoxide **4** speeds up the reaction time from 24 to 18 h.[76] The oxidation rate in methanol was, however, again slow, so that many functional groups in the sulfides were got destroyed.[77]



In 1998, Ravikumar et al.[78] reported the transformation of various sulfides into sulfoxides by H_2O_2 in hexafluoro-2-propanol (HFIP) as the solvent. The oxidation reactions in HFIP proceed smoothly with excellent yields of sulfoxides. Unfortunately, the HFIP is poisonous, expensive and volatile, which severely restrict its use in practical organic synthesis.

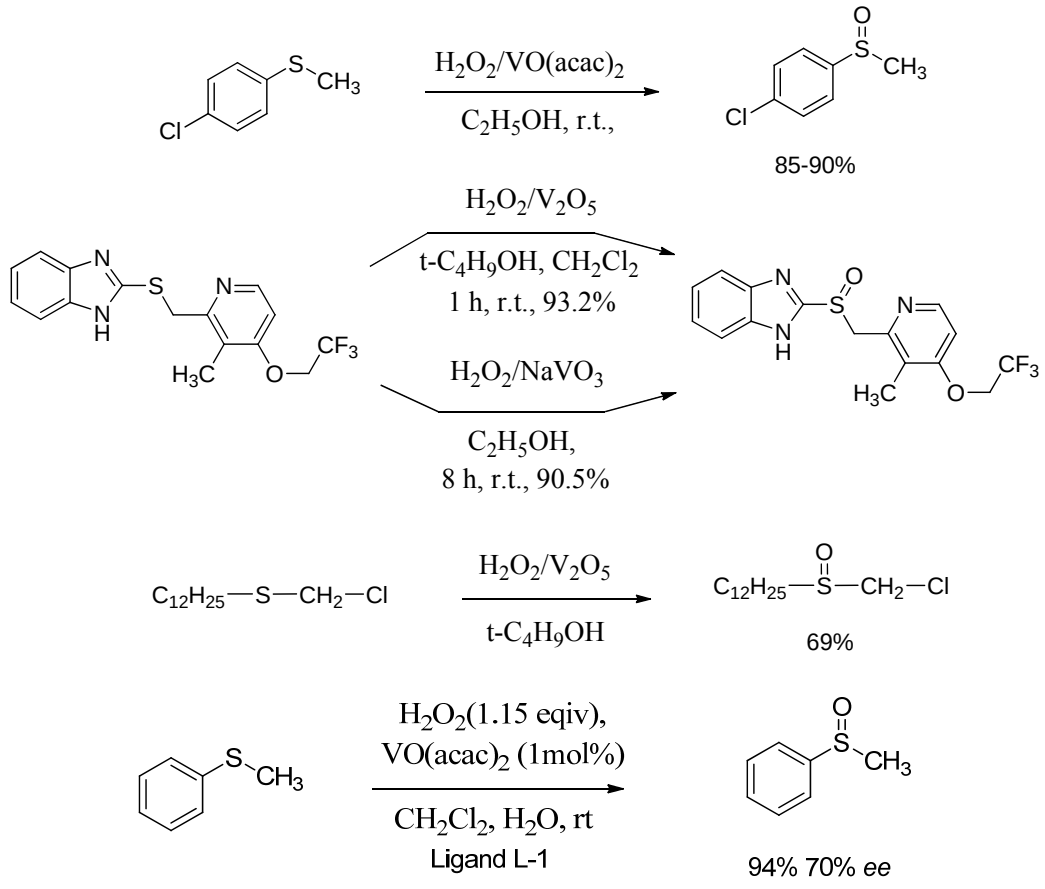
Recently, a new convenient and selective oxidation method of some alkyl phenyl sulfides to the corresponding sulfoxides was reported by Xu et al.[77] A large number of sulfides were tested in an oxidation by 30% aqueous H_2O_2 at room temperature in phenol as a solvent. This system is highly efficient and selective for the oxidation of various sulfides within a short reaction time and the authors found that the functional groups, even the highly reactive carbonyl, were unaffected.

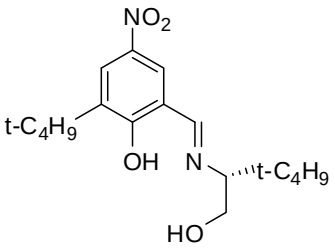
With respect to such aspects of innocuous chemistry, significant effort has been devoted to the development of sulfide oxidation in green solvents, such as supercritical carbon dioxide ($scCO_2$),[79] water[80] and polyethylene glycol.[81] In all these study, the solvent was mainly selected for its solubilizing properties on sulfide substrates or to favor the polar transition state expected for these oxidations.

J2) Metal catalysis in the oxidation of sulfides to sulfoxides by hydrogen peroxide

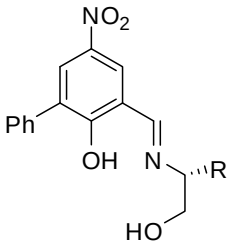
Dialkyl sulfides were shown to be oxidized with an excess of hydrogen peroxide in an alcoholic solvent at room temperature, even in the absence of any catalyst. Oxidation of diaryl sulfides can be achieved by the use of H_2O_2 only with various metal catalysts (Ti, Mo, Fe, V, W, Re, Ru and Mn).[82] By the use of chiral transition metal catalysts, selective transformation of a prochiral to a chiral sulfoxide was also demonstrated. Generally the chirality was acquired through a chiral ligand and late transition metals, such as Ti, V, Mo or Mn, produced the more active catalysts. It has been also found that the incorporation of these metals (Ti, V) in a zeolite framework affords valuable heterogeneous catalysts for the oxidation of sulfides under mild conditions.[83] In the following sections we will briefly review the main achievements in this area based on the specific metal used.

J2.1. Vanadium catalysts Vanadium complexes or salts were deeply investigated as catalysts for the oxidation of various sulfides.[84] The easily available V(V) species ammonium metavanadate (NH_4VO_3), vanadium pentoxide (V_2O_5), and sodium metavanadate ($NaVO_3$) were the most tested and applied reagents in these processes.[85] Vanadium(IV) compounds with various chiral ligands L-1 to L-10 were found to play an important role in the synthesis of a wide range of chiral sulfoxides and were deeply investigated.[86] Vanadium(IV) acetylacetonate [$(CH_3COCH_2COCH_2)_2$-VO] and vanadium(IV)–Schiff base L-1 complex was successfully applied for the first time in 1995 by Bolm and Bienewald for the oxidation by H_2O_2 of thioanisole to the corresponding sulfoxide with good enantioselectivity and under relative mild conditions.[87] Since 1995, vanadium(IV)–Schiff base complexes were modified by introducing an additional element of chirality into the salicylic aldehyde moiety in order to increase the selectivity of the sulfide oxidation.



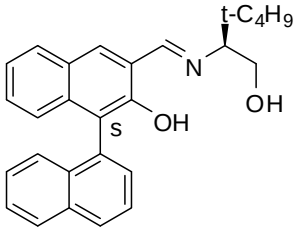


L - 1

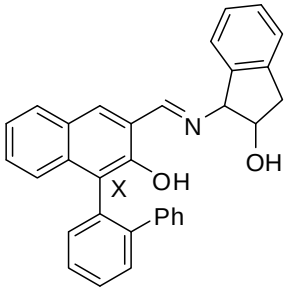


L - 3 R = i-C_3H_7

L - 4 R = i-C_4H_9

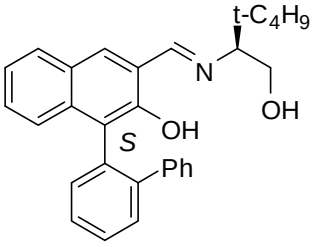


L - 2

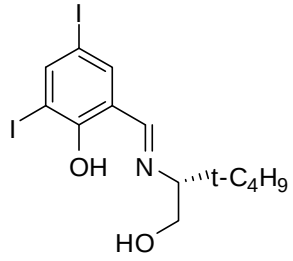


L - 5, X = *S*

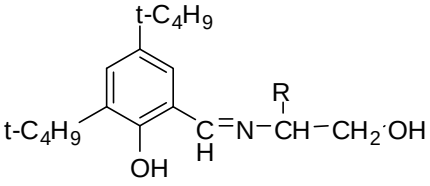
L - 6, X = *R*



L - 7



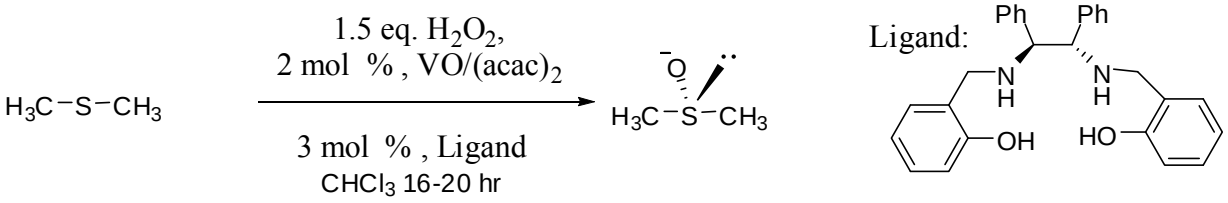
L - 8



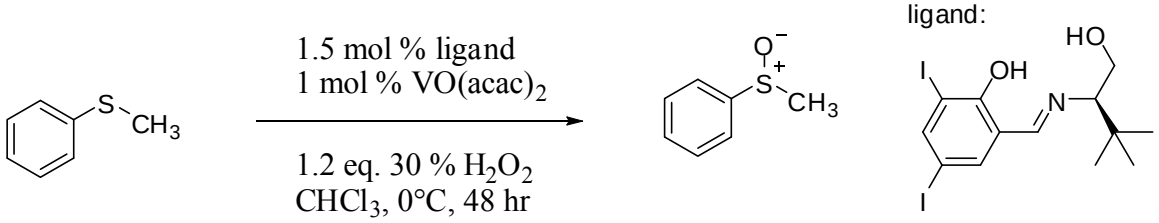
L - 9, R = Benzyl

L - 10, R = t-C_4H_9

High enantioselectivity was obtained with chiral vanadium-salan complex.[88]



The combination of very high enantiomeric excess with high yield was the consequence of an efficient initial asymmetric oxidation followed by an efficient kinetic resolution and makes the reported system very practical for the asymmetric oxidation of simple alkyl aryl sulfides.[89]



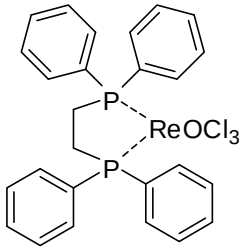
J2.2. Rhenium catalysts Several rhenium compounds acts as catalysts for the oxidation of sulfides. From an industrial point of view, the rhenium compounds are very attractive due to their non-toxicity, ease of storage and operation, air stability and resistance to autoxidation reactions.[90]

CH_3ReO_3

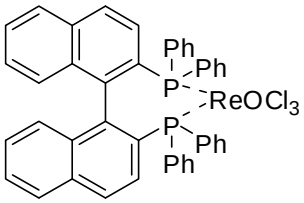
C - 1

$Re(PPh_3)_2OCl_3$

C - 2

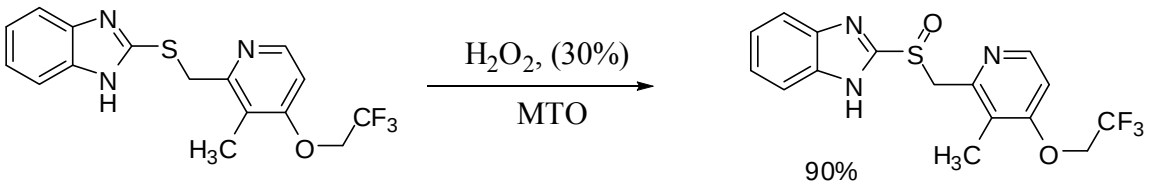


C - 3

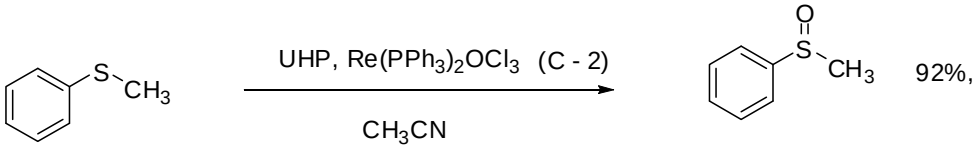


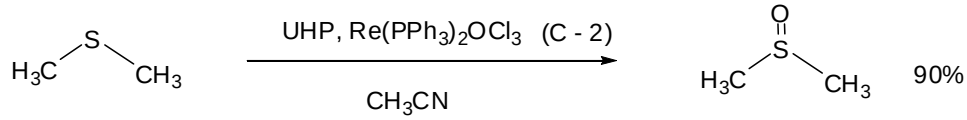
C - 4

Methyltrioxorhenium (MTO) (catalyst C-1) was found to be a particularly versatile oxygen-transfer catalyst for the oxidation of various sulfides by H_2O_2.[91] MTO was reported to have a high solubility in water and chloroform, dichloromethane, methanol, ethanol and acetonitrile. With this oxidant in methanol as solvent, anti-ulcer drug Lansoprazole (8) was synthesized with high yield (90%) and excellent purity (99.95%).[99]

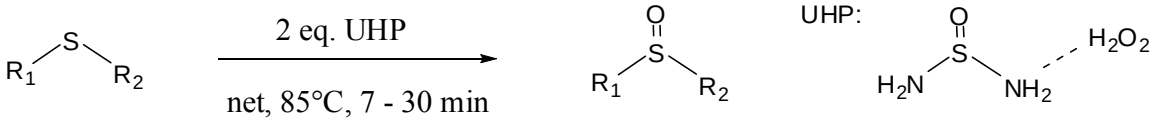


In 1998, Gunaratne et al.[92] reported the use of the rhenium (V) catalysts C-1 to C-4 for the oxidation of sulfides by a urea–hydrogen peroxide (1:1) adduct (UHP). The oxidation was carried out in various solvents such as chloroform, dichloromethane and acetonitrile. It was found that the use of catalyst C-2 limits sulfone formation the dialkyl sulfide is more easily oxidized than the alkyl aryl sulfide in the presence of the catalyst C-2.





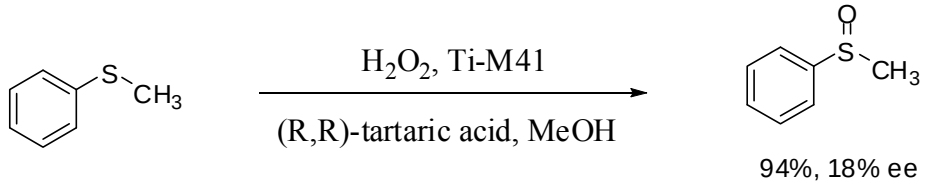
Urea-hydrogen peroxide adduct (UHP) is stable, inexpensive and an easily handled reagent. UHP is used in an efficient solid state oxidation sulfides to sulfoxides and sulfones,[93]



J2.3. Titanium catalysts In recent decades, much work has been done in the discovery of new Ti-containing zeolites as catalysts for the selective oxidation of sulfides into sulfoxides. A wide range of these catalysts such as Titanium trichloride ($TiCl_3$),[94] TS-1,[95] TS-2,[96] Ti-b,[97] Ti-MCM-41 (Ti-M41),[98] Ti-HMS,[99] and Ti-MMM[100] show good catalytic properties in a range of mild selective oxidations of sulfides with aqueous hydrogen peroxide.

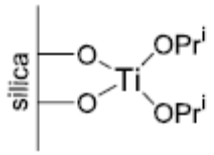
Titanium silicate TS-1, developed by the ENI researchers, has become an important commercial oxidation catalyst, typically used for oxidation of important industrial intermediates, i.e. caprolactam and alkene epoxides.[101] This catalyst was demonstrated to be applicable to the oxidation of relatively small sulfides, while Ti-b and Ti-mesoporous materials to the bulkier ones. Hulea et al.,[102] Robinson et al.,[103] and Reddy et al.[104] compared the activity of Ti-b, TS-1 and TS-2. The TS-1 and Ti-b have the same high activity towards the oxidation of small-sized substrates such as diethyl sulfide and Ti-b was more active than TS-1 in the oxidation of hindered molecules, such as di-n-butyl sulfide and diphenyl sulfide, due to its bigger pore diameter, TS-1 as a catalyst for oxidation. It was found that, the more hindered the sulfides, the less the sulfones were formed.

Oxidation of the methyl phenyl sulfide by H_2O_2 on Ti-MCM-41(Ti-M41) in various solvents and with or without a chiral modifier (*R,R*)-tartaric acid was studied by Iwamoto .[105] They observed that, when methanol was used as the solvent in the oxidation of thioanisole without the chiral modifier, the sulfoxide was obtained with a yield of 28 and 9% ee. Application of (*R,R*)-tartaric acid allowed to increase both yield (94%) and enantio-selectivity (18%). When the oxidations in the presence of (*R,R*)-tartaric acid were carried out in different solvents it was noticed that the polarity of the solvent had an influence on the asymmetric oxidation of sulfide.

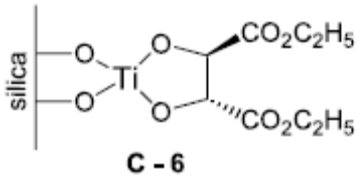


Kagan et al.[106] reported for the first time the use of titanium tetra-isopropoxide [$Ti(Oi\text{-}Pr)_4$] and diethyl tartrate as catalysts in the asymmetric oxidation of sulfide by hydrogen peroxide in 1984. Fraile and co-workers[107] supported $Ti(Oi\text{-}Pr)_4$ on silica and then treated this catalyst (C-5) with (R)-tartaric acid or diethyl (R)-tartrate. The catalysts obtained in this manner (C-6 and C-7) were found to be a highly

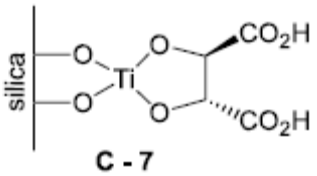
suited to the oxidation of sulfides into the corresponding sulfoxides by H_2O_2 and *tert*-butyl hydroperoxide (TBHP).



C - 5

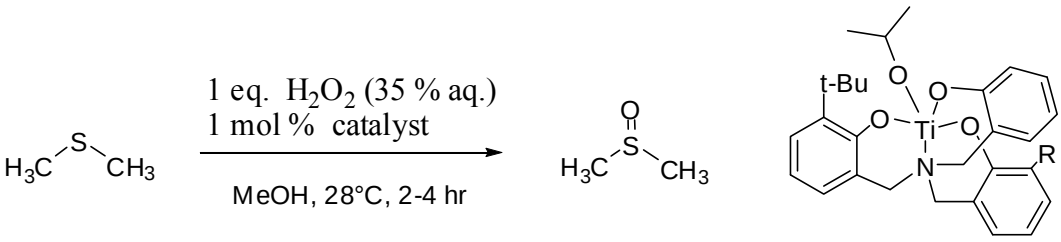


C - 6

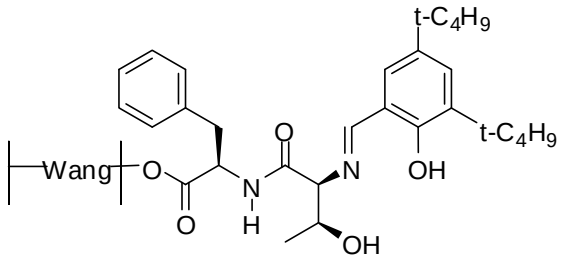


C - 7

An air and moisture tolerant complex of Ti(IV)[108] with a C3-symmetric triphenolate amine ligand efficiently catalyzes sulfoxidation reactions at room temperature without previous activation using aqueous hydrogen peroxide as oxidant.



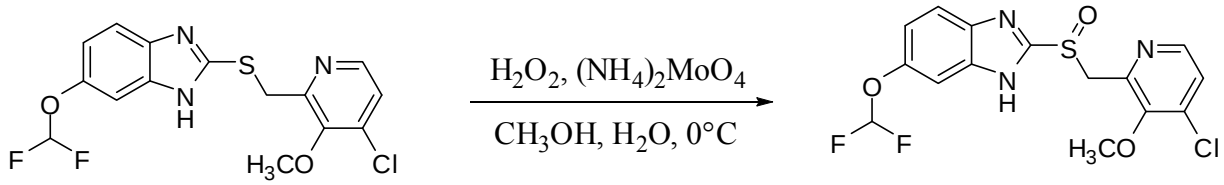
In 2001, Green and co-workers[109] reported a new efficient protocol for the oxidation of various alkyl aryl sulfides by aqueous hydrogen peroxide with a titanium–ligand complex supported on Wang resin (L-11). These authors synthesized several sulfoxides with a very good conversion of the sulfides into the sulfoxides with moderate enantioselectivity.



L -11

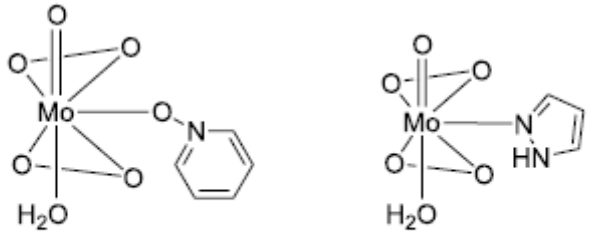
J2.4. Molybdenum catalysts Several molybdenum compounds are known as selective catalysts for the oxidation of various sulfides. Molybdenum salts such as molybdyldiacetylacetonate [$MoO_2(acac)_2$],[110] hexacarbonylmolybdenum [$Mo(CO)_6$] and molybdenum peroxide [MoO_5] are widely used as catalysts for the oxidation of sulfides by H_2O_2.[111] One of the main intermediates in pantoprazole (anti-ulcer agent)

synthesized[95] via the oxidation of sulfide [5-(difluoromethoxy)-2-{[(3-methoxy-4-chloro-2-pyridinyl)-methyl]thio}-1H-benzimidazole] by H_2O_2 in the presence of ammonium molybdate with very good yield (83%).



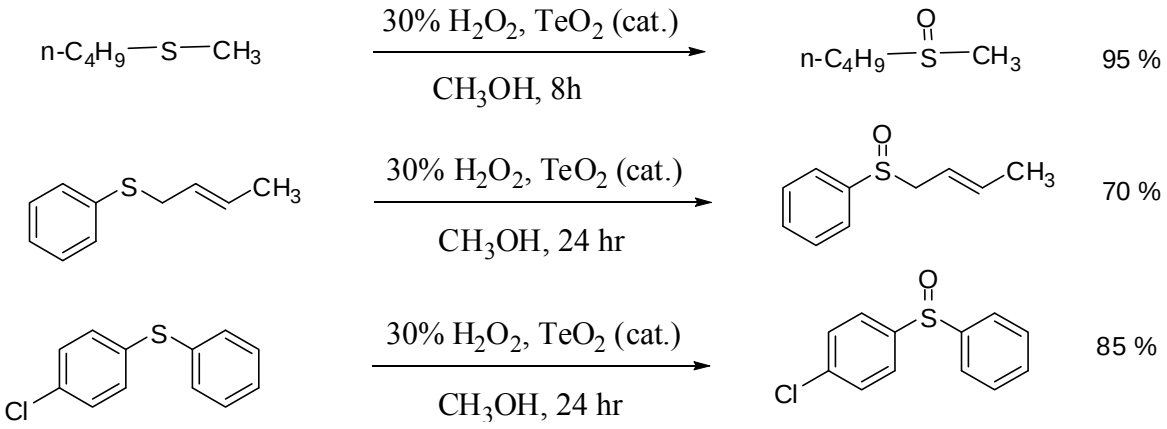
The substitution of Si^{4+} ions in an Al-free silicalite framework with Mo^{5+} ions gives a very efficient catalytic system for the oxidation of sulfides. The interest in these catalysts has increased in recent decades.[112] Raghavan and co-workers[113] have reported a hydrothermal synthesis of Al-free Mo-silicalite-1 (MoS-1). This catalyst is chemo-selective for oxidation of various sulfides into the corresponding sulfoxides by 30% H_2O_2 without the generation of sulfones.

Molybdenum(VI) (oxo,diperoxo)-pyridine-N-oxide (C-8) and molybdenum(VI) (oxo,diperoxo)-pyrazole (C-9) complexes coated on silica gel were investigated by Batigalhia and co-workers[114] as an oxidation system for the conversion of aliphatic and aromatic sulfides into the corresponding sulfoxides in high yield. By using complexes C-8 and C-9, carbonyl groups was not affected.



C - 8 C - 9

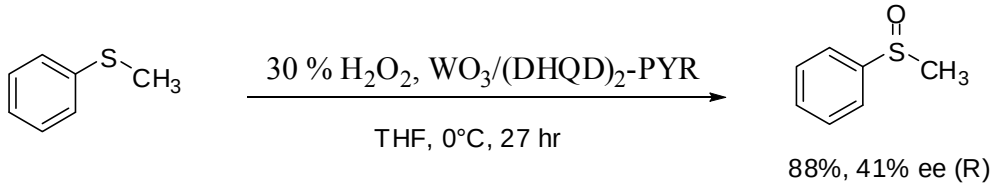
J2.5. Tellurium catalysts The complex H_2O_2–TeO_2 was described as a remarkably selective agent for the oxidation of sulfides into the corresponding sulfoxides.[115] In 1990, Kim et al. investigated the oxidation of various sulfides by the use of this catalytic system. The obtained results indicated that both aromatic and aliphatic sulfides are transformed into the sulfoxides, with high yield at room temperature. The oxidation of aliphatic sulfides, however, proceeds much more smoothly and in a shorter reaction time than the aromatic derivatives.



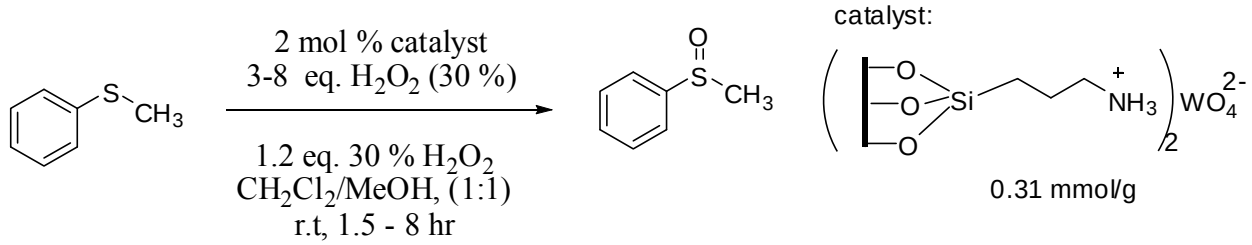
J2.6. Tungsten catalysts Tungsten catalyst systems such as the peroxotungsten complex [$WO(O_2)_2$, $HMPT/H_2O$],[116] tungstic oxide (WO_3),[117] tungstic acid [H_2WO_4],[118] hexacarbonyl tungsten [$W(CO)_6$],[116] $H_3PW_{12}O_{40}$, [$H_3(P(W_3O_{10})_4{\cdot}H_2O$],[119] [$C_5H_5N(n\text{-}C_{16}H_{33})]_3PO_4[W(O)(O_2)_2]_4$,[120] Na_2WO_4 and other tungsten complexes with various quaternary ammonium salts as phase-transfer catalysts[121] are used for the oxidation of sulfides.

Sato et al.[26] have investigated the oxidation of sulfides into the corresponding sulfoxides by H_2O_2 in the presence or absence of Na_2WO_4, $C_6H_5PO_3H_2$ and a phase-transfer catalyst (PTCZ[$CH_3(n\text{-}C_8H_{17})_3N$]$HSO_4$). The susceptibility of the sulfides to H_2O_2 was found to be highly dependent on the structure of the sulfides.

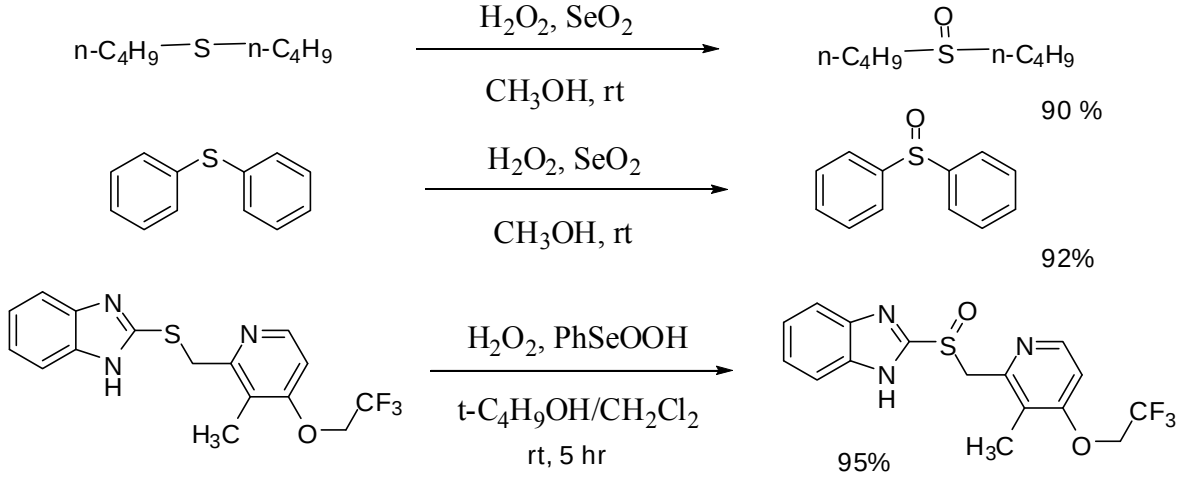
Thakur et al.[122] found a new tungsten heterogeneous catalytic system (WO_3–30% H_2O_2) useful for the asymmetric oxidation of various sulfides in the presence of cinchona alkaloids such as hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [(DHQD)2–PYR] with high yields and with good enantioselectivity. The oxidation of sulfides possessing benzyl group proceeded with the best enantioselectivity. The oxidation of phenyl benzyl sulfide by the use of WO_3–cinchona alkaloids as the catalyst was tested in various solvents and best yield of methyl phenyl sulfoxide 4 was achieved in THF.



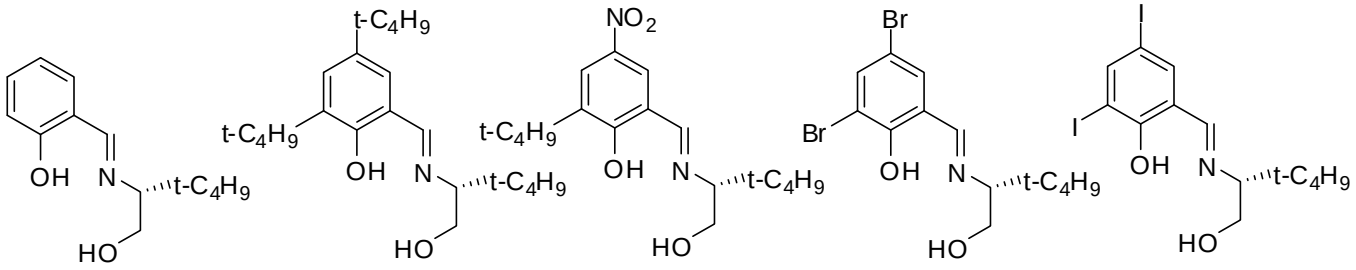
Various aromatic and aliphatic sulfides are selectively oxidized to sulfoxides and sulfones in good to excellent yields using 30% H_2O_2 in the presence of a recyclable silica-based tungstate interphase catalyst at room temperature.[123]



J2.7. Selenium catalysts Some selenium compounds are known to be efficient catalysts for the preparation of different sulfoxides. The use of selenium dioxide as a catalyst for the selective oxidation of dibutyl sulfide and diphenyl sulfide to the corresponding sulfoxides by hydrogen peroxide in methanol as the reaction medium was disclosed by Drabowicz et al.[102] Sulfoxides were obtained with high yields (92 and 90%, respectively). The application of benzeneselenic acid (PhSeOOH) as a catalyst for the oxidation of 2[[[3-methyl-4-(2,2,2-tri-fluoroethoxy)-2-pyridinyl]methyl]-thio]-1H-benzimidazole by 35% H_2O_2 allowed the synthesis of sulfoxide with excellent yield (95%). The reaction was carried out in a mixture of dichloromethane and *t*-butanol as the solvents at a temperature of 15–20°C.[124]

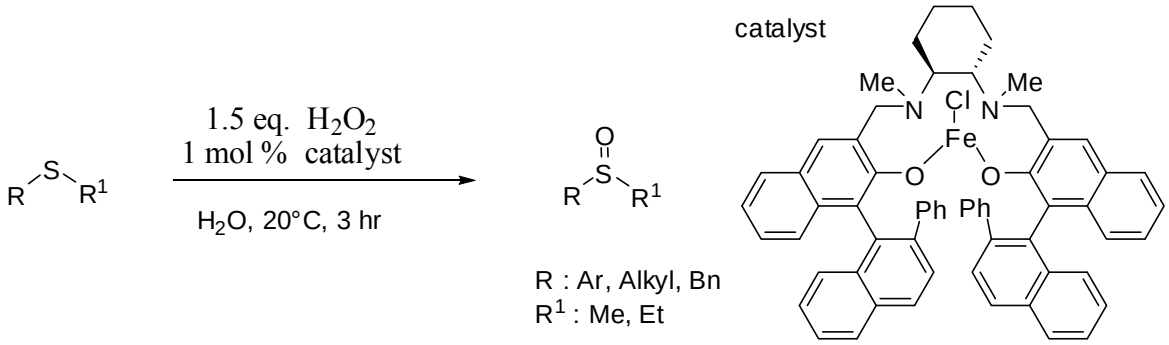


J2.8. Iron catalysts Recently, researcher attention was focused on iron complexes as H_2O_2 promoters such as $[Fe(acac)_3]$,[125] $Fe(NO_3)_3/FeBr_3$,[126a] Fe(Salen)[126b] and $[Fe_2O(pb)_4\text{-}(H_2O)_2](ClO_4)_4]$ (pb = 4,5-pinene-2,2,0-bipyridine).[126c] However, those iron-catalysed processes involves either complicated ligands to stabilize iron reactive species, or toxic solvents to promote the reaction. Iron complexes have a bigger advantage over many of the other catalysts due to their presumed non-toxicity and commercial availability and expected low cost. Legros and Bolm studied the iron-catalysed asymmetric oxidation of alkyl aryl sulfides in dichloromethane at room temperature, using H_2O_2 as the oxidising agent in the presence of various iron(III)–Schiff base complexes (L-12 to L-16). The sulfides were oxidised into the corresponding chiral sulfoxides with good enantioselectivity and moderate yields.

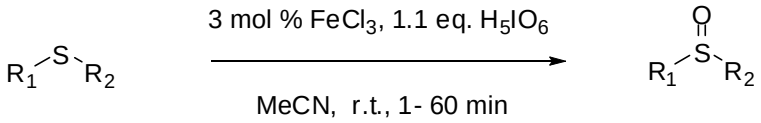


L - 12 **L - 13** **L - 14** **L - 15** **L - 16**

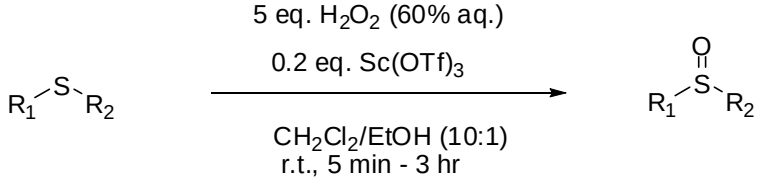
A chiral Fe(salan) complex serves as an efficient catalyst for asymmetric oxidation of sulfides using hydrogen peroxide in water without surfactant. Not only alkyl aryl sulfides but also various methyl alkyl sulfides were oxidized to the corresponding sulfoxides with high enantioselectivities.[127]



An excellent method for the selective oxidation of sulfides to sulfoxides[128] with periodic acid (H_5IO_6) catalyzed by $FeCl_3$ in MeCN has been devised. The reported procedure is fast, simple and the yields are excellent in most cases with reaction time of less than 2 minutes.



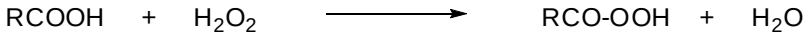
J2.9. Other metals For the oxidation of sulfides other metals complexes or salts were reported as catalysts such as, scandium,[129] manganese,[130] copper,[131] platinum,[132] magnesium,[133] cobalt,[134] silver,[135] zinc,[136] osmium and zirconium[137]. Scandium catalyst $Sc(OTf)_3$ deserves a special mention for the high yield, the compatibility with many widely used protecting groups, suitability for solid-phase applications and minimum over-oxidation.



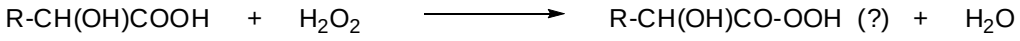
5.2.3 - Oxidations of organic compounds by ethyl lactate/hydrogen peroxide: a New Eco-Friendly Peroxyacids-like System.

As indicated in the introduction, we were interested in the use of organic solvents working as activators of hydrogen peroxide for oxidations of organic substrates. In principle, wide precedents exist for these systems because every organic molecule appears to be unstable in the presence of hydrogen peroxide. However our goal was to activate hydrogen peroxide toward specific substrates and not against the compound itself and this aspect has been less extensively investigated. In this direction, several potential solvent can be excluded owing to their known high reactivity toward hydrogen peroxide. For example, several ketones, aldehydes, amines gives rise in the presence of hydrogen peroxide to peroxide intermediates are so dangerous that their fast, uncontrolled, decomposition can occur. The only system of this type usefully applied until now are the liquid carboxylic acids which are known to afford sufficiently stable percarboxylic acids (peroxyacids) to be widely used as radical initiators, oxidant reagents, and sterilizing media, even if under appropriate defined conditions which avoid the formation of dangerous diacylperoxides.

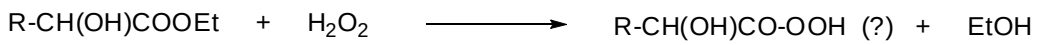
In general inorganic and organic acids undergo in the presence of hydrogen peroxide a reversible addition process to electrophilic centers (i.e. carbonyl group in carboxylic acid) producing at the same time the activated peroxyacid species and their stabilizing conditions toward decomposition.



Following a literature screening of the wide variety of peroxyacids known until now and industrially applied, our attention was attracted by the environmental friendly peroxyacid arising from biological low cost building blocks of alfa-hydroxyacid structure, e.g. lactic, tartaric and citric acids. We were surprised that no structural data were available from literature for these compounds, despite the fact that systems containing these products were claimed in patents as efficient oxidants and disinfectants.[138] This observation was further confirmed in our recent ^{17}O-NMR study[139] of in situ formed species from the corresponding acids, which was unable to identify any stable peroxide specie, in contrast with the easily identified peroxyacids arising from simple carboxylic acids. Moreover, in this study carbon dioxide was established as relevant decomposition product, suggesting a specific behavior of these alfa-hydroxycarboxylic acid/H_2O_2 mixtures, quite different from classical stable peroxyacids solutions.

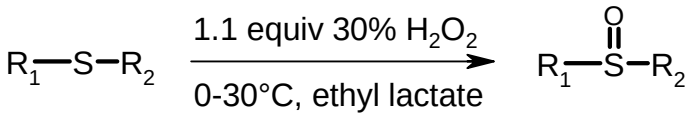


In order to better control the formation of these elusive percarboxylic acids we decide to use an alternative method for their synthesis, the perhydrolysis of the corresponding esters, but we found analogous difficulty in isolating any peroxide intermediate.



However, in the ester solvent the decomposition was slow enough to allow investigation of trapping reaction of possible intermediates with organic substrates. Between the systems investigated, the ethyl lactate/hydrogen peroxide was the most promising because selective oxidations of organic substrates, including conversion of sulfides to sulfoxides, were easily identified. The relevant aspect of this finding is that ethyl lactate is a green and economically viable alternative to traditional solvents: it is fully biodegradable, non-corrosive, non-carcinogenic and non-ozone depleting and has good solvating properties towards both unipolar and polar organic substrates; moreover, the so formed co-products, lactic acid and ethanol, were found to be easily recycled. In fact, ethyl lactate is approved by the U.S. FDA as pharmaceutical and food additive and has been generally recognized as a safe (GRAS) solvent.[140] The molecular structure of ethyl lactate possess a specific topology of hydrogen bonds, present as well in other alpha-hydroxyesters,[141] which allows the formation of intra- and intermolecular associations with ethyl lactate, as either proton donor or proton acceptor.[142] On the other hand, ethyl lactate is soluble in paraffin oils, which fact imposes the formation of significant van der Waals interactions.[143] Thus, this ester offers diverse solvent properties that may cover a large number of solutes. Consequently, there are reports in the literature of several attempts to use ethyl lactate as an extraction solvent. Typical examples are the extraction of carotenoids from different sources, such as tomatoes,[144] carrots and corn,[145] the recovery of bioactive bicyclic diterpene sclareol using ethyl lactate combined with CO_2 in a gas anti-solvent procedure,[146] recovery of squalene from olive oil deodorizer distillates[147] and of α-tocopherol from triglycerides.[148] Moreover natural ethyl lactate is a chiral compound [(−) ethyl L-lactate] with potentiality to induce enantioselectivity for chiral sulfoxides. All these data suggested us to investigate more deeply this system which appears to have a great potentiality to perform on industrial scale.

The investigation started with a screening of conditions on representative aryl-, vinyl and alkyl-substituted sulfides **1a-f**. Room temperature, near stoichiometric amount of 70% H_2O_2 and ethyl lactate in significant excess (40:1 molar ratio) were used in these experiments, obtaining the results collected in Table 5.1.



1 **2**

1a; $R_1 = CH_3$; R_2 = Ph — **2a**; $R_1 = CH_3$; R_2 = Ph

1b; $R_1 = R_2 = CH_2Ph$ — **2b**; $R_1 = R_2 = CH_2Ph$

1c; $R_1 = R_2$ = Ph — **2c**; $R_1 = R_2$ = Ph

1d; $R_1 = CH_3$; R_2 = 4-OMe-Ph — **2d**; $R_1 = CH_3$; R_2 = 4-OMe-Ph

1e; $R_1 = R_2$ = n-Bu — **2e**; $R_1 = R_2$ = n-Bu

1f; $R_1 = R_2 = CH_2$-CH=CH_2 — **2f**; $R_1 = R_2 = CH_2$-CH=CH_2

1g; $R_1 = CH_3$; R_2 = 4-NO_2-Ph — **2g**; $R_1 = CH_3$; R_2 = 4-NO_2-Ph

1h; $R_1 = CH_3$; R_2 = 4-CH_3-Ph — **2h**; $R_1 = CH_3$; R_2 = 4-CH_3-Ph

01i; $R_1 = CH_3$; R_2 = 4-CH_3O_2C-Ph — **2i**; $R_1 = CH_3$; R_2 = 4-CH_3O_2C-Ph

1m; $R_1 = C_{12}H_{25}$: $R_2 = CH_2CH_2SPh$ — **2m**; $R_1 = C_{12}H_{25}$; $R_2 = CH_2CH_2SPh$

1n; R_1 = Ph; $R_2 = CH_2CH_2SC_{12}H_{25}$ — **2n**; R_1 = Ph; $R_2 = CH_2CH_2SC_{12}H_{25}$

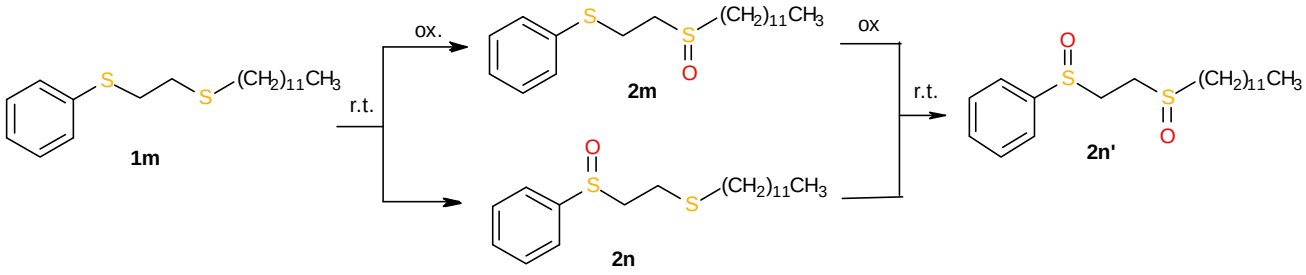
Table 5.1 - Oxidation of sulfides **1a-f** by H_2O_2 (1.1:1 molar ratio) in ethyl lactate (25°C)

Sulfide	**Additive (mol. %)**	**time (h)**	**Conv. (%)**	**----- Selectivity (%) ----**	
				R_1R_2SO (2)*	**$R_1R_2SO_2$ (3)**
1a	-	6 (24)	46 (99)	99 (83)	1 (17)
1b	-	6 (24)	45 (100)	85 (79)	15 (21)
1c	-	6 (24)	0 (2)	- (100)	- (100)
1c	*p*TSA (5)	6 (24)	48 (86)	100 (94)	0 (6)
1d	-	6 (24)	73 (92)	96 (91)	4 (9)
1e	-	6 (24)	24 (75)	100 (94)	0 (6)
1f	-	6 (24)	40 (80)	100 (92)	0 (8)

*No enantiomeric induction was observed in the obtained sulfoxide.

With methyl phenyl sulfide (**1a**) a conversion of 46% with near complete selectivity for the corresponding sulfoxide was reached in 6 hours at 25°C. By extension of the reaction time to 24 hours a conversion of 99% was obtained with a 83:17 relative ratio of sulfoxide to sulfone. The oxidation of methyl 4-methoxyphenyl sulfide (**1d**) was faster than the unsubstituted derivative **1a** (73% conversion in 6 hr) and more selective (sulfoxide to sulfone ratio 91:9). Dibenzyl sulfide (**1b**) behaves similarly to **1a,** without any by-product of oxidation at the benzylic position. On the contrary, diphenyl sulfide (**1c**) was only marginally oxidized in 24 h (2%), but the reaction was again promising when a catalytic amount (5%) of *p*-toluensulphonic acid (PTSA) was added to the system. The oxidation of di-n-butyl sulfide (**1e**) was slower than substrate **1a** with a 24% conversion in 6 hr and 75% after 24 hr, with higher selectivity for sulfoxide **2e**. The diallyl sulfide (**1f**) was of intermediate reactivity with good selectivity for sulfoxide **2f** and without any evidence of epoxidation at the double bond also at high conversion.

In order to understand better the influence of substituents on the relative reactivity of investigated sulfides, the model compound dodecyl 2-phenylthioethyl sulfide (**1m**), bearing two differently substituted sulfur atoms (arylalkyl and dialkyl), was synthesized and its oxidation with different oxidizing reagents was investigated. The compound was easily prepared by nucleophilic substitution of 2-chloroethyl phenyl sulfide with dodecanthiol in the presence of sodium hydroxide in ethanol (see experimental part). The aim of these experiments was to devise a simple approach to distinguish different oxidants from their chemoselectivity in oxidation of the dialkyl sulfide or phenylalkyl sulfide moiety of this substrate to give the alternative sulfoxides **2m** and **2n**, and the disulfoxide **2n'**. The oxidant system hydrogen peroxide in different solvents (including ethyl lactate) and *m*-chloroperbenzoic acid were used in this comparative study. Scheme 5.1 summarizes the structures of monosulfoxide isomers **2m** and **2n** and the disulfoxide **2n'** observed in these experiments. The distribution of these products is collected in Table 5.2.



Scheme 5.1 – Oxidation products of dodecyl 2-(phenylthio)ethyl sulfide (**1m**) by H_2O_2, *m*-CPBA and H_2O_2/ethyl lactate.

When an excess of oxidant was used, the oxidation affords essentially the disulfoxide **2n'** (Table 5.2, entry 6-7), whereas using stoichiometric amount of oxidant the sulfoxide **2m** was always obtained in preference over **2n** (Table 5.2, entry 1-5). However, hydrogen peroxide in ethyl acetate shows the best selectivity for **2m**, m-CPBA the lowest and ethyl lactate/H_2O_2 system an intermediate value with a propensity to form the disulfoxide **2n'**. The structure of disulfone **2n'** were confirmed by the comparison of the aromatic proton signals in ^{1}H-NMR spectra with the one of the isomers **2m**, independently prepared from **1m** by

oxidation with hydrogen peroxide in ethyl lactate and in ethyl acetate, respectively (see experimental part). As shown in Figure 5.1, the aromatic proton signals in the ^{1}H-NMR spectra of compound **2n'** are significantly shifted towards higher δ values compared to those of compound **2m** and starting reagent **1m**. Also ^{13}C-NMR signals were diagnostic to discriminate the isomers because the aromatic carbon bearing the differently substituted sulfur atom resonates at δ 134.39 and 131.55 ppm for **2n'** and **2m**, respectively, as expected for the more electron-withdrawing power of sulfoxide that sulfide substituent. Finally, the structure of **2n'** was confirmed by MS analysis.

Table 5.2 – Distribution of sulfoxide products **2m** and **2n'** in the oxidation of dodecyl(2-phenylthio) ethyl)sulfane (**1m**) with H_2O_2 in different solvents compared with *m*-CPBA.

Entry	Solvent	Oxidant	t (h)	Conv. (%)	Selectivity (%)	
					2m	2n'
1	CH_2Cl_2	H_2O_2	24	62	88	12
2	$(MeO)_2CO$	H_2O_2	48	47	85	15
3	Ethyl acetate	H_2O_2	144	19	96	4
4	*t*-Butanol	H_2O_2	48	54	85	15
5	Ethyl lactate	H_2O_2	5	88	65	35
6	Ethyl lactate*	H_2O_2	5	100	0	100
7	CH_2Cl_2*	*m*CPBA	5	43	1	99

*[Oxidant]/[**1m**] mol ratio = 2.

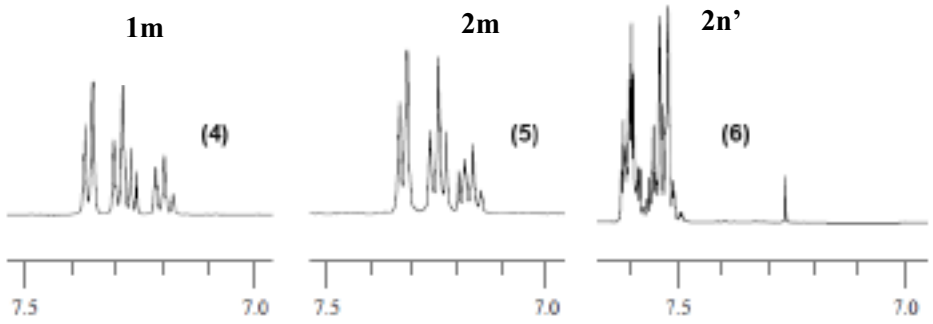


Figure 5.1 - ^{1}H-NMR spectra of sulfoxide isomers **2m** and **2n'** and sulfide **1m** in the range 7.0-7.5 ppm

The data of Table 5.2 clearly indicate a close analogy between the selectivity given by *m*-chloroperbenzoic acid (*m*-CPBA) and by the H_2O_2/ethyl lactate system, whereas hydrogen peroxide in other solvents (i.e. dichloromethane, dimethyl carbonate, *tert*-butanol and in particular ethyl acetate) shows a more high selectivity for alkyl substituted sulfide. Moreover, in these last solvents the oxidation of **1m** by H_2O_2 was remarkably slower, as generally observed in uncatalysed reactions of hydrogen peroxide. Interestingly, the selectivity observed with *m*-CPBA acid for disulfoxide **2n'** was also lower that the one observed with our system, confirming that a selective peroxyacid like intermediate is operative under the condition investigated.

This trend was generally observed also with other substrates, as reported in Table 5.3, where comparison is made between the selectivity sulfoxide/sulfone and conversions at the same reaction time, using the solvents ethyl lactate and dichloromethane with the oxidant hydrogen peroxide and *m*-CPBA. Methyl phenyl sulfide (**1a**), dibenzyl sulfide (**1b**), and diphenyl sulfide (**1c**) were selected as substrates for this study.

Table 5.3 - Selectivity trends in the oxidation of sulfides **1a-c** by hydrogen peroxide in dichloromethane and ethyl lactate vs. *m*-CPBA in the same solvents

Entry	Sulfide	Oxidant	Solvent	t (h)	Conv. (%)	Selectivity (%)	
						$R_2S=O$	R_2SO_2
1		H_2O_2	CH_2Cl_2	6	25	>98	<2
2	**1a**	H_2O_2	Ethyl lactate	6	46	>98	<2
3		*m*-CPBA	CH_2Cl_2	6	100	77	23
4		H_2O_2	CH_2Cl_2	6	66	85	15
5	**1b**	H_2O_2	Ethyl lactate	6	45	83	17
6		*m*-CPBA	CH_2Cl_2	6	100	65	35
7		H_2O_2	CH_2Cl_2	6	0	-	-
8		*m*-CPBA	CH_2Cl_2	6	100	85	15
9	**1c**	H_2O_2	Ethyl lactate	6	0	-	-
10		H_2O_2 *p*-TSA	Ethyl lactate	6	48	>98	<2
11		H_2O_2 *p*-TSA	CH_2Cl_2	6	0	-	-

After 6 hours, hydrogen peroxide in dichloromethane was relatively efficient in the oxidation of dibenzyl sulfide **(1b)** (66% conversion), moderate with methyl phenyl sulfide **(1a)** (24%) and completely inefficient with diphenyl sulfide **(1c)** (even in the presence of catalytic amount (5%) of a strong acid (*p*TSA)). In general, the peroxyacid *m*-CPBA was more reactive than H_2O_2 but suffers from a lower selectivity sulfoxide/sulfone.

The system H_2O_2/ethyl lactate shows an intermediate reactivity with high selectivity with methyl phenyl sulfide **(1a)**, moderate with dibenzyl sulfide **(1b)**, and no reactivity with diphenyl sulfide **(1c).** However, this last substrate was again efficiently oxidized in the presence of PTSA with a near complete selectivity for the sulfoxide at moderate conversions (48%). This activation by strong acid is however not related to the formation of the peroxyacid of PTSA because the system PTSA/H_2O_2 in CH_2Cl_2 was completely unreactive under analogous experimental conditions.

Attempts to use solid perhydrates (clathrate complexes of hydrogen peroxide), i.e. urea/H_2O_2 and picolinic acid/$2H_2O_2$[149] in CH_2Cl_2 were successful and afforded results similar to the those obtained with hydrogen peroxide alone, showing only a lower reactivity (see experimental part).

Finally, in order to improve information on the nature of the intermediate, a limited kinetic study on the effect of five *para* substituents (H, OMe, Me, COOMe, and NO_2) on the reactivity of X-phenyl methyl sulfides in the oxidation by ethyl lactate/H_2O_2 system was carried out. The observed rate constant (k_{obs}) were deduced from the decay curve of sulfide against time, quantitatively determined by gas chromatography, or from the decay of the peroxide by iodometry. Pseudo second order kinetic in sulfide concentration were found to fit better the experimental data than first order and the experimental rate constants were deduced from the plot of 1/[Sulfide] against time. The influence of temperature on oxidation of **1a** was also briefly investigated in the range 288-313 °C. The results of this analysis are summarized in Table 5.4.

Table 5.4 – Oxidation rate constants of sulfides **1a**, **1d**, **1g**, **1h**, and **1i** (0.20 M) by hydrogen peroxide (0.20 M) in ethyl lactate

1	**T**	**k_{obs} ($M^{-1}s^{-1}$)**	**R**
1a	288	3.71×10^{-3}	0.9899
1a	298	8.50×10^{-3}	0.9910
1a	313	2.42×10^{-3}	0.9887
1d	298	18.30×10^{-3}	0.9983
1g	298	1.42×10^{-3}	0.9951
1h	298	12.40×10^{-3}	0.9967
1i	298	3.50×10^{-2}	0.9923

A tipical plot used to recover the obsrved rate constant in the sulfoxidation of methyl p-tolyl sulfide **1h** is reported in Figure 5.2. The good linearity observed in the plot untill about 90% conversion of starting sulfide is indicative of a good selectivity in the oxidation to sulfoxide **2h**, with minor interference for the consecutive oxidation reaction of the sulfoxide to sulfone. The second order dependence of the rate is also indicative of the good overall stoichiometry and related to the equimolar amount of reagents used.

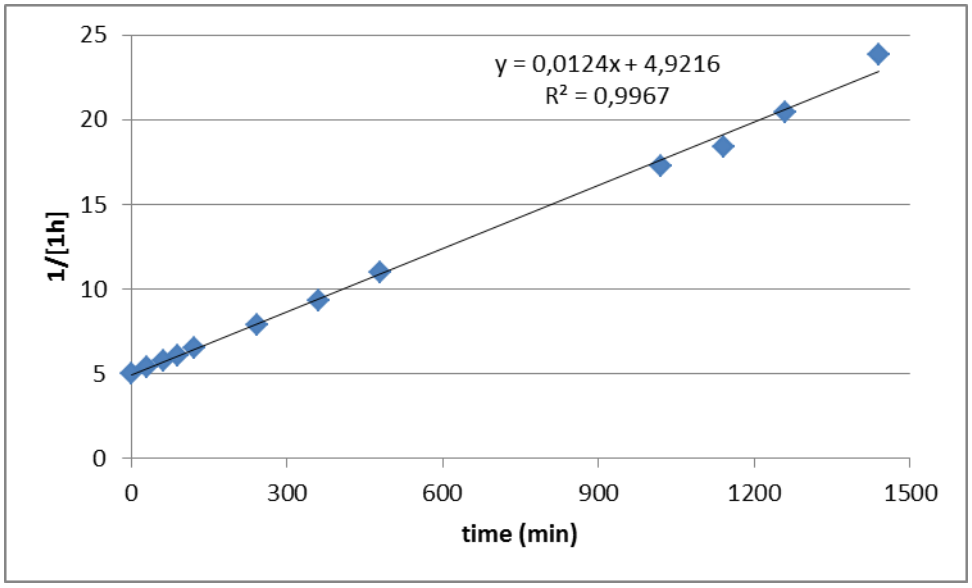


Figure 5.2 – Second order rate constant deduced from experimental data for the oxidation of **1h** by the system ethyl lactate/hydrogen peroxide (25°C, $[H_2O_2]$ = [**1h**] = 0.20 M)

From the results of Table 5.4 is possible to deduce two independent information on the kinetic of the reaction: one related to the effect of temperature and the second to the effect of substituents.

The rates of oxidation of sulfide model **1a** were determined at three different temperatures (Table 5.4, first three rows), collecting data untill about 70% conversion to avoid the consecutive oxidation reaction to sulfone. Despite the low number of data, we are confident that an estimate of the activation energy and preexponential factor of the reaction can be deduced. In fact, when the rate data were fitted as ln k_{obs} against 1/T, a good correlation was obtained (0.9991) which allows to obtain the kinetic activation parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$) reported in Table 5.5. A parallel analysis of oxidation of **1a** with *m*-CPBA affords the other data reported in Table 5.5.

Table 5.5 – Kinetic parameters for the oxidation of sulfide **1a** (0.20 M) by hydrogen peroxide (0.20 M) in ethyl lactate in the temperature range 288-313 K (from data in Table 5.4).

Oxidant	$E_a^{\ddagger}$ (kJ·mol^{-1})	ln A	$\Delta H^{\ddagger}$ (kJ·mol^{-1})	$\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})	$\Delta G^{\ddagger}$ (kJ·mol^{-1})
Perlactic acid	53.4± 1.2	16.9	53.4± 1.2	-105± 5	84.7± 2
m-CPBA	33± 2.5	18.0	33± 2.5	-77± 7	60.0± 4

The data in Table 5.5 indicate that the oxidation of **1h** exhibits an activation energy similar to one of peroxybenzoic acid. The large negative entropy is consistent with an orientation of reactants and solvent molecules in the transition state, in which significant charge separation along the reaction coordinate is circumvented via a 1,n-intramolecular hydrogen transfer. The negative activation entropy is common to oxidations with other peroxyacids. Moreover, $\Delta S^{\ddagger}$ value for the reaction of the sulfides with *m*-CPBA is less unfavourable than those with perlactic acid, though the $\Delta H^{\ddagger}$ is more favourable. The trends may reflect different transition state solvation or intramolecular hydrogen bonds requirements of charged and uncharged peroxyacids.

As concern the effect of para substituents on phenyl ring, a correlation was attempted between the kinetic data of Table 5.4 and Hammett substituent constants. Good correlation was found against sigma-para (σ_p) constants as reported in Figure 5.3. The negative ρ value observed (-1.04, i.e. electron-donating groups accelerate and electron-withdrawing retard reaction when substituted on sulfide but act conversely when substituted in the peroxide) is indicative of a partial positive charge created on sulfur atom in the transition state. Similar negative values (ranging from -0.7 to -1.2) were observed in the oxidation of similar substrates with peroxyacids, with hydrogen peroxide alone (ρ = -1.5)[150] or under catalysis of transition metal salts (V, W) and with high valent oxo anions (CrO_4^{2-}, MnO_4^-, IO_4^-).

Finally, in order to better understand the activating effect of the strong acid PTSA on the oxidation of sulfides in our system, a parallel experiment was carried out at 25°C on the system acetic acid/H_2O_2, which is well known to be catalyzed by strong acids, affording stable solution of the peracetic acid (PAA). We have followed the kinetic of the PAA formation and the total content of peroxidic species by using the iodometric titration. To avoid significant equilibration of the peroxide in the acidic conditions, the titrations were carried out rapidly with temperatures below 10°C.[151] The peracetic acid concentration [PAA] was determined directly from the thiosulphate titration of iodine liberated upon mixing with potassium iodide, whereas the total peroxide concentration [Ox] was determined from the initial titre plus the additional titre obtained upon the addition of ammonium heptamolybdate solution

(5%), which catalyzes the very slow reaction between hydrogen peroxide and iodide ions. The results obtained for the uncatalyzed and PTSA catalyzed reactions are reported graphically in Fig. 5.4 (a) and (b), respectively.

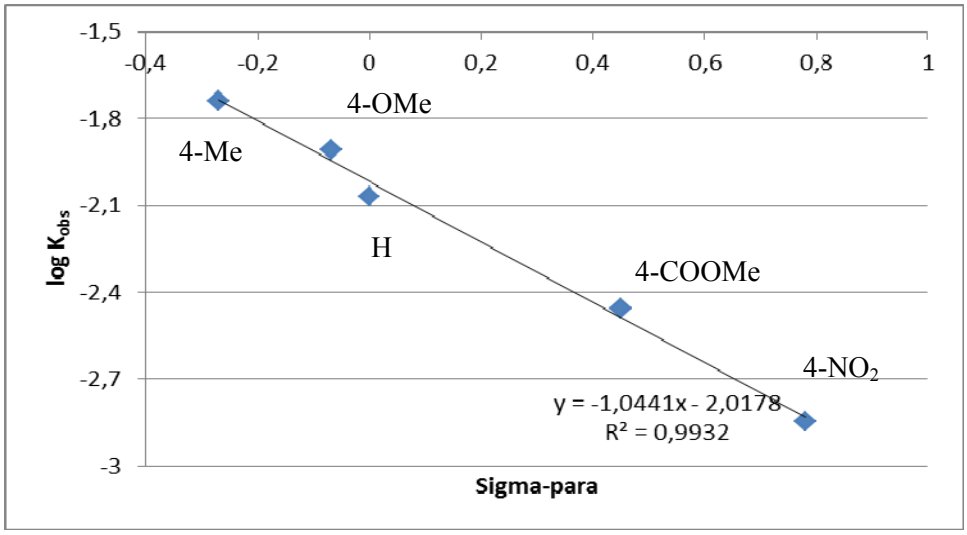
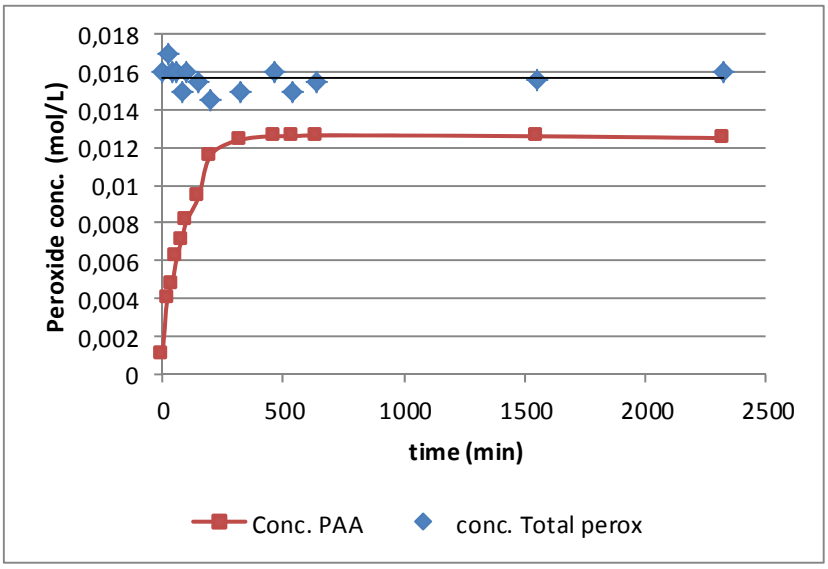


Figure 5.3 – Hammett plot for the oxidation of X-substituted methyl phenyl sulfides **1a**, **1d**, **1g**, **1h**, and **1i** by the system ethyl lactate/hydrogen peroxide (25°C)

Analyzing the data of Figure 5.4 as a pseudo first order kinetics in H_2O_2, the observed rate constant of 2.9×10^{-4} min^{-1} and 9.2×10^{-3} min^{-1} were deduced, respectively, for the uncatalyzed and PTSA catalyzed reaction. An increase in rate of 32 times is deduced under acid catalysis. Taking into account that these experiments were carried out at 0.2 M concentration of PTSA, whereas the reactions in ethyl lactate/H_2O_2 a concentration of PTSA was 0.01 M, an increase in rate with the last system > 20 times can be expected in the formation of the peroxylactic acid. Attempts to carry out similar experiments on ethyl lactate/H_2O_2 systems fail because peroxyacid and H_2O_2 could not distingished by titration.

(a)



(b)

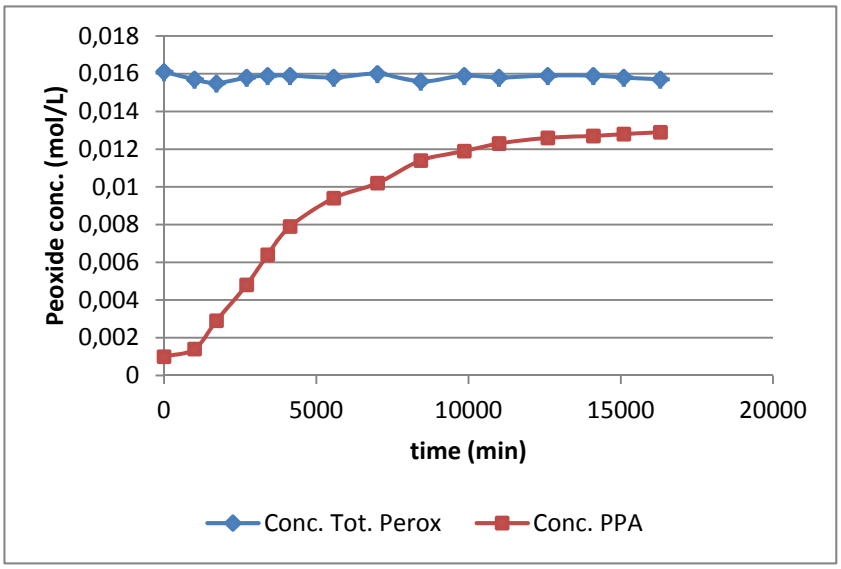


Figure 5.4 – Synthesis of peracetic acid from acetic acid and 30% hydrogen peroxide

(a) without p-toluensulfonic acid (PTSA), (b) with PTSA (0.2 M)

(25°C, [CH_3COOH] = 15.5 M, [H_2O] = 6.7 M, [H_2O_2] = 0.020 M)

Discussion.

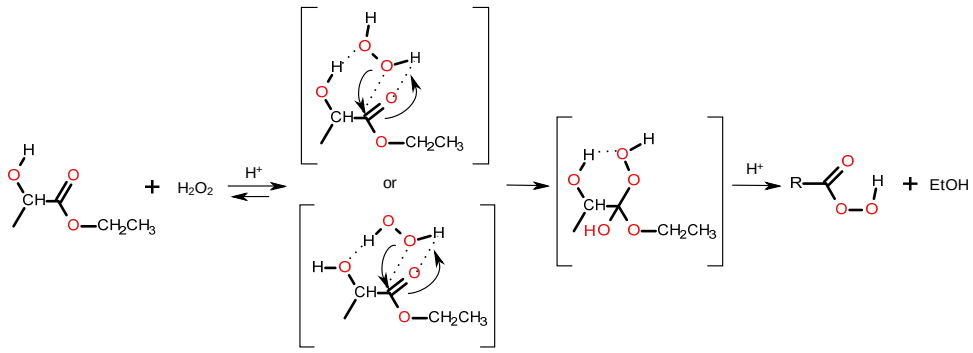
As indicated in the previous section the reaction of hydrogen peroxide with organic sulfides (**1**) in ethyl lactate as solvent occurs under mild conditions, requires near stoichiometric amount of hydrogen peroxide with a selectivity ratio between the products sulfoxide (**2**)/sulfone (**3**) from high at moderate conversion (< 50%) to moderate at high conversion. Both aspects were dependent on substituents present on sulfide, whereas no interference were observed from benzylic C-H bond nor from terminal double bonds. Water, ethanol and lactic acid, quantitatively detected in the reaction, does not inhibit significantly the reaction, as proved by the their addition of more than stoichiometric amount to the starting reaction mixture before adding the peroxide, with only minor decrease in rate. Moreover, a systematic increase in rate was observed with the ethyl lactate/H_2O_2 system when compared with analogous ethyl carboxylate (i.e. ethyl acetate)/hydrogen peroxide system. No significant enantiomeric induction was observed with the methyl aryl sulfoxides investigated.

The overall data obtained point out to the formation of perlactic acid as intermediate in the interaction of hydrogen peroxide and ethyl lactate (eq. 2). However, this perhydrolysis appears to be much faster than simple interaction of H_2O_2 with aliphatic esters (i.e. eq. 3), as well evidenced from the astonishing difference in behavior in the oxidation of disulfide **1m**.

$$\text{R-CH(OH)COOEt} + H_2O_2 \rightarrow \text{R-CH(OH)CO-OOH} + \text{EtOH} \qquad \text{(eq. 2)}$$

$$CH_3COOEt + H_2O_2 \rightarrow CH_3CO\text{-}OOH + EtOH \qquad \text{(eq. 3)}$$

An anchimeric assistance of the OH group (via the two alternative forms of Scheme 5.2 in which the OH group of lactate acts as hydrogen donor or as hydrogen acceptor toward hydrogen peroxide) along with the slightly higher electrophilic nature of carbonyl carbon atom must be present to explain the higher reactivity observed.



Scheme 5.2 – Suggested anchimeric assistance in the formation of peroxylactic acid by perhydrolysis of ethyl lactate.

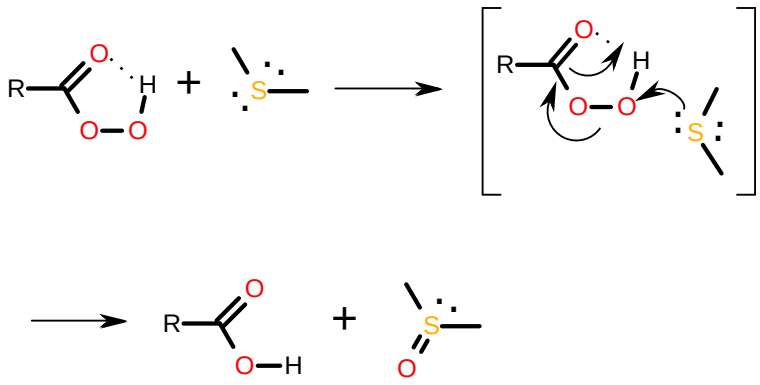
However, in principle this addition/substitution reaction can be reversible, as generally found in the synthesis of peroxyacid from carboxylic acid and H_2O_2. In these cases an equilibrium constant of 4.1 was measured at 25°C for peracetic acid from data of figure 5.6 and we suppose that a similar value of the equilibrium constant is operative also under our conditions. However, until now we were unable to determine any equilibrium between ethyl lactate and perlactic acid, but the existence of this fast equilibrium can explain why we can observe very slow oxidations (24-48 h), but also very fast reactions (i.e. < 15 minutes with phosphines, see following section).

In analogy with the catalytic effect of added strong acid in the formation of peroxycarboxilic acid from the corresponding carboxylic acid, the formation of peroxylactic acid is presumably catalyzed by PTSA and this can explain the significant increase in yield of diphenyl sulfoxide (**2c**) in the oxidation of diphenyl sulfide (**1c**). Moreover, PTSA can have a catalytic effect also on the oxygen transfer reaction from the peroxyacid (Modena has indicated that presence of trifluoroacetic acid as a catalyst accelerates the reaction of diaryl sulfides with peroxybenzoic acid)[152] and not only in the formation of peroxylactic acid itself. This hypothesis is difficult to verify kinetically under our conditions owing to the multiple role of acid in the sequence of the reactions involved in our system.

Moreover, it must be taken into account that also the lactic acid produced by the oxidation reaction can have an analogous, but probably less relevant catalytic effect, because carboxylic acids are generally stronger acids than the corresponding peroxyacids. For example, peracetic acid has a pK_a of 8.2, whereas acetic acid has a pK_a of 4.7 and an analogous effect is expected for peroxylactic acid.

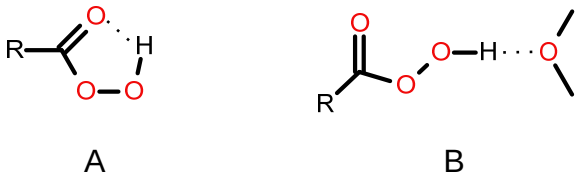
As concerns the oxidation mechanism of organic sulfides by peroxyacids, Overberger and Cummins[153] found that, using para substituted peroxybenzoic acids in toluene and isopropyl alcohol at -20 to -65°C, the reaction was first order in peroxyacid and first order in sulfide, with no apparent catalysis from the resulting benzoic acid. The reactions were characterized by low enthalpies of activation (21-46 $kJ \cdot mol^{-1}$) and large negative entropies of activation (-67 to -142 $J \cdot mol^{-1} \cdot K^{-1}$). Electron withdrawing

substituents on the peroxyacid increased the rate (a Hammett plot giving ρ = +0.91), whereas the electron withdrawing substituents on phenyl sulfides decrease the rate (a Hammett plot giving ρ from – 0.7 to -1.5). These authors suggested that the reaction occurs by a nucleophilic attack of a cyclic hydrogen bonded form of the peroxy acid by sulfide (scheme 5.3).



Scheme 5.3 - Proposed mechanism for oxidation of organic sulfides by peroxyacids

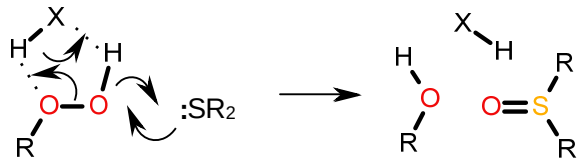
The oxidation was found to proceed faster in toluene than in isopropyl alcohol with lower energies and entropies of activation. Rate studies by Modena[154] with peroxybenzoic acid in a variety of solvents ($CHCl_3$, CH_2Cl_2, CCl_4, benzene, DMF, dioxane, t-BuOH, EtOH, MeOH, CF_3CH_2OH) demonstrated a rate increase with a change of solvent character from basic to non-basic solvents. There appears to be a general correlation of the rates with the capacity of peroxy acids to exist in either a chelate form (A) or an open-chain, solvated configuration (B).



A B

In the hydroxylic solvents, the reaction of sulfides with hydroperoxide or H_2O_2 was a second order overall, first order in both. It is not retarded by free radical inhibitors, but is clearly subject to acid catalysis.[155] Two mechanisms are offered to explain the above observations. The first (Scheme 5.4, equation 4) consists of a one-step interaction of sulfide with the peroxide-solvent complex. The dotted lines represent new bonds being formed, and the solid lines indicate the bonds that will break. The second

(Scheme 5.4, equations 5-7), involves an acid-base reaction between the peroxide and solvent with the resulting ion $ROO^{+}H_2$ as the active oxidant.



Eq. 4

$$RO\text{-}OH + H\text{-}X \rightarrow RO\text{-}^{+}OH_2 + X^{-} \qquad \text{Eq. 5}$$

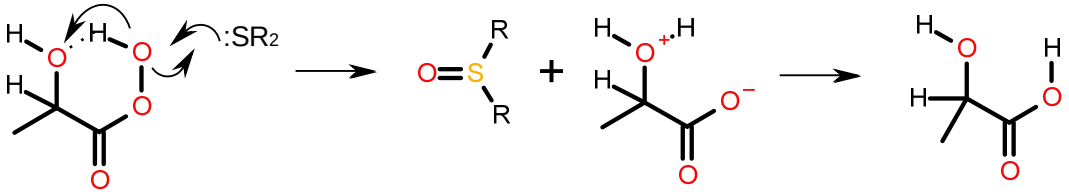
$$RO\text{-}^{+}OH_2 + R_1SR_2 \rightarrow ROH + R_1{}^{+}S(OH)R_2 \qquad \text{Eq. 6}$$

$$R_1{}^{+}S(OH)R_2 + X^{-} \rightarrow HX + R_1S(O)R_2 \qquad \text{Eq. 7}$$

Scheme 5.4 - Mechanistic alternatives in the oxidation of organic sulfides by hydrogen peroxide

Both mechanisms require the catalytic effect of a solvent, which varies according to its acidity, or added acid which assumes the role of solvent HX. Later Edwards[156] proposed that these reactions are influenced by solvation of the ground state of both the substrate and peroxyacids, and also the transition state. He proposed structures for the transition state in both protic and aprotic solvents which involve the bypassing of charge separation (scheme 5.4, eq. 4), proposing a mechanism involving formation of a sulphenium cation intermediate in the slow step.

In our study, the peroxylactic acid can display a similar activation by internal hydrogen bonding between the hydrogen of the peroxyacid and the basic oxygen of C-OH, as suggested in Scheme 5.5, whereas the catalysis of strong acid can follows the mechanism of Scheme 5.4, eq. 5-7.

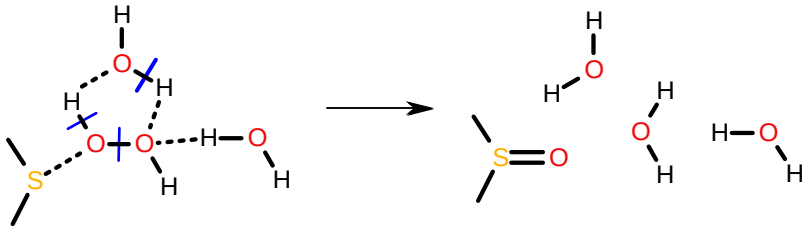


Scheme 5.5 – Supposed intramolecular activation active in perlactic acid

The influence of sulfur substituents on kinetic and chemo-selectivity of oxidation of sulfides to sulfoxides is relatively clear when substituents are on an aryl group linked to sulfur than when are directly linked to sulfur. Whereas in fact in the first case good correlations are generally observed for all peroxides with Hammett sigma *para* and *meta* substituent parameters (all negative ρ values from -0.7 to -1.5), a complex trend is observed for alkyl and aryl substituents. Also a recent paper stressed that linear free energy correlations fail for these reactions, and only applying the triparametric correlation equation of LDR theory can be obtained a quantitative description of structural effects on chemical reactivity.[157]

In general, however, peroxyacids oxidize more quickly arylalkyl substituted sulfides than alkyl substituted and diaryl substituted ones. This is generally interpreted as due to a combination of electronic and steric effects, the last being prevalent on the diaryl sulfides. On the contrary, it is well documented that hydrogen peroxide oxidize sulfides in the sequence Me_2S > n-Bu_2S > MeSPh > Ph_2S, the same order observed with high valent oxidants Cr(VI) and Mn(VII), I(VII).[158] In our experiments we observe that H_2O_2 in different solvents, and in particular in ethyl acetate, reacts slowly with **1m** but with a remarkable preference for the dialkyl substituted sulfur atom to give **2m**, whereas the system ethyl lactate/H_2O_2 was less selective affording significant yield of aryl substitetd sulfoxide **2n**. Meta-chloroperbenzoic acid (*m*-CPBA) behaves similarly to ethyl lactate/H_2O_2 system, but with even lower selectivity.

The different selectivity observed with hydrogen peroxide in different solvents and in ethyl lactate reflects the fact that hydrogen peroxide cannot be the effective oxygenating specie in the ethyl lactate/H_2O_2 system. Moreover, the increased reactivity of ethyl lactate/H_2O_2 system is in line with the general observation that peroxyacids are normally 10^3 (H_2O_2 with acid catalysis) to 10^7 (H_2O_2 without acid catalysis) times more reactive as oxidants than H_2O_2 or alkyl hydroperoxide.[159] This trend has been ascribed to the more organized transition state necessary for hydrogen peroxide, which requires the involvement of other hydrogen donor molecules (i.e. H_2O in scheme 5.6) to stabilize the transition state, and to the lower stabilization of HO^-anion respect to the $RCOO^-$carboxylate anion.

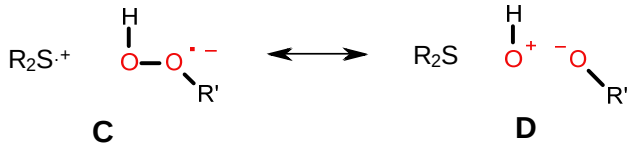


Scheme 5.6 – Hydrogen bonding in the activated state of oxidation of sulfide by hydrogen peroxide

Our best rationale at this time is that the electron-withdrawing substituents lower the energy of the O−O σ* orbital of the peroxyacid, which has the effect of moving the TS closer to the reactants side of the reaction coordinate with a complementary lowering of the activation barrier with a different

organization of hydrogen bonds in the transition state. This also means that electron-withdrawing substituents on peroxide induce a more hard electrophilic character to oxygen that H_2O_2[160] and our intermediate lies within *m*-CPBA and H_2O_2, as can be expected for peroxycarboxylic acids. The increase of positive charge on the sulfur atom in the transition state from *m*-CPBA, our "perlactic acid" and H_2O_2 therefore can explain both the lower rate and the higher selectivity (higher Hammett ρ values in methyl phenyl sulfide oxidation). The high selectivity observed with ethyl lactate/H_2O_2 system compared with other unsubstituted peroxycarboxylic acids is certainly to ascribe to a greater importance of intramolecular proton transfer in stabilizing starting reagent and transition state.

At the same time, alkyl sulfides are more soft nucleophiles than the aryl ones as indicated by the softness parameter μ of 0.73 for dibutyl sulfide and -0.03 to 0.02 for diphenyl sulfide.[161] It has been pointed out that oxidations by peroxyacids can be written as if they involve HO^+ as an electrophilic intermediate, although there is strong evidence that such an intermediate is never a free species, and we can write the transition states **C** or **D** for sulfide oxidation as resonance hybrids. Nucleophilicities have been related to ionization potential, and a description of the transition state as the following resonance hybrid fits this hypothesis.



C **D**

The ionization potentials of sulfide derivatives increase from diphenyl sulfide to phenyl methyl sulfide to dibutyl sulfide (Table 5.6) and this trend was not observed with peroxyacids and H_2O_2 but the generally observed lower reactivity of diphenyl sulfide has been justified by steric hindrance in solution. The lower ionization potential of aryl substituted sulfides compared with the alkyl substituted ones does not agrees with the results of oxidation with peroxyacid and H_2O_2 but the general trend of increasing amount of aryl alkyl sulfide oxidation in the disulfide **1m** (lower selectivity) follows the increased preference for electron-transfer in the transition state. Mowever, it must be pointed out that with dialkyl sulfides the HOMO is localized on the heteroatom (n_S (p_y) orbital), while this is not necessarily the case for aryl alkyl derivatives. In thioanisole **1a**, for example, one electron pair of sulfur atom is coplanar with the aromatic ring and the HOMO is a π (p_z) orbital.

Table 5.6 – Ionization potential of sulfide **1a**, **1d**, and **1e**.

Sulfide	IP/eV	Orbital type	Ref.
$(CH_3)_2S$	8.40	$n(p_y)$	Ref A
$(n\text{-}Bu)_2S$	8.22	$n(p_y)$	Ref. A[162]
$PhSCH_3$	8.03	$\pi(p_z)$	Ref. B[163]
PhSPh	7.90	$\pi(b1)$	Ref. C[164]

Thus, H_2O_2 would selectively oxidizes the dialkyl substituted sulphur, giving the corresponding sulfoxide through a sulfur-cation intermediate, (Scheme 5.4, Table 5.1 - entries 1, 2, 3, 4), while *m*-CPBA and other peroxyacids would lead to the formation of aryl substituted sulfoxide by means of an electrophilic attack on the aryl substituted sulphur (Scheme 5.4, Table 5.1 - entry 6).

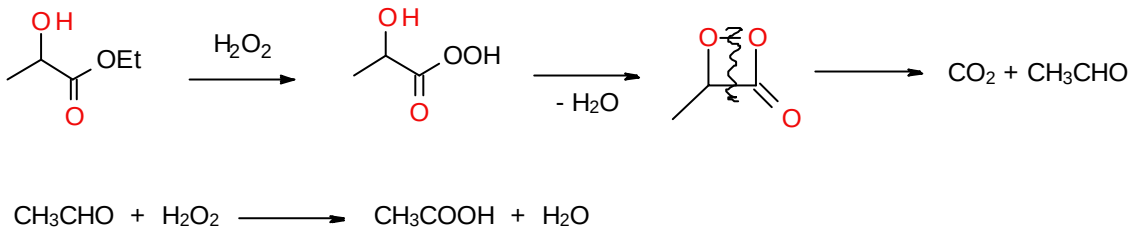
As concern the selectivity sulfoxide to sulfone is known that peroxyacids are relatively selective for the first oxidation stage. For example, peracetic acid in acetic acid oxidizes diphenyl sulfide to sulfoxide about a thousand times faster than the sulfoxide to sulfone,[165] and *m*-CPBA is about fifty times more reactive in the same direction. The peroxydic specie involved in our system appears to have selectivity reminiscent of simple peroxycarboxylic acids (about 50-100 times) and also this supports its peroxyacid nature.

A final point to point out is the apparent unreactivity of electron poor sulfides (i.e. **1d**) towards the ethyl lactate/H_2O_2 system in the absence of PTSA at 25°C. Under these conditions, or in total absence of any substrate, the ethyl lactate/H_2O_2 system undergoes a slow spontaneous decay of the total peroxide as measured by iodometric titration. The decay rate is much faster than the one generally observed with other aliphatic and organic peroxyacids, which are known to react at moderate to low temperature by auto decomposition to produce parent acids and oxygen, with a decomposition rate, v, maximized at the pK_a 10, and following Equation 8.

$$\text{Rate law } v = k\,[\,RCO_3H]\,[RCO_3^-] \qquad [8]$$

At higher temperatures, the thermal decomposition is mainly homolytic and the dissociation energy of the O-O bond has been reported from activation energies to be 30 to 34 kcal·mol^{-1}.

The instability of the system ethyl lactate/hydrogen peroxide must be related to a specific reactivity of the intermediate involved; therefore, if peroxylactic acid is the intermediate, there must be a special intramolecular reactivity of this compound. Between the several reaction pathways envisaged, the intramolecular cyclization to give 4-methyldioxetanone (a four membered peroxylactone) can be envisaged as a plausible labile intermediate decomposing by CO_2 extrusion to acetaldehyde (Scheme 5.7). Carbon dioxide was effectively detected during the spontaneous decay of the ethyl lactate/H_2O_2 system, whereas acetaldehyde was detected only in trace amount, but acetic acid was observed in near stoichiometric amount. The formation of this compound can be explained if the intermediate acetaldehyde is fast oxidized by oxygen insertion.



Scheme 5.7 – Proposed reaction sequence for the spontaneous decay of perlactic acid

The decay of the oxidant intermediate can explain why ethyl lactate/H_2O_2 system is unable to epoxidize 1-octene, even in the presence of *p*TSA. The presence of this competitive reaction is a clear limit of our system which can therefore work only with substrates reacting faster than the spontaneous decay of peroxy intermediate.

Sulfides belong to a class of compounds sufficiently reactive to trap the intermediate oxidant and this make possible to obtain sulfoxides in synthetically useful yield. To prove this aspect we have collected in Table 5.7 the results reported in literature for the oxidation of thioanisole **1a** by hydrogen peroxide under the catalysis of different reagents, organic and inorganic and compared with our best data at 25 and 45 °C. The potentiality of this oxidation is clear as concern mild condition, selectivity, number and complexity of reagents, green solvent use, and cost. The only main limit is that the reaction is relatively slow but we know that can be accelerated by strong acids.

Table 5.7 - Comparison of the potential activity of ethyl lactate with reported catalysts in the oxidation of methyl phenyl sulfide **1a** by hydrogen peroxide

Entry	**Catalyst** (mol ratio)	**Conditions**	**Time (min)**	**Yield (%)**	**References**
1	-	Ethyl lactate/H_2O_2 25°C	1080	94*	This thesis
2	-	Ethyl lactate/H_2O_2 45°C	240	92*	This thesis
3	β−Cyclodextrin	H_2O, 100°C	240	89	[166]
4	WO_3/MCM-48	MeOH, r.t.	240	97	[167]
5	$Mn(TPPBr_3)OAc$	CH_2Cl_2, r.t.	2	-	[168]
6	Carbon-based solid acid	CH_2Cl_2, reflux	10	94	[169]
7	SiO_2-W_2-Py	MeOH/CH_2Cl_2, 8°C	150	90	[170]
8	UHP (1.5)	Solid state, reflux	15	80	[171]
9	$(Bu_4N)_3[PMo_{12}O_{40}]$/Fap	Solid state, 4°C	4320	85	[172]
10	Cyanuric chloride (0.4)	THF, r.t.	10	96	[173]

*Under optimized conditions (1:1 molar ratio H_2O_2/ethyl lactate)

EXPERIMENTAL

Chemicals and reagents.

Chemicals (dodecanthiol, 2-cloroethyl phenyl sulfide, dibenzyl sulfide, diphenyl sulfide, diallyl sulfide, di-n-butyl sulfide, H_2O_2, *m*-CPBA, *p*TSA,) and solvents (ethanol, dichloromethane, methanol, dimethyl carbonate, ethyl acetate, *tert*-butanol, (−) ethyl L-lactate) were purchased from Fluka, Merck and Aldrich chemical companies and used without further purifications, unless expressly indicated. The 4-X-phenyl methyl sulfides (X = H, OMe, Me, COOMe, NO_2) used in kinetic determination were freshly distilled or crystallized from hexane.

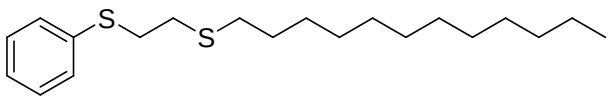
General Methods.

^{1}H-NMR (400 MHz) and **^{13}C-NMR** (400 MHz) spectra were recorded with a Bruker AV 400 equipment using a 5 mm multinuclear probe with reverse detection. Generally, 16 scans were acquired with an acquisition time of 5 seconds. All NMR data are referred to TMS as internal standard (δ units).

GC-MS analyses were performed using an Agilent 6890 Gas Chromatography (GC) system equipped with a 30m × 0.250mm HP-5MS GC column and an Agilent 5973 Mass Selective Detector (MSD). Data were elaborated with the Agilent software using NIST reference MS database.

Synthesis of dodecyl 2-(phenylthio)ethyl sulfide (**1m**).

To a solution of dodecanthiol (0.015 mmol, 3.57 mL) in ethanol (15 mL), aqueous 10% NaOH solution (6 mL) was added under stirring at room temperature. The resulting mixture was added in 10 minutes to the solution of 2-cloroethyl phenyl sulfide (0.015 mmol, 2.19 mL) in ethanol (15 mL). The resulting reaction mixture was heated at reflux under vigorous stirring for 15 minutes. Then, the system was cooled at room temperature and the white precipitate present was filtered, washed with ethanol and then recrystallized from methanol, obtaining the dodecyl 2-(phenylthio)ethyl sulfide as white crystals in 46 % yield.



Mp 34-35 °C. MS (ESI): m/z = 361.2 $[M+Na]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.89 (t, J = 6.7 Hz, 3 H), 1.25-1.40 (m, broad, 18 H), 1.55 (m, 2 H), 2.53 (t, J = 7.3 Hz, 2 H), 2.73 (m, 2 H), 3.10 (m, 2 H), 7.20 (m, 1 H), 7.29 (m, 2 H), 7.36 (m, 2 H) (Figure 5.5a). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 14.02, 22.63, 28.82, 29.18, 29.29, 29.47, 29.55, 29.58, 29.60, 29.71, 31.62, 31.87, 32.24, 34.17, 126.37, 128.95, 129.88, 135.62 (Figure 5.5b).

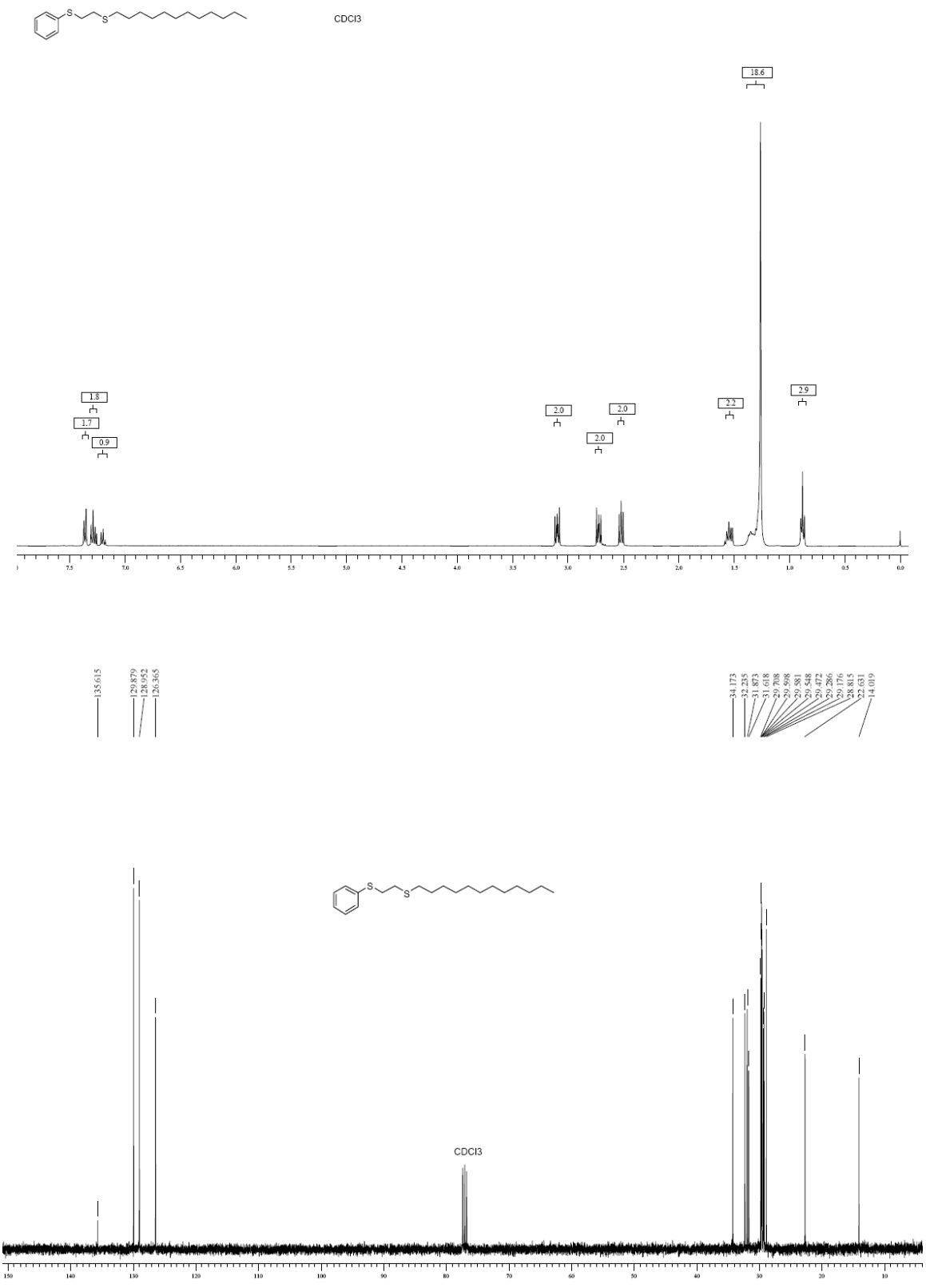
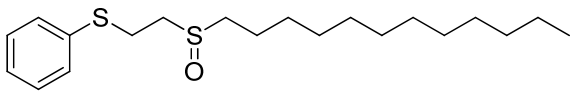


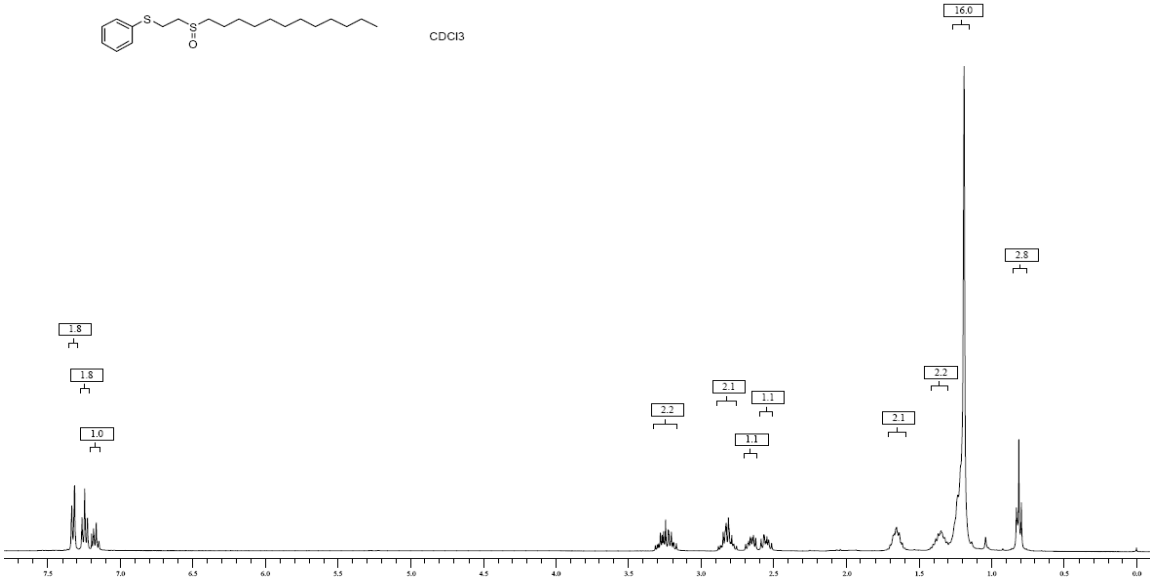
Figure 5.5 – a) ^{1}H-NMR and b) ^{13}C-NMR spectra of disulfide **1m**.

Synthesis of 2-(dodecylsulfinyl)ethyl phenyl sulfide (2m).

The obtained dodecyl 2-(phenylthio)ethyl sulfide **1m** (0.36 g, 3.065 mmol) was dissolved in 30 mL of CH_2Cl_2, then an equimolar amount of 70 % aqueous H_2O_2 was added. The resulting solution was stirred at ambient temperature for 9 days, monitoring the reaction by GC-MS analysis. Then, the solution was diluted in 30 mL of H_2O, extracted with CH_2Cl_2 (3x20 mL) and the combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica-gel, (AcOEt as eluent), obtaining 0.65 g of (**2g**) as white solid (60 % isolated yield).



Mp 74-75°C, MS (ESI): m/z = 377.3 $[M\text{-}Na]^+$, ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.88 (t, J = 6.7 Hz, 3 H), 1.26 (m, broad, 18 H), 1.44 (m, 2 H), 1,73 (m, 2H), 2.62 (m, 1 H), 2.71 (m, 1 H), 2.89 (m, 2 H), 3.31 (m, 2 H), 7.23 (m, 1 H), 7.31 (m, 2 H), 7.39 (m, 2 H) (Figure 5.6a). ^{13}C-NMR δ (ppm) 14.05, 22.60, 22.64, 27.02, 28.80, 29.14, 29.28, 29.30, 29.48, 29.56, 31.87, 51.60, 52.62, 126.97, 129.20, 130.32, 134.39 (Figure 5.6b).



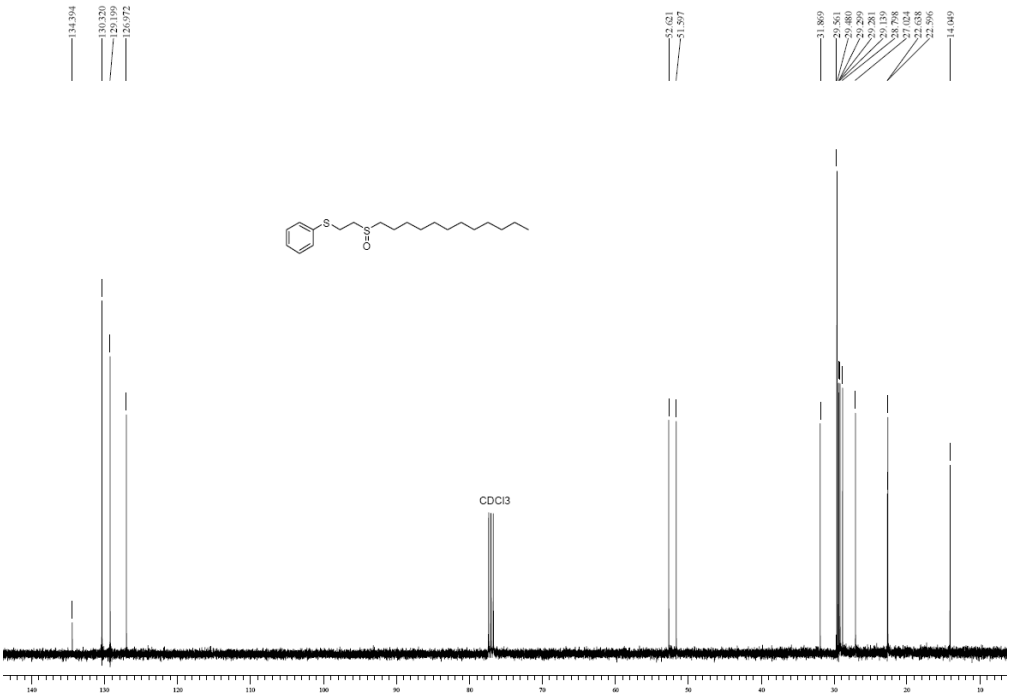
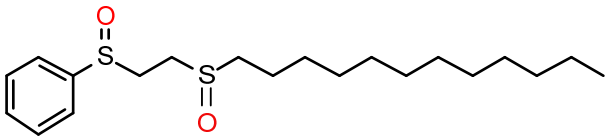


Figure 5.6 – a) ^{1}H-NMR and b) ^{13}C-NMR spectra of sulfoxide **2m**.

Synthesis of dodecyl 2-(phenylsulfinyl)ethyl sulfoxide (**2n'**).

The disulfide **1m** (0.150 g, 0.44 mmol) was dissolved in 5 mL of ethyl lactate, then a two equimolar amount of 70 % aqueous H_2O_2 was added. The resulting solution was stirred at ambient temperature for 5 hours, monitoring the reaction by ^{1}H-NMR analysis. Then, the reaction mixture was evaporated under reduced pressure, obtaining 0.153 g of dodecyl 2-(phenylsulfinyl)ethyl sulfoxide **2n'** as white solid (90 % yield). The compound was purified by crystallization from ethanol.



Mixture of diastereoisomers (*rac*-(*R,R-S,S*) pairs and *meso*-(*R,S-S,R*) forms) with the *meso* form prevailing. Mp 186-187 °C. MS (ESI): m/z = 393.1 $[M\text{-}Na]^{+}$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.87 (t, J = 7.0 Hz, 3 H), 1.20-1.30 (m, broad, 16 H), 1.36-1.46 (m, broad, 2 H), 1.66-1.74 (m, broad, 2 H), 2.58-2.78 (m, 2 H), 2.88-3.10 (m, 2 H), 3.32, 3.42 (m, 2 H), 7.50-7.56 (m, 3 H), 7.58-7.62 (m, 2H) (Figure 5.7a). ^{13}C-NMR δ (ppm) 14.0, 22.5, 22.6, 28.7, 29.1, 29.2, 29.4, 29.5, 31.8, 43.3, 48.9, 53.0, 123.9, 129.4, 131.3, 131.6 (Figure 5.7b). The sample was contaminated by a small amount of monosulfoxide **3n**.

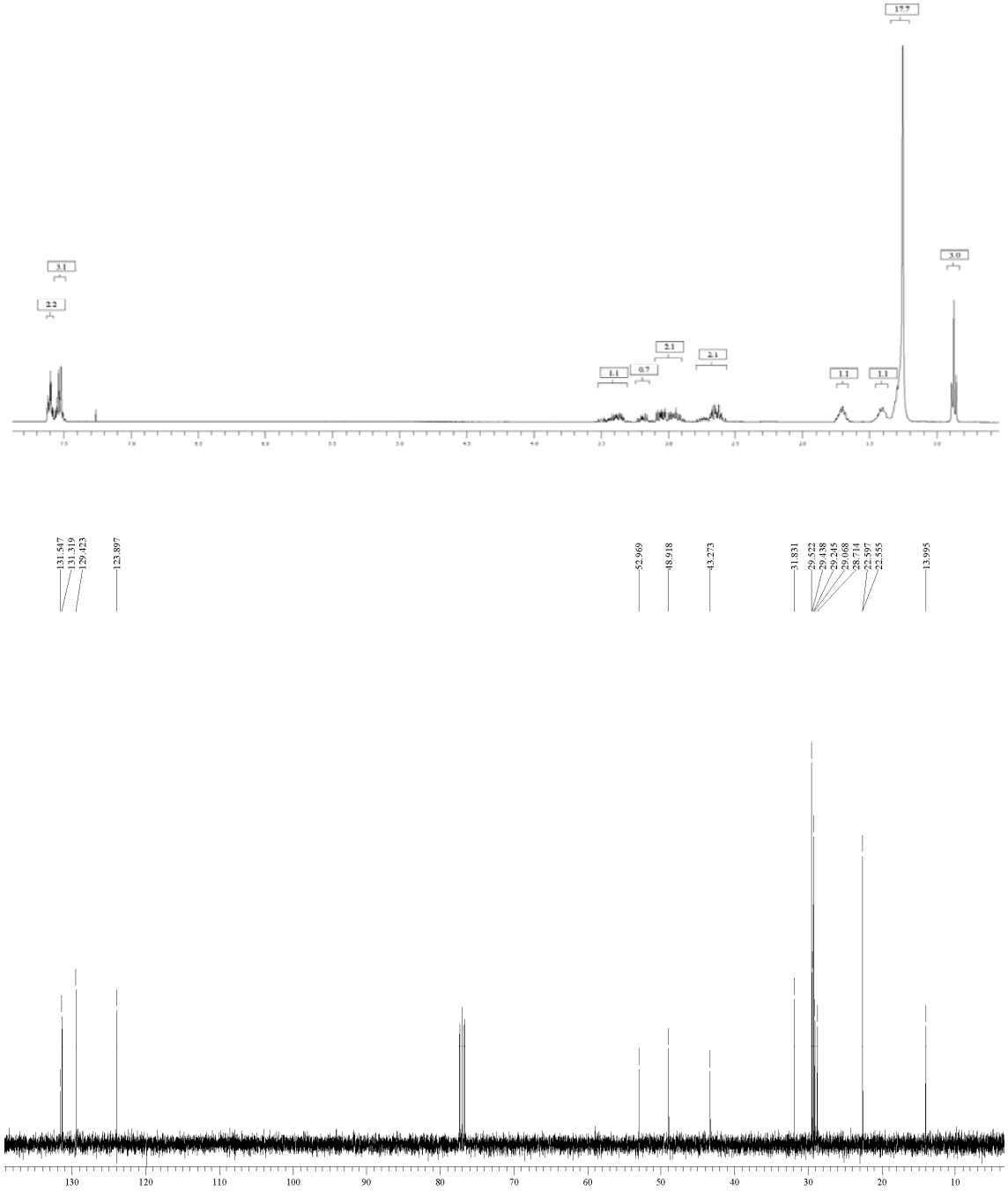


Figure 5.7 – a) ^{1}H-NMR and b) ^{13}C-NMR spectra of disulfoxide **2n'**.

General oxidation procedure of sulfides 1a-1f.

Sulfides **1a-f** (2.0 mmol) were dissolved in ethyl lactate (10 mL), then the oxidant (70 % H_2O_2 or *m*-CPBA 2.0 mmol) and PTSA (0.1 mmol, (if needed) were added. The resulting solutions were stirred at 25°C for 6-24 hours (Table 1 and Table 3). The reactions were followed by GC-MS analysis with appropriate internal standard and the products were identified by isolation or by comparison with authentic samples. The presence of sulfones contaminating sulfoxides was easily identified by ^{1}H-NMR as can be seen in Figure 5.8 (i.e. in the oxidation of **1a**).

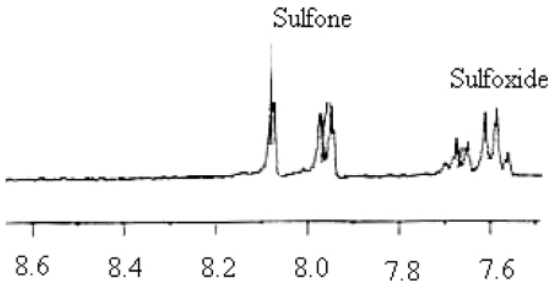


Figure 5.8 – ^{1}H-NMR of a mixture of sulfoxide and sulfone in the oxidation of compound **1a**

Methyl phenyl sulfoxide (**2a**). The product was obtained as a colorless liquid (Mp 30.0-30.5 °C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62–7.60 (m, 2H, ArH), 7.51–7.44 (m, 3H, ArH), 2.68 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 145.6, 130.9, 129.2, 123.4, 43.8. IR: ν(cm^{-1}) 3056, 2914, 1655, 1583, 1476, 1444, 1090, 1048, 957, 748, 692. EI-MS, m/z (%): 140.00 (79) [M^+].

Methyl phenyl sulfone (**3a**). Mp 89.0-90.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 3.06 (s, 3H), 7.56-7.60 (m, 2H), 7.65-7.69 (m, 1H), 7.95-7.97 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 44.67, 127.32, 129.34, 133.67, 140.58.

Dibenzyl sulfoxide (**2b**). With this substrate, no oxidation was observed at the benzylic position. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.43–7.26 (m, 10H, Ph); 3.92 (dd, ^1J = 12 and 15 Hz, 4H, –CH_2–Ph). ^{13}C-NMR (100 MHz, $CDCl_3$): 57.1 (C–Ph), 130.0 (*o*-C), 128.8 (*p*-C), 128.8 (*m*-C), 128.2 (*q*-C). IR ν(cm^{-1}): 3031, 2958, 1602, 1454, 1032, 775, 699. MS (m/z) 231 (M+1).

Diphenyl sulfoxide (**2c**). Diphenyl sulfide **1c** (0.44 mmol, 0.150 g, density 1.113 g/ml), and *p*TSA (5% wt.) were added in sequence to a solution of ethyl lactate (5 mL) and H_2O_2 (0.44 mmol (conc. 70%, 0.017 mL, density 1.29). The resulting solution was stirred at room temperature for 24 hours. Conversion (from ^{1}H-NMR): 48 % after 6 h and 86 % after 24 h were determined by GC-MS. The product was obtained as a white solid. Mp 72.0-73.08 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66–7.64 (m, 4H), 7.49–7.42 (m,

6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 145.6, 131.0, 129.3, 124.8; IR: ν(cm^{-1}) 3048, 1580, 1476, 1441, 1087, 1037, 737, 694. EI-MS, m/z (%): 202.01 (100) [M^+] 185, 154, 109, 97, 77, 65, 51.

Diphenyl sulfone (**3c**). Mp 128.0-129.0°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.47-7.58 (m, 6H), 7.95-7.98 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) d 127.66, 129.27, 133.15, 141.60.

Methyl 4-methoxyphenyl sulfide (**2d**). The product was obtained as a pale yellow solid (Mp *86-88* °C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70–7.52 (m, 2H, ArH), 7.03–7.01 (m, 2H, ArH), 3.84 (s, 3H, OCH_3), 2.69 (s, 3H, $SOCH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 161.9, 136.4, 125.4, 114.8, 55.5, 43.9. IR: ν(cm^{-1}) 2852, 1460, 1374, 1247, 1045. EI-MS, m/z (%): 170.00 (19) [M^+].

Di-*n*-butyl sulfoxide (**2e**). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.61 (t, 4H, *J* = 6.2 Hz), 1.73-1.66 (m, 4H), 1.47-1.40 (m, 4H), 0.90 (t, 6H, *J* = 7.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 13.3, 21.7, 24.3, 51.6; IR: ν(cm^{-1}) 2874, 1469, 1381, 1288, 1130, 1288, 1130, 1097, 1024, 772. MS (m/z) 163 (M+1).

Di-n-butyl sulfone (**3e**). Mp 46-47°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.98 (t, 6H, J =□7.4 Hz), 1.45-1.53 (m, 4H), 1.78-1.85 (m, 4H), 2.93-2.96 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.53, 21.78, 23.93, 52.46.

Diallyl sulfoxide (**2f**). The carbon-carbon double bonds in allyl sulfides remained intact during the oxidation. Bp 245-6°C at 760 mmHg. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 5.94-5.86 (m, 2H), 5.48-5.38 (m, 4H), 3.52 (d, 4H, *J* 6.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 54.2, 123.9, 126.0.

Diallyl sulfone (**3f**). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 3.71 (d, 4H, J =7.6 Hz), 5.46 (dd, 2H, J = 1.2, 16.8 Hz), 5.51 (dd, 2H, J = 1.2, 10.4 Hz), 5.95 (tdd, 2H, J = 7.6, 10.4, 16.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 55.90, 124.78, 124.84.

Methyl 4-nitrophenyl sulfoxide (**3g**).[ref. **174**] Mp 102-103°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.41 (d, 2H, J = 8.1 Hz), 7.85 (d, 2H, J = 8.1 Hz), 2.83 (s, 3H).

Methyl 4-methylphenyl sulfoxide (**3h**). Mp 73-75°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.28 (d, 2H, J = 7.7 Hz), 7.50 (d, 2H, J = 7.7 Hz), 2.70 (s, 3H), 2.45 (s, 3H). FT-IR (nujol) / cm^{-1} 1083 (S-O), 810, 3049.

Methyl 4-(methylsulfinyl)benzoate (**3i**). Mp 87-89°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.06 (d, 2H, J = 7.9 Hz), 7.88 (d, 2H, J = 7.9 Hz), 3.81 (s, 3H), 3.33 (s, 3H). FT-IR (nujol) / cm^{-1} 1083 (S-O), 1735 (C=O), 812, 3047.

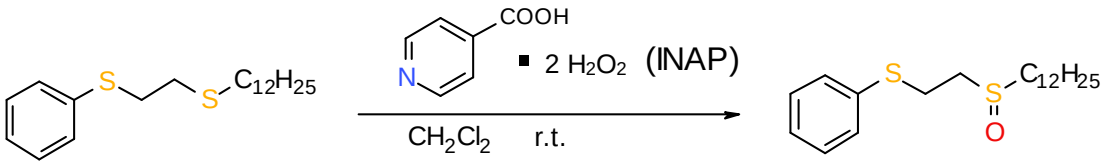
Kinetic measurement of the catalytic effect of PTSA on the formation of peracetic acid (PAA).

Peroxyacid concentrations were determined iodometrically as follows: five ml of the sample was taken and placed in a conical flask containing 25 ml KI with a concentration of 0.079 mol/L and 10 ml of potassium hydrogen phthalate with a concentration of 0.24 mol/L. Starch was added as an indicator. The reaction between iodide and peracetic acid is very fast and the liberated iodine was titrated with 0.005 mol/L sodium thiosulphate solution delivered from a 50 ml burette. The titration was accurate to ± 0.01 ml. The titration was then continued to an end point after the addition of 1ml ammonium heptamolybdate (3.2×10^{-3} mol/L), no further color development was observed for over one minute. The volume of thiosulphate achieved after addition of ammonium heptamolybdate gave the total peroxide concentration (peracetic acid and hydrogen peroxide). The procedure was repeated over a period of 12 days until the peracetic acid had reached equilibrium. The results of the peracetic acid and total peroxide are reported against time in the plot of figure 5.4.

Kinetic measurement for oxidation of X-phenyl methyl sulfides by ethyl lactate/H_2O_2.

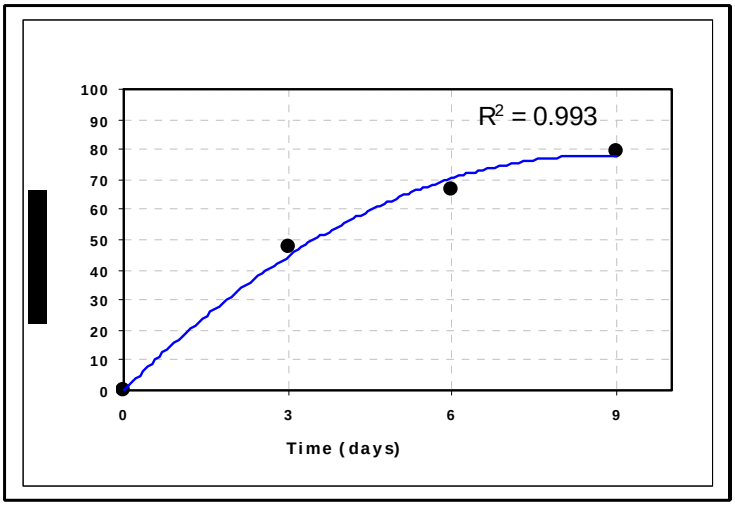
The kinetic runs of oxidation of aryl methyl sulfides with hydrogen peroxide were carried out in L(-) ethyl lactate with equimolar amount (0.2 M) of the sulfide and hydrogen peroxide (0.2 M). The prepared solution (100 ml) was subdivided in 15 vials in a thermostatic bath and the reaction allowed to proceed at 25°C (or 15 and 40°C). Each vial was withdrawn at appropriate time intervals and added to acetic acid-sodium acetate buffer (pH- 4-5) with few drops of 5% ammonium molybdate solution and analyzed measuring the disappearance of the oxidant by iodometric/$Na_2S_2O_3$ titration procedure. The collected data for disappearance of oxidant was plotted as 1/[ox] against time and found to show good linearity. In the case of methyl phenyl sulfide a parallel kinetic determination in the same condition was carried out at 25 °C following the decay of sulfoxide formation by GC-MS. A linear plot of 1/[sulfoxide] against time was obtained (Figure 5.2). From the slope of the plot the specific rate constant was deduced. The results obtained are collected in Table 5.4.

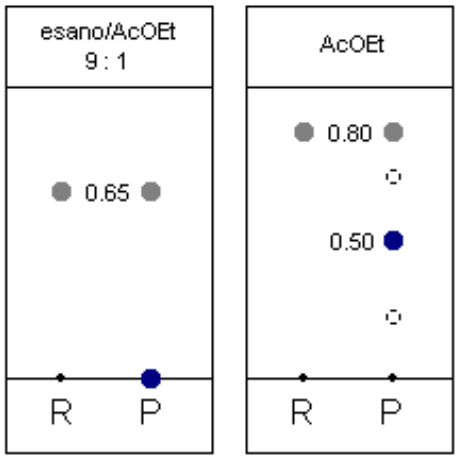
Oxidation of 1m with Isonicotinic acid·2H_2O_2 Perhydrate (INAP).



In a round bottom flask at r.t. was made a solution of disulfide **1m** (1.036 g, 3.065 mmol) in CH_2Cl_2 (30mL). Under stirring, the solid INAP adduct (0.293 g, 1.53 mmol) was added to the solution and the system was allowed under stirring at ambient temperature for 9 days, controlling the course of the reaction every 3 days. After filtration of the reaction mixture 0.156 g of isonicotinic acid were recovered. The products were purified by flash chromatography on silica-gel, with AcOEt as eluent. By ^{1}H-NMR analysis the following data were obtained.

t (days)	**1m** Conv. %	Selectivity %	
		2m	**2n + 2n'**
3	48	86	14
6	67	86	14
9	79	85	15





5.3 - Oxidation of Reduced Phosphorus Organic Compounds by the Ethyl lactate/Hydrogen peroxide couple

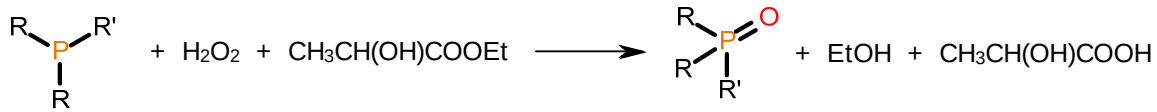
This chapter describes (i) a quick and selective method for the oxidation of reduced forms of organic phosphorous reagents (e.g. phosphines, phosphites, phosphinites, and phosphonites) to the corresponding P=O derivatives (phosphine oxides, phosphates, phosphinates and phosphonates) by the ethyl lactate/hydrogen peroxide reagent and (ii) the methods that allow the safe and efficient purification of these products.

Tertiary phosphine oxides (a term which encompasses both trialkyl and triaryl phosphine oxides) represent a class of compounds of commercial importance in the detergent, cosmetic, metal/acid separations, and nanotechnology fields. The most simple method to obtain phosphine oxides is the exposure of the corresponding phosphines to air.[175,176] However, this approach is surprisingly limited since even in solution many triaryl phosphines, such as triphenyl phosphine, are not efficiently oxidized in air. The mechanistic bases of this phenomenon were recently described.[177] A drawback of this method is that the exposure of alkyl phosphines to air can afford numerous products involving insertions of oxygen into phosphorus-carbon bonds.[175] Methods to transfer one single oxygen atom per phosphine have been described,[178] but the necessary reagents are not readily available and would have to be synthesized first. The alternative reaction with aqueous H_2O_2 were also investigated and the reaction was found to proceed smoothly at room temperature and in a well-defined manner, but surprisingly not general. Moreover, isolation of phosphine oxide under these conditions were complicated by adducts formation of H_2O_2 with phosphine oxides of different stoichiometry $R_3P{=}O{\cdot}(H_2O_2)_x$ (x = 0.5–1.0).[179]

Similar oxidations of other reduced organic phosphorus derivatives of general formula [$PR_x(OR)_{3-x}$ with x = 0-2] were also less systematically investigated and oxidations at phosphorus generally observed but with significant limitations in yield and selectivity.[180] Phosphites (x = 3) are ester of phosphorous acid (H_3PO_3) and are converted by oxidation at phosphorous atom into phosphates $O{=}P(OR)_3$; phosphinites (x = 1) are esters of phosphinous acids (R_2POH) and are converted by oxidation into phosphinates $O{=}PR_2(OR)$; phosphonites (x = 2) are esters of phosphonous acids ($RP(OH)_2$) and are converted by oxidation into phosphonates $O{=}PR(OR)_2$. These $PR_x(OR)_{3-x}$ classes of compounds have found useful applications as metal ligands to tune the electronic properties of the chelating atoms and as antioxidant or flame retardant agents for polymers and coatings. The corresponding P=O oxygenated derivatives are also known for their important biological activity (several natural phosphates, i.e. DNA, phosphatyl choline, AMP, and several cofactors play a relevant role in living cells) and have found uses as insecticides, herbicides, pharmaceutical products, and nerve gas. Moreover, organic phosphates are of technological importance as solvents, flame retardant agents and plasticizers, whereas phosphonates have

found specific applications as herbicide (glyphosate) and bisphosphonates are a class of drugs to treat osteoporosis.

On these bases we decide to investigate the oxidant couple ethyl lactate/hydrogen peroxide for the oxidation of these classes of phosphorus compounds, firstly focusing the attention on representative alkyl and aryl substituted phosphines (**4a-4f**). The oxygenation reaction at phosphorus atom was found generally fast, selective, and efficient at 0-20°C affording the corresponding phosphine oxide (**5a-5f**) in good to excellent yield (Table 5.8). With the diphosphine derivative **5f** was easy to control the insertion of one or two P=O bonds. In all experiments conversion and yield determinations were derived either by ^{31}P-NMR analysis of crude reaction mixture or by crystallization after evaporation under vacuum of ethyl lactate, in case by washing with water and recrystallization from an appropriate solvent.



4a; R = R' = CH_3
4b; R = R' = n-Bu
4c; R = R' = c-C_6H_{11}
4d; R = R' = n-C_8H_{17}
4e; R = R' = Ph
4f ; R = Ph; R' = $CH_2CH_2P(Ph)_2$

5a; R = R' = CH_3
5b; R = R' = n-Bu
5c; R = R' = c-C_6H_{11}
5d; R = R' = n-C_8H_{17}
5e; R = R' = Ph
5f ; R = Ph; R' = $CH_2CH_2P(Ph)_2$
5f' ; R = Ph; R' = $CH_2CH_2PO(Ph)_2$

Table 5.8 – Experimental conditions (0-20°C) used in the oxidation of phosphine **4a-4f** to the corresponding phosphine oxides **5a-5f'** by the couple ethyl lactate(S)/hydrogen peroxide

4	**[H_2O_2]/[4]**	**[S]/[4]**	**t (min)**	**5 (NMR Yield %)**	**5 (Isolated Yield %)**
4a*	1.2	20	15	98 (**5a**)	84 (**5a**)
4b*	1.1	15	20	99 (**5b**)	95 (**5b**)
4c*	1.1	20	60	92 (**5c**)	90 (**5c**)
4d*	1.1	30	40	99 (**5d**)	93 (**5d**)
4e*	1.1	20	60	96 (**5e**)	94 (**5e**)
4f**	1.1	40	120	85 (**5f'**)	75 (**5f'**)
4f**	10.0	40	40	100 (**5f**)	98 (**5f**)

* Procedure 1: a solution of ethyl lactate/H_2O_2 was firstly prepared at 0°C and then the phosphine added. ** Procedure 2: H_2O_2 was added to a solution of phosphine **4** in ethyl lactate

As reported in Table 5.8, a near stoichiometric amount of H_2O_2 was generally necessary to obtain near quantitative conversion of **4** to phosphine oxides **5**. Only with substrate **4f** a large excess of H_2O_2 was necessary to convert to the corresponding di phosphine oxide **5f'**. With a moderate excess of H_2O_2 (1.1 : 1) yield in monophosphine oxide **5f** was observed is moderate yield (75 % by NMR and 75% by crystallization). Moreover, with **4f** a longer time was necessary for the complete disappearance of the substrate.

The results of the last column of Table 8 refer to the isolation procedure developed. Water, ethanol, and ethyl lactate were eliminated by vacuum evaporation, whereas lactic acid was eliminated by dissolving the crude mixture in methylene chloride, adding $MgSO_4$ and drying. This procedure was developed owing to the strong ability of tertiary phosphine oxides to complex with polar hydrogen bonding species. This phenomenon is related, as suggested by theoretical and experimental studies, to the fact that P=O bonds are polar, stronger, and shorter than conventional double bonds,[181] with values of P-O and P-C bond length of 1.476 and 1.809 Å (Me_3PO)[182] and C-P-O and C-P-C angles of 114.4° and 104.1°, respectively.[183] We have used IR spectroscopy as a powerful tool for quickly analyzing the nature and purity of phosphine oxides and their various adducts, characterizing the involved species and optimizing the two most promising procedures for obtaining clean phosphine oxides. When complex with water was present, a stretching of $\nu_{P\text{-}O}$ was observed at 40-60 cm^{-1} higher than the corresponding pure compound, accompanied by a broad OH stretching at 3400-3000 cm^{-1} and a diagnostic band at 1647 cm^{-1} corresponding to the overtone of the O-H bond absorption.[184] For pure trimethylphosphine oxide, experimental values for the frequency were 1163 cm^{-1} and 699 cm^{-1} for $\nu_{P\text{-}O}$ stretching and $\nu_{P\text{-}C}$ stretching, respectively, whereas the $\delta_{C\text{-}P\text{-}C}$ bending and $\delta_{C\text{-}P\text{-}O}$ bending presented a value of 249 cm^{-1} and 317 cm^{-1}, respectively. With longer alkyl groups, i.e. tri-n-butylphosphine oxide the frequency of P=O stretching was slightly lower (1153 cm^{-1}), whereas with triphenylphosphine oxide was higher (1194 cm^{-1}). Figure 5.9b and Figure 5.9c are typical examples of differences in IR spectrum of hydrated and anhydrous form of n-Bu_3PO.

Also ^{31}P-NMR analysis can be usefully applied to follows the reaction fate and the purification procedure, because the $\delta(^{31}P)$ was found to be dependent on the concentration of H_2O in several unpolar solvents. $^{31}P\{^1H\}$-NMR chemical shifts were measured relative to external 85% H_3PO_4 with downfield values being taken as positive. The ^{31}P chemical shift of $Bu_3P{=}O{\cdot}H_2O$ changes from 44.65 to 43.60 ppm upon dilution of a 0.11 molar to a 0.05 molar solution in D_6-benzene and from 48.33 to 47.04 ppm in $CDCl_3$. This substantial reduction of chemical shift reflects the fact that with the adduct formation the P-O bond order and its polarity decreases, in accordance with the IR analysis above indicated.

The phenomenon is the basis of the analytical use of phosphine oxides as probes for the surface acidity of oxide supports, such as silica or alumina, due to their strong interactions with surface hydroxyl groups, so undergoing partial quaternization.[185]

The ^{31}P chemical shift of uncomplexed phosphine oxide was also dependent on substitution, going from 30.15 for triphenyl phosphine to 51.52 for tricyclohexylphosphine. A representative trend for the ^{31}P, ^{1}H (P-C-H) and ^{13}C (C-P) chemical shifts of the isolated phosphines are collected in Table 5.9. All the data follow the general trend reported in literature for the effect of substituents on phosphorus atom.[186]

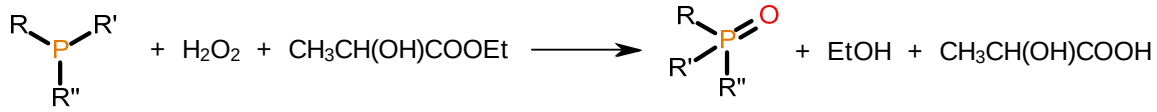
Table 5.9 – ^{31}P- , ^{13}C- *and* ^{1}H-*NMR relevant data in $CDCl_3$ for phosphine oxides **5a-5e***

5	δ(^{13}P)	δ(^{1}H)*	δ(^{13}C)*	$^{2}J(^{31}P\text{-}^{1}H)$ Hz*	$^{1}J(^{31}P\text{-}^{13}C)$ Hz*
5a	38.77	1.50	18.05	12.7	70.1
5b	48.58	1.66	27.61	nd**	65.0
5c	51.52	1.72	35.19	nd**	60.8
5d	48.46	1.64	27.95	12.8	65.2
5e	30.15	-	132.30	-	102.6

* H and C refer to the atom nearest to phosphorous in phosphine; nd** not determined

The use of the ethyl lactate/H_2O_2 couple was then extended to other reduced phosphorus species, i.e. phosphites, phosphinites and phosphonites of general formula [$PR_x(OR)_{3-x}$ with x = 0-2]. Phosphites (**6a-c**) were converted into phosphates O=P(OR)$_3$ (**7a-c**), phosphinites $PR_2(OR)$ (**6e**) into phosphinates $O=PR_2(OR)$ (**7e**), and phosphonites $PR(OR)_2$ (**6d**) into phosphonates $O=PR(OR)_2$ (**7d**). Only representative examples of substrates were selected for the reaction. In particular, all compounds tested were commercial products available at purity higher than 95% (Aldrich).

The results obtained in reactions with derivatives **6a-6e** are reported in Table 5.10.



6a; R = R' = R'' = OCH_3
6b; R = R' = R'' = OC_2H_5
6c; R = R' = R'' = OPh
6d; R = Ph, R' = R'' = OCH_3
6e; R = R' = Ph; R'' = OC_2H_5

7a; R = R' = R'' = OCH_3
7b; R = R' = R'' = OC_2H_5
7c; R = R' = R'' = OPh
7d; R = Ph, R' = R'' = OCH_3
7e; R = R' = Ph; R'' = OC_2H_5

Table 5.10 – Experimental conditions (0°C) used in the oxidation of phosphite **6a-6b** phosphonite **6c** and phosphinite **6d** to the corresponding phosphates **7a-7b**, phosphonate **7c** and phosphonite **7d** by the couple ethyl lactate(S)/hydrogen peroxide

Compound	$[H_2O_2]/[6]$	[S]/[6]	t (min)	Product (NMR Yield %)
$P(OEt)_3$ **6a**	1.0	20	15	88 (**7a**)
$P(OMe)_3$ **6b**	1.2	20	15	82 (**7b**)
$P(OPh)_3$ **6c**	1.2	40	60	87 (**7c**)*
$PPh(OMe)_2$ **6d**	1.2	15	20	92 (**7d**)
$PPh_2(OEt)$ **6e**	1.1	20	60	91 (**7e**)

* including a 10% of ethyldiphenylphosphate. Reaction carried out at 20°C

From the results of Table 5.10 is apparent that the oxidation proceeds efficiently, but the yield were generally lower than phosphines. In general, aromatic phosphites are shown to be of inferior reactivity to H_2O_2/Ethyl lactate couple as compared with aliphatic phosphites and relatively more drastic conditions were necessary. Moreover, trialkyl phosphites (Me, Et) afforded lower yield owing a rearrangement to dialkyl alkylphosphonate acid. This behavior is reminiscent of dimethyl sulfoxide as oxidant,[187] but with lower interferences. Under the conditions of Table 5.10 no significant trans-esterification was observed with methyl derivatives **6a** and **6d**, whereas with triphenylphosphite **6c** some ethyl scrambling was observed in the final phosphate **7c**. On the contrary, after several hours trans-esterification was significant in all cases and complicates the reaction mixture, therefore a fast purification procedure at 0-20°C was adopted.

The oxidation of trialkylphosphites was quite exothermic, therefore efficient cooling was necessary also to reduce the hydrolysis side reaction. Estimation of the enthalpy (ΔH) for the reaction was obtained by DSC of triethyl phosphite/H_2O_2 (1:1, 0.5 M) solution in ethyl lactate.

$$P(OEt)_3(l) + H_2O_2(l) \quad f \quad OP(OEt)_3(l) + H_2O(l); \qquad \Delta H = -116{\cdot}3 \text{ kcal/mole}$$

The deduced value of -116.3 kcal/mol is in a reasonable agreement with the reported data for reaction in water, where hydrogen peroxide is the only oxidant.[188]

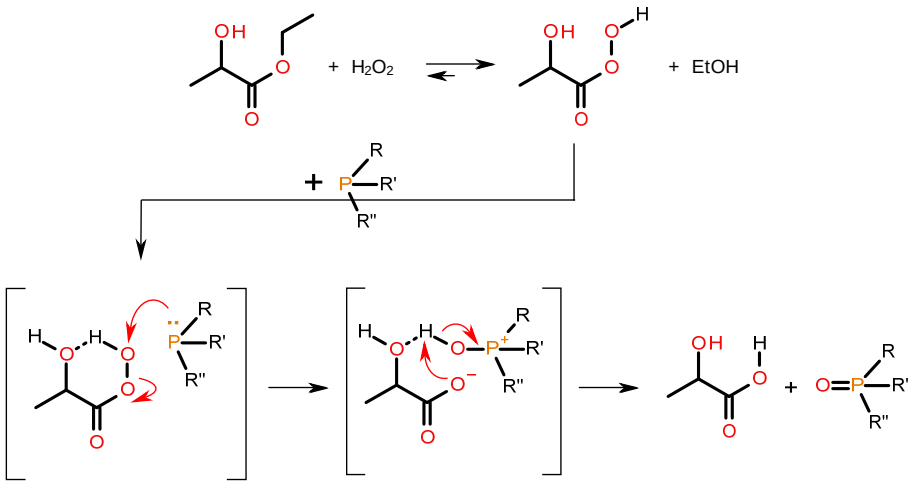
The reaction mixture was also analyzed by FT-IR or ^{31}P-NMR techniques, owing to remarkable differences in spectra of reagents and products. The aryl phosphites have resolvable signals in the region of 127–130 ppm, phosphates in the region of −15 to −18 ppm, whereas trialkyl phosphites show signals in the region of 137–140 ppm and product phosphates in the region of 2 to -20 ppm.[189] Arylposphinites and arylphosfinates generally show ^{31}P signals in the range 110-120 ppm and 20-30 ppm, respectively, whereas arylphosphinates and arylphosphonates in the range 111-125 and 25-35 ppm, respectively. In FTIR spectra the strong bands at 1250-1290 cm^{-1} and 1040-1090 cm^{-1} were observed for the P=O and P-O stretching mode of phosphites and phosphates, respectively. Authentic samples of dimethyl phenylphosphonate (**7d**)[190] and ethyl diphenyl-phosphinate (**7e**)[191] were obtained by reported procedures. Representative data for FTIR frequency and ^{31}P signals of substrates and products for reaction of Table 5.10 are collected in Table 5.11.

Table 5.11 – *^{13}P-NMR and FTIR relevant data for phosphites, phosphinites and phosphonites* ***2a-2e*** *and the corresponding oxidation products* ***2a-2e***

6	**δ(^{13}P) ppm***	**δ(P-O) cm^{-1}**	**7**	**δ(^{13}P) ppm***	**δ(P=O) cm^{-1}**
6a	139	1057	**7a**	2.1	1282
6b	137	1035	**7b**	1.0	1260
6c	128	1196	**7c**	-16.0	1299
6d	119	1065	**7d**	22.2	1252
6e	111	1072	**7e**	30.1	1223

* with external reference to 85% phosphoric acid in water.

The overall data obtained confirm that reduced organophosphorus derivatives are fast enough to trap the intermediate formed in the redox system H_2O_2/ethyl lactate and that the oxidation occurs mainly, or exclusively, at the phosphorus atom, with very limited degradation of alkyl side chains or C-P rearrangements. These results can be interpreted, as in reactions with sulfides, as due to electrophilic addition to phosphorus of electrophilic oxygen of peroxylactic acid in a so fast process that prevent significant side reactions. Scheme 5.8 summarizes the proposed reaction mechanism. For a discussion on formation, structure and decay of the intermediate peroxylactic acid see the previous chapter on oxidation of sulfides.



Scheme 5.8 – Proposed mechanism for oxidation of phosphorous compounds by peroxylactic acid

In scheme 5.8 is delineated the possible role of hydrogen bonding in the transition state to increase the selectivity and control the rate of the process. It is well known the hydrogen bonding has a significant effect on peroxide bond stabilization and on P=O complexation. The combined effect of hydrogen bond in starting substrate and final oxo-phosphorus derivative can favor both the kinetics and the selectivity of the reaction. In fact, preliminary results indicate that hydrogen peroxide in ethyl acetate react slower than in ethyl lactate towards trialkylphosphines and that dialkylsulfides are less reactive than trialkylphosphine. Moreover, the reactivity of phosphine were accelerated by decrease of the steric hindrance around the phosphorus atom and by an increase of electron density on the phosphorous atom. This suggests that the electron density on heteroatoms play a relevant role in the reaction and further supports that the reaction involves an intermediate and not simply hydrogen peroxide.

Finally, it must be underlined that our data cannot fully exclude the involvement of an electron-transfer mechanism from the electron rich phosphorus atom and the oxidant peroxide intermediate, followed by a recombination with rearrangement of a proton.

EXPERIMENTAL

Representative procedure for the synthesis of the phosphine oxides (4a–4f) from tertiary phosphines by ethyl lactate/hydrogen peroxide couple.

For each oxidation the same procedure was applied, except for minor deviations for **4a** (a trimethylphosfine 1 M solution in THF was used) and **4f** (see the procedure described for compound **5f**). In a Schlenk flask, which was cooled to 0°C, ethyl lactate (50 mL) was added followed by a 1.1 equivalent of concentrated aqueous H_2O_2 solution (35 weight % in H_2O, 17.10 mL, 176.0 mmol H_2O_2) via syringe under stirring. Then, Bu_3P (**4b**, 3.552 g, 17.56 mmol) was added under vigorous stirring. The reaction

mixture was stirred for 30 min. and allowed to slowly warm to room temperature. After 2 h, the homogeneous solution was transferred into a round bottom flask with a metal cannula. ^{31}P NMR and/or IR analyses proved that the oxidation process was quantitative. The solvent was removed in vacuo at 40°C, and **5b** was obtained as a white solid (3.67 g, 95% yield). All phosphine oxides **4a**–**4e** were colorless crystalline solids, and they were characterized by ^{31}P-NMR, ^{1}H-NMR, ^{13}C-NMR and IR spectroscopy, as well as their melting points.

Trimethylphosphine oxide (**5a**). The crude product was purified by sublimation at 70°/1 mm;[192] Mp 140°-3°. IR spectrum, ν cm^{-1}: 1160 (P=O). NMR (δ, $CDCl_3$), ^{31}P{^{1}H} 38.79 (s); ^{1}H 1.51 (d, $^{2}J(^{31}P\text{-}^{1}H)$ = 12.8 Hz); ^{13}C{^{1}H} 18.06 (d, $^{1}J(^{31}P\text{-}^{13}C)$ = 70.0 Hz). The spectrum showed no extraneous absorption when recorded with the δ = 1.51 peaks 10 times full scale.

Tributylphosphine oxide (**2b**)**.** Mp 67-69°C. IR spectrum, δ cm^{-1} 1153 (P=O) (Figure 5.9b). NMR (δ, $CDCl_3$), ^{31}P{^{1}H} 48.56 (s); ^{1}H 1.69–1.64 (m, 6H, PCH_2), 1.57–1.49 (m, 6H, PCH_2CH_2), 1.42 (sextet, 6H, $^{3}J(^{1}H\text{-}^{1}H)$ = 7.2 Hz, CH_2CH_3), 0.92 (t, 9H, $^{3}J(^{1}H\text{-}^{1}H)$ = 7.2 Hz, CH_3); ^{13}C{^{1}H} 27.63 (d, $^{1}J(^{31}P\text{-}^{13}C)$ = 65.0 Hz, PCH_2), 24.29 (d, $^{3}J(^{31}P\text{-}^{13}C)$ = 14.2 Hz, CH_2CH_3), 23.75 (d, $^{2}J(^{31}P\text{-}^{13}C)$ = 3.9 Hz, PCH_2CH_2), 13.60 (s, CH_3). The compound was also isolated as hydrate whose FTIR spectrum is collected in Figure 5.9c.

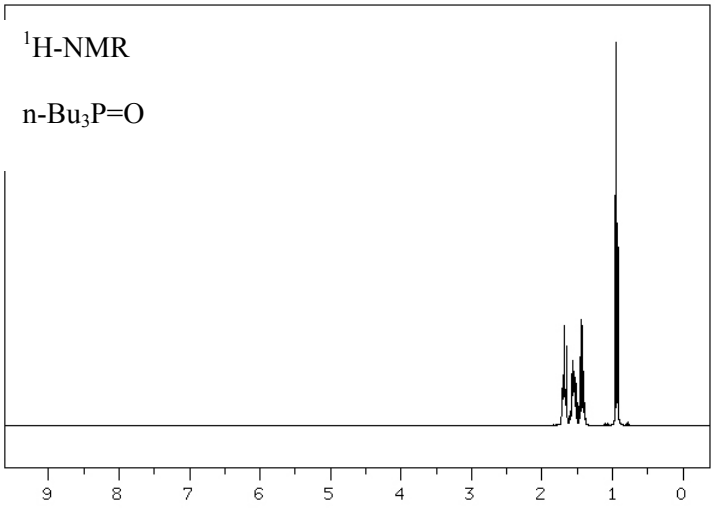


Figure 5.9a – ^{1}H-NMR Spectra of solid n-Bu_3PO from reaction of n-Bu_3P with ethyl lactate/H_2O_2.

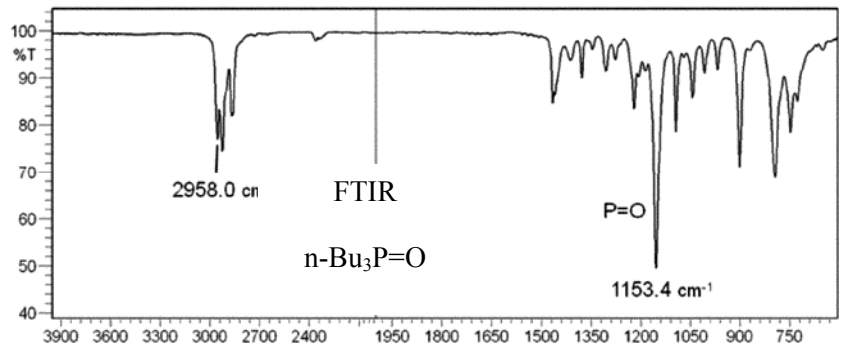


Figure 5.9b - FTIR Spectra of solid n-Bu_3PO from reaction of n-Bu_3P with ethyl lactate/H_2O_2.

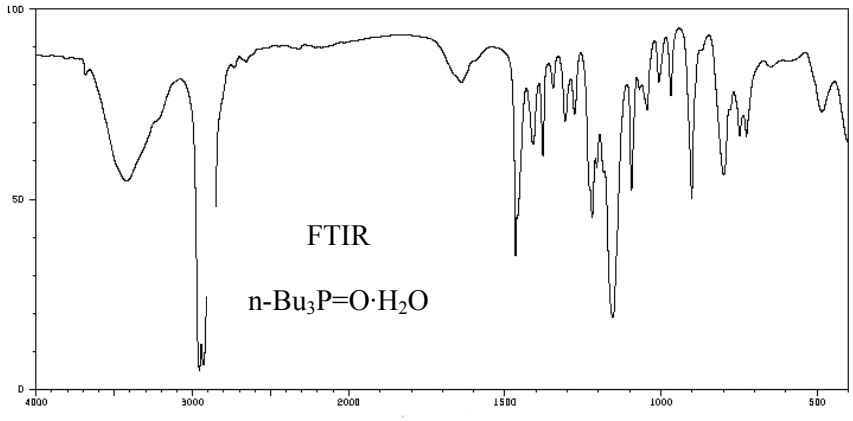


Figure 5.9c - Infrared Spectra of solid complex n-$Bu_3PO{\cdot}H_2O$

Tricyclohexylphosphine oxide (**2c**). Mp 155-157°C. FTIR spectrum, ν cm^{-1}: 1140 (P=O). NMR (δ, $CDCl_3$): $^{31}P\{^1H\}$ 49.9 (s); ^1H 1.91 (br d, 6H, $^2J(^1H\text{-}^1H)$ = 12.8 Hz, PCHCH_{eq}), 1.9–1.8 (m, 9H, PC$H_{ax}$$CH_2CH_{eq}$), 1.75–1.7 (m, 3H, PCH$(CH_2)_2CH_{eq}$), 1.5–1.4 (m, 6H, PCHC$H_{ax}$), 1.30–1.18 (m, 9H, PCHCH_2CH_{ax}CH_{ax}); $^{13}C\{^1H\}$ 35.37 (d, $^1J(^{31}P\text{-}^{13}C)$ = 60.7 Hz, PCH), 26.93 (d, $^3J(^{31}P\text{-}^{13}C)$ = 11.6 Hz, PCHC$H_2$$C_{H2}$), 26.34 (d, $^2J(^{31}P\text{-}^{13}C)$ = 2.9 Hz, PCHCH_2), 26.14 (d, $^4J(^{31}P\text{-}^{13}C)$ = 1.4 Hz, PCH$(CH_2)_2CH_2$).

Trioctylphosphine oxide (**2d**). Mp 51-52°C. IR spectrum, ν cm^{-1}: 1150 (P=O) (Figure 10). NMR (δ, $CDCl_3$), $^{31}P\{^1H\}$ 49.91 (s);^1H 1.67–1.59 (m, 6H, PCH_2), 1.58–1.48 (m, 6H, PCH_2CH_2), 1.40–1.32 (m, 6H, PCH_2CH_2CH_2), 1.32–1.18 (br m, 24H, $(CH_2)_4CH_3$), 0.85 (t, 9H, $^3J(^1H\text{-}^1H)$ = 7.1 Hz, CH_3); 1;$^{13}C\{^1H\}$ 31.78 (s, CH_2CH_2CH3), 31.39 (d, $^3J(^{31}P\text{-}^{13}C)$ = 13.6 Hz, P$(CH_2)_2CH_2$), 29.09 (s, P$(CH_2)_3CH_2$), 29.04 (s, P$(CH_2)_4CH_2$), 27.95 (d, $^1J(^{31}P\text{-}^{13}C)$ = 65.0 Hz, PCH_2), 22.61 (s, CH_2CH_3), 21.70 (d, $^2J(^{31}P\text{-}^{13}C)$ = 3.7 Hz, PCH_2CH_2), 14.06 (s, CH_3).

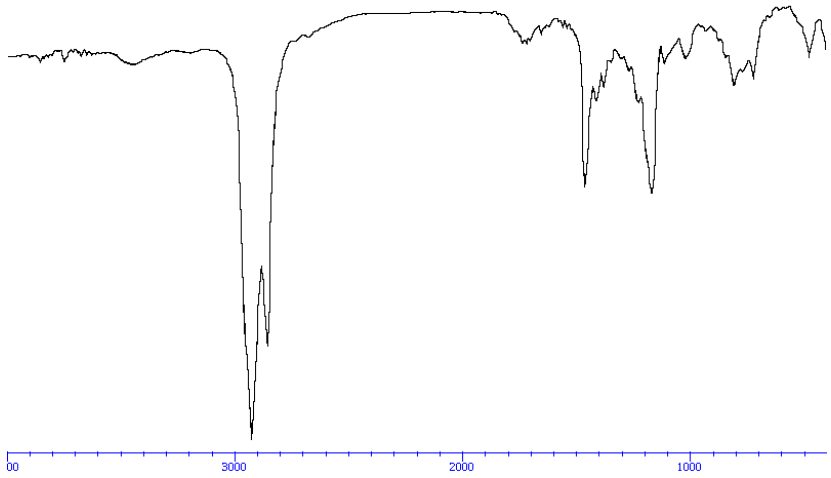


Figure 5.10 - FTIR spectrum (in KBr) of solid (c-$C_6H_{11})_3PO$ (**5c**) from reaction of (c-$C_6H_{11})_3P$ with ethyl lactate/H_2O_2 couple

Triphenylphosphine oxide (**5e**). Mp 156–158°C; IR spectrum, ν cm^{-1} 3050, 1580, 1486, 1445, 1310, 1189 (P=O), 1120, 1097, 1082, 999, 920, 870, 757, 724, 700. NMR (δ, $CDCl_3$), $^{31}P\{^1H\}$ 29.10 (s); ^1H 7.70–7.64 (m, 6H, H_o), 7.57–7.52 (m, 3H, H_p), 7.49–7.43 (m, 6H, H_m); $^{13}C\{^1H\}$ 132.54 (d, $^1J(^{31}P\text{-}^{13}C)$ = 103.4 Hz, C_i), 132.07 (d, $^2J(^{31}P\text{-}^{13}C)$ = 9.9 Hz, C_o), 131.89 (d, $^4J(^{31}P\text{-}^{13}C)$ = 2.8 Hz, C_p), 128.46 (d, $^3J(^{31}P\text{-}^{13}C)$ = 12.1 Hz, C_m). NMR (δ, D_6-DMSO), $^{31}P\{^1H\}$ 26.2 (s). MS (EI, 70 eV) m/z (rel. int.), 277 (100). Impurity of starting triphenylphosphine can be deduced from the ^{31}P-NMR at -6 ppm.

1,2-bis(diphenylphosphinyl)ethane (**5f**). *Synthetic procedure*: 1,2-Bis-(diphenylphosphino)ethane (**4f**, 10.0 g, 25.2 mmol) was dissolved in ethyl lactate (200 mL). To the solution in a thermostatic bath at 20°C was added dropwise under stirring hydrogen peroxide (30 mL, 30% wt-% solution in water) in 30 min. The completion of the reaction (approx. after 15 min) was determined by SiO_2/TLC (elution with DCM). The ethyl lactate was evaporated under vacuum at 20°C and the residue, diluted in DCM (200 ml), was washed with water (2 × 100 mL), dried on anhydrous $MgSO_4$, and filtered. The solvent was removed to afford a white solid. Recrystallisation (methanol/ethyl acetate) of the solid gave 1,2-bis(diphenylphosphinyl)ethane **5f** as an amorphous white solid (10.6 g, 97%). Mp 275-276 °C (lit.,[193] mp 276-278 °C). FTIR spectrum, ν cm^{-1} 1177 (P=O). NMR (*δ*, 162 MHz $CDCl_3$), $^{31}P\{^1H\}$ 31.6 (s, 2P). NMR (*δ*, 400 MHz, $CDCl_3$), 2.55 (4H, br d, J = 2.4 Hz), 7.45 (8H, dd, ^4J = 7.1, 7.1 Hz), 7.51 (4H, dd, J = 7.1, 7.1 Hz), 7.69-7.74 (8H, m); MS (ESI) m/z 431.2 ($[M+H]^+$, 64%), 453.2 ($[M+Na]^+$, 100%).

1,2-Bis(diphenylphosphino)ethane monoxide (**5f'**, DPPEO). Mp 196-198°C. FTIR spectrum, ν cm^{-1} 3052, 1937, 2903, 1588, 1480, 1435, 1182, 1122, 1106, 1069, 1025, 997, 881, 783, 727, 692, 712, 536,

513, 504, 474. NMR (δ, 162 MHz $CDCl_3$), $^{31}P\{^1H\}$ 32.4 (s, P=O), -11.3 (d, P, $^4J(^{31}P\text{-}^{31}P)$ = 48.3 Hz). NMR (δ, 400 MHz, $CDCl_3$), 2.28 (4H, br s), 7.30-7.39 (10H, m), 7.41-7.46 (4H, m), 7.49-7.53 (2H, m), 7.61-7.66 (4H, m). MS (ESI) m/z 415.2 ($[M+H]^+$, 100%), 437.2 ($[M+Na]^+$, 100%). The compound was isolated in trace amount (7%) by column chromatography (hexane: ethyl acetate 8:2) from crystallization waters of previous reaction. Its structure was attributed by ^{31}P- and ^1H-NMR (Fig. 5.11) and by TLC (DCM). This compound was isolated in 65% yield when the reaction was carried out as above but with stoichiometric amount of H_2O_2 (2.86 ml). The remaining starting 1,2-Bis-(diphenylphosphino)ethane (**4f**) can be identified by ^{31}P analysis from the peak at -13 ppm.

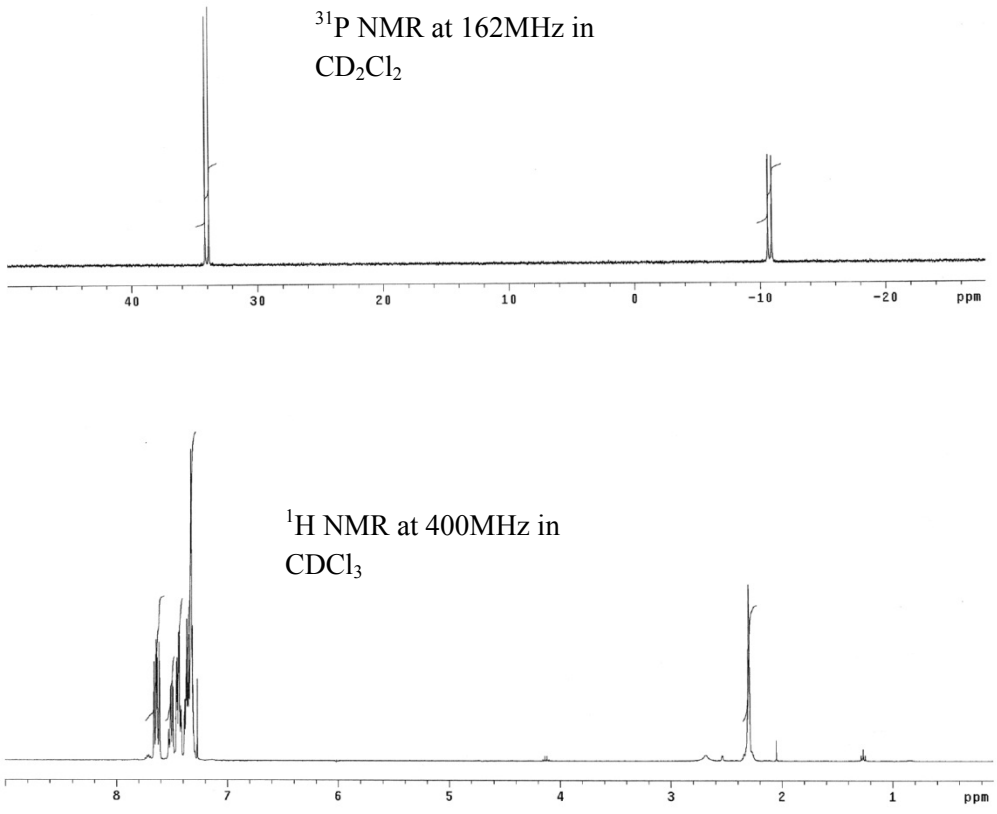


Figure 5.11 – ^{31}P and ^1H-NMR spectra of DPPEO (**5f'**) from reaction of DPPE (**4f**) with ethyl lactate/H_2O_2 couple

Oxidation of phosphites, phosphinites and phosphinates. *Representative procedure*: In a Schlenk flask cooled to 0°C, 30 mL of ethyl lactate and 2.10 mL (22.0 mmol) of H_2O_2 solution (36 weight % in H_2O) was dropped under stirring. Then, triethylphosphite (**6a**, bp 158°C, d = 0.96 g/ml, 3.47 g, 20.02 mmol) was added under vigorous stirring. The reaction mixture was stirred for 15-30 min. and analyzed by ^{31}P NMR and/or FTIR to detect the disappearance of starting reagent. Then, the solvent was removed in vacuo at 10°C, and **7a** was obtained as a colorless liquid (3.23 g, 88% yield, bp 215°C). The oxidation products **6a**–**6e** were characterized by ^{31}P-NMR, ^1H-NMR, ^{13}C-NMR and FTIR spectroscopy, as well as their gas

chromatographic retention time and MS spectra. Trimethyl-, triethyl, and triphenylphosphite were identified by co-injection in GC-MS with authentic samples (Aldrich, purity >98%).

Dimethyl phenylphosphonate (**7d**). Clear viscous liquid; IR spectrum, ν cm^{-1} 3060, 2955, 2852, 2256, 2201, 2137, 2078, 1593, 1439, 1252, (P=O), 1045. NMR (δ, $CDCl_3$), $^{31}P\{^1H\}$ 22.20 (s); ^1H 7.73 (2H, dd, $J(^1H\text{-}^1H)$ = 13.6, 7.5 Hz), 7.50 (1H, t, $^2J(^1H\text{-}^1H)$ = 7.5 Hz), 7.40 (2H, td, $J(^1H\text{-}^1H)$ = 7.5, 4.0 Hz), 3.68 (6H, d, $^4J(^{31}P\text{-}^1H)$ = 11.2 Hz); $^{13}C\{^1H\}$ 132.7 (d, J = 12 Hz), 131.9 (d, J = 39 Hz), 128.6 (d, J = 60 Hz), 126.9 (d, $^1J(^{31}P\text{-}^{13}C)$ = 750 Hz), 52.7 (d, J = 22 Hz). MS (EI, 70 eV) m/z (rel. int.), 186 (64), 185 (100), 155 (27), 141 (57), 91 (54), 77 (38).

Ethyl diphenylphosphinate (**7e**). Mp 56–57°C. IR spectrum, ν cm^{-1}: 1221 (P=O). NMR (δ, $CDCl_3$), $^{31}P\{^1H\}$ 30.10 (s); ^1H 1.273 (1, 3H, t, J=6.81), 3.97 (2, 2H, q, J=6.81), 7.33 (7, 4H, dd, J=8.08, J=1.72), 7.38 (8, 4H, dd, J=8.08, J=7.5), 7.68 (9, 2H, tt, J=7.5, J=1.72).

5.4 – Oxidation of carbonyl compounds by the Ethyl lactate/Hydrogen peroxide.

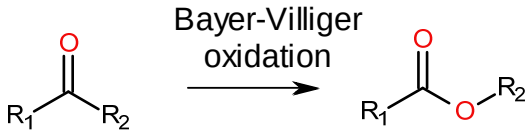
5.4.1 - Introduction.

In the last few years Baeyer-Villiger oxidation is become an important research topic due to the wide applications of its products lactones and esters e.g. in the gas and oil industry, for the synthesis or production of gasoline additives,[194] perfume components,[195] monomers like ε-caprolactone[196197] Remarkable applications of this reaction appeared in the synthesis of and pharmaceutical materials (e.g. antiviral, antiproliferative and imunosupressor agents),[198] anticancer drug mithramycin, natural products and steroid-peptide conjugates, chiral substituted γ-butyrolactones and biologically important substances,[199] such as alkaloids,[200] macrocyclic antibiotics, lignan lactones,[201] antileukemics, flavour components and pheromones.

The field was covered by several reviews which offer a comprehensive analysis of both synthetic and mechanistic details of the reaction: in **1999**, M. Renz and B. Meunier published a microreview on "100 Years of Baeyer–Villiger Oxidations",[202] in **1994** A. Wrobleski discussed the recent developments in metal-assisted asymmetric Baeyer-Villiger oxidations.[203] Later on, for the enantio-, regio- and/or chemo-selective Baeyer-Villiger reactions several metal catalyst and enzymes, such as monooxygenases, were used. Enzymatic BV oxidation has been an efficient strategy for the last 20 years; most of the results have been summarized in several recent reviews: in **1997** by Willetts,[204] in **1998** by Stewart,[205] Roberts,[206] C. Bolm,[207] and Strukul G.,[208] in **1999** by C. Bolm,[209] in **2003** by J. M. Woodley et al.,[210] in **2004** by H. Namasivayam**,**[211] and Sheldon R. A.,[212] in **2009** by Kayser M. M.,[213] and in **2010** by T. Pazmino, Dudek

and Fraaije.[214] Recent reviews appeared in **2011** by H. Leisch,[215] and very recently a mini-review in **2012** by M. T. Reetz,[216] and a communication by M. W. Fraaije was published.[217]

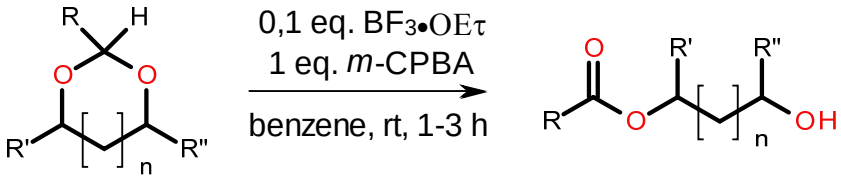
The **Baeyer–Villiger oxidation** is an organic name reaction in which ketones are oxidized to an esters, cyclic ketones to lactones and aromatic aldehydes to phenols (Dakin Reaction) by using oxidants like peroxy acids (*m*-CPBA) or hydrogen peroxide.[218] Baeyer-Villiger (BV) oxidation is named after the 1905 recipient of the Nobel Prize in Chemistry to German chemist Johann Friedrich Wilhelm Adolf von Baeyer (1835-1917) and the Swiss chemist Victor Villiger (1868-1934). Key features of the Baeyer-Villiger oxidation are its stereo specificity and predictable regiochemistry.[219]



5.4.2 - Reagents and catalyst used for Baeyer-Villiger reaction.

The reagents used in Baeyer Villiger oxidation to carry out this oxidative rearrangement includes peroxyacids, peroxosalts, hydrogen peroxide (H_2O_2) in the presence of different transition metal catalysts and under different reaction conditions, also molecular oxygen is used in the presence of enzymes, zeolite or clay based catalysts,[220] some other catalyst applied are hydrotalcites and stibium-containing hydrotalcite,[221] silica supported sulfuric acid catalyst,[222] and use of ultrasound.[223]

a) Peroxyacids. The more exploited reagents for BV reaction are peroxyacids, such as *meta*-chloroperbenzoic acid (*m*-CPBA), peroxybenzoic acid (PBA), peracetic acid (PAA), trifluoroperoxyacetic acid (TFPAA),[224] bis[trimethylsilyl] peroxide (BTSP), monoperoxyphthalic acid and peroxymonosulfuric acid (H_2SO_5) (Caro's acid, the original reagent used in the **1899**), potassium peroxomonosulphate supported on hydrated silica also known as "reincarnated caro's acid". If product formed in the reaction is acid sensitive, reaction is buffered with disodium hydrogen phosphate to prevent transesterification or hydrolysis.[225] Along with the traditional Baeyer-Villiger reaction to convert ketones to an esters and cyclic ketones to lactones, very recently Y. Yoshida *et al.* used hypervalent λ3-Bromane strategy for selective transformation of primary aliphatic and aromatic aldehydes to formic acid esters,[226] and J. Y. Kim *et al.* converted cyclic acetals to hydroxy esters,[227]



a) Inorganic peroxosalts and Ionic liquids. Several peroxosalts was proved efficient in BV reaction, i.e. magnesium salt of monoperoxyphthalic acid (MMPP)[228], sodium percarbonate[229] ($Na_2CO_3 \cdot 1.5H_2O_2$), or in combination with catalysts (i.e. thioureas[230] and selenoxides[231]). The peculiarity of ionic liquid to dissolve salts and organic compounds suggest the possible use of these media for catalytic BV oxidations. Methyltrioxorhenium and hydrogen peroxide in the ionic liquid [bmim]BF_4 (1-n-butyl-3-methylimidazolium $(bmim)^+$) was the first to be applied, then bis(trimethylsilyl) peroxide (BTSP) was used in the same solvent[232] or with triflate ccounterion ([bmim]OTf),[233] and more recently the Chrobok's group performed the oxidation with Oxone ($2KHSO_5.KHSO_4.K_2SO_4$) in a variety of ionic liquids with [bmim]BF_4 and [Hmim]OAc offering the maximum yields (95-96%).[234]

c) Metals catalysts. The application of transition metal catalysis to BV reactions was started by Mares and co-workers,[235] using Mo(VI) picolinato and dipicolinato complexes in the presence of H_2O_2 (90%) as terminal oxidant. Later, compounds of other metals, such as Co,[236] Cu,[237] Ni,[238] Sn and tin-containing zeolites [239] and clay supported Sn,[240] W,[241] Re,[242] V/Mo,[243] Pd(II)[244] and Pt(II),[245] [$(Me)ReO_3$] (MTO),[246] Arsonated Polystyrenes,[247] were also shown to catalyze the BV oxidations.

d) Molecular oxygen. Attempts to use oxygen to replace traditional organic peroxyacids has been reported,[248] but with limited success unless with enzymes.

e) Microwave. Microwave accelerated BV synthesis of lactones was investigated by Ritter in 2006, after that in 2009 L. Wang and in 2011 Chowdhury used successfully this technique.[249]

f) Enzymes. In the recent years enzymes were largely applied in BV oxidations and several aspects of the field (**Baeyer-Villiger monooxygenases** (**BVMOs**)) is covered by research articles and reviews. BVMOs represent valuable oxidative biocatalysts because BVMOs are often remarkably enantio-, regio- and/or chemoselective while accepting a broad range of substrates. However, there are also several problems associated with this type of catalyst: a) the water as the reaction medium, solubility of the organic reactant and product is low in the aqueous phase thus averting inhibition; b) substrate specificity; c) enzyme purification, the stoichiometric use and the costs of cofactors such as NADPH and BVMO's themselves, because lengthy purification steps are required, d) thermal stability of monooxygenase; e) enzymes activity at a broad pH range; f) in case of in-vivo oxidations, metabolically active microbial cells introduce complications on their own.

5.4.3 – Mechanism of Bayer-Villiger reaction.

Very recently in 2012 a good paper was published[250] by Shu Xingtian *et al.* on the mechanisms for Baeyer-Villiger oxidation of cyclohexanone with hydrogen peroxide in different systems. The following classification was made: 1) non-catalyzed reaction mechanism, 2) thermally activated radical reaction mechanism, 3) Brönsted acid catalyzed reaction mechanism, 4) solid Lewis acid catalyzed C=O activation mechanism, 5) solid Lewis acid catalyzed H_2O_2 activation mechanism.

In 1948, Criegee proposed that this reaction involves the formation of a tetrahedral intermediate by the nucleophilic attack of the peroxyacid onto the ketone.[251] This intermediate is often referred to as the Criegee-intermediate. A few years later, the exact mechanism of the oxygenation reaction was confirmed when a study on the Baeyer-Villiger oxidation of O^{18}-labeled benzophenone showed that the labeled oxygen ended up as the carbonyl oxygen of the formed ester.[252] Around the same time it was recognized that also enzymes were able to catalyze Baeyer-Villiger reaction.[253] This was concluded from the observation that a biological BV reaction occurred during the biotransformation of steroids by fungi. It took two decades until the first BV monooxygenases (BVMOs) were isolated and characterized.[254] From then on, a number of microbial BVMOs have been reported revealing several recurring biochemical characteristics.

Here we briefly summarize the mechanisms related to BV reaction by a) chemical reagents, including b) non enzymatic asymmetric metal complexes, and c) biocatalytic approaches.

a) Chemical Reagents. With peroxidic compounds a general mechanism is operative which involves, initially, the addition of peroxy group to the carbonyl carbon, forming a tetrahedral Criegee like intermediate. The transition state for this step is envisioned as a hydrogen relay involving the peroxidic groups with a linear O-H-O interactions.[255] Then, one of the group attached to carbonyl carbon is migrated onto the electron deficient oxygen atom in a concerted step, which is the rate determining step (Fig. 5.12). In the transition state for this migration the R-C-O-O dihedral angle should be 180° in order to maximize the interaction between the filled R-C sigma bond and the antibonding O-O sigma bond. This step is also (at least) assisted by two or three hydrogen bonds (and/or peroxyacid units) enabling the hydroxyl proton to shuttle to its new position.[255] The migrating group is usually the one that can best stabilize positive charge. If the migrating carbon is chiral, the stereochemistry is retained. The migratory aptitude of various substituent's attached to carbonyl carbon is approximately: hydrogen > tertiary alkyl > cyclohexyl > secondary alkyl, aryl > primary alkyl > methyl.

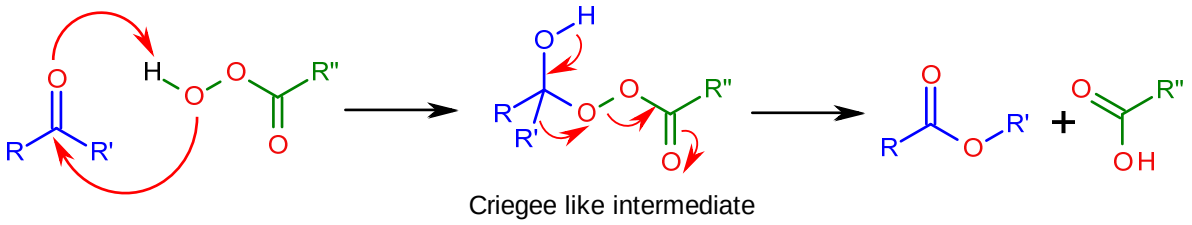


Figure 5.12 – Accepted mechanism for the BV reaction of ketones by peroxyacids

Non-enzymatic asymmetric Baeyer-Villiger reactions.

Metals are frequently employed in Baeyer-Villiger oxidations as catalyst.[256] An objective of modern chemistry is to exploit metals also for an asymmetric variant of this reaction, thereby overcoming the limitations of enzymatic procedures. When a metal is used it may serve in different ways to promote the oxidation: Lewis-acid metals can catalyze both the attack of a peroxy species to the carbonyl group and the subsequent rearrangement.[257] Furthermore, they may play a catalytic role in the *in-situ* formation

of an oxidant. Thus, the presence of nickel, copper or iron has proved suitable for the generation of an oxidizing agent effective in Baeyer-Villiger oxidations when oxygen was combined with an aldehyde, presumably with the intermediate appearance of acyl radicals and peroxyacids.[258]

Oxygen could be utilized together with an aldehyde as co-reductant in Baeyer-Villiger oxidations catalyzed by nickel or copper salts. By means of these catalysts substituted cyclohexanones were converted to the corresponding oxepanones (caprolactones) in good yields.[259] The subsequent development of a chiral catalyst led to the (*S,S*)-copper complex of Figure 5.13. Among numerous variants this complex with two bidentate ligands of the salox type turned out to be the best one for the aerobic oxidation of ketones to lactones in an enantioselective manner.[260, 261]

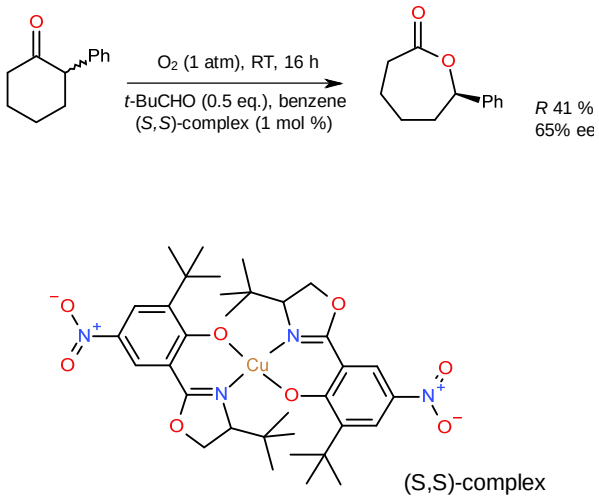


Figure 5.13 - Chiral copper complex used in the first asymmetric Baeyer-Villiger reaction.

B) Biocatalytic Reaction

Monooxygenases are enzymes that catalyze the insertion of a single oxygen atom from molecular oxygen into an organic substrate. In order to perform this reaction monooxygenases have to activate O_2, as no reaction will occur without activation due to the triplet spin-state of this molecule. This activation occurs upon donation of electrons to molecular oxygen, after which oxygenation of the organic substrate can occur. In most cases, monooxygenases utilize (in)organic cofactors to transfer electrons to molecular oxygen for its activation.

As most of oxidant enzymes, monooxygenases require nicotinamide coenzymes as electron donors, e.g. coenzyme NADPH. The type of reactive oxygen-intermediate that is formed depends on which cofactor is present in the monooxygenase. In figure 5.14 is summarized the proposed mechanism for the BV oxidation of cyclohexanone catalyzed by monoxygenases with flavin coenzyme. In some cases no cofactor is even involved.

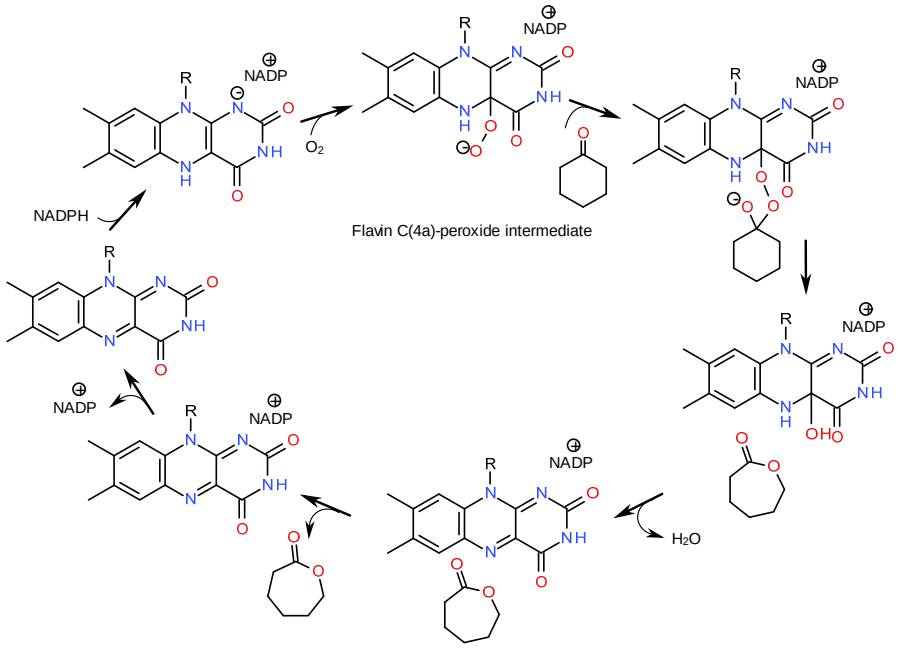


Figure 5.14 - Proposed Mechanism of Baeyer–Villiger Monooxygenases (BVMOs).

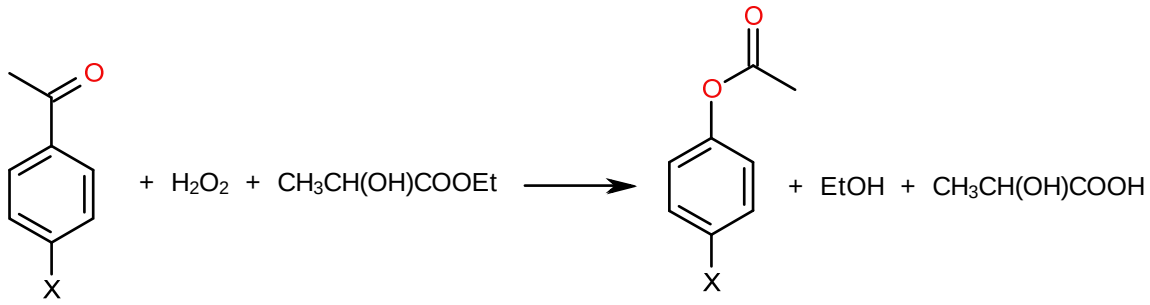
The mechanism of these flavin-dependent enzymes has been thoroughly studied. Enzyme bound flavin in the reduced form reacts with oxygen to form an alkyl hydroperoxide, FAD-OOH, which adds nucleophilically to the carbonyl function with formation of the Criegee intermediate in the rate-determining step. Thereafter, fragmentation with sigma bond-migration occurs; this step is conceptually identical to the traditional mechanism of BV reactions using stoichiometric amounts of alkyl hydroperoxides, peroxyacids, or H_2O_2. The same stereoelectronic requirement involving anti-periplanar arrangement of the C-C-O-O unit and subsequent sigma bond-migration were found to be operative in order to fulfill a favorable orbital interaction. In the case of BVMOs, this step is followed by water elimination occurring in the oxidized flavin, which is subsequently reduced by NADPH.

In practical applications whole cells are generally preferred. If an in vitro version is chosen by using isolated BVMO, then an NADPH regeneration system has to be included (e.g., an alcohol dehydrogenase with isopropanol as the reductant). In such cases the BVMO should be thermally robust.

5.4.4 – Oxidation of Carbonyl Compounds by Ethyl lactate/H_2O_2.

On the basis of our previous experience of oxidation of sulfides and phosphines with ethyl lactate/hydrogen peroxide system, it was of interest to verify if also carbonyl compounds could react with our intermediate "peroxylactic acid" to give the Bayer-Villiger reaction.[262] The experiments were focused on aromatic carbonyl compounds **8a-8d** in order to test the possible synthesis of phenol esters **9a-9d**. The

results reported in Table 5.12 summarize the results obtained under mild conditions (neat ethyl lactate, 25°C, 0.5 M concentration of ketone and H_2O_2).



8a; X = H
8b; X = CH_3
8c; X = OCH_3
8d; X = 2,4-diOCH_3
8e; X = 4-NO_2

9a; R = H
9b; X = CH_3
9c; X = OCH_3
9d; X = 2,4-diOCH_3
9e; X = 4-NO_2

Table 5.12 – BV oxidation of substituted acetophenones **8a-8e** to the corresponding acetates **9a-9e** by the couple ethyl lactate(S)/hydrogen peroxide*

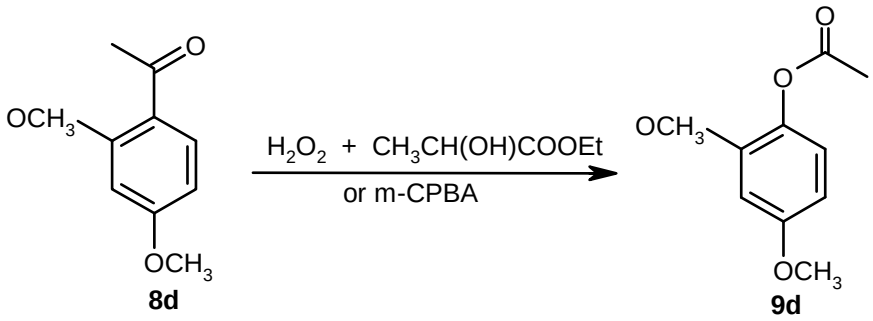
8	Catalyst**	$[H_2O_2]/[8]$	t (h)	9 (GC-MS Yield %)	9 (Isolated Yield %)
8a	-	1.5	24	25 (**9a**)	20 (**9a**)
8a	pTSA(0.1)	1.1	12	79 (**9a**)	71 (**9a**)
8b	pTSA(0.1)	1.5	16	83 (**9b**)	80 (**9b**)
8c	-	1.1	8	91 (**9c**)	88 (**9c**)
8d	pTSA(0.1)	1.1	6	84 (**9d**)	82 (**9d**)
8e	-	2.0	48	1 (**9e**)	- (**9e**)
8e	pTSA(0.2)	2.0	48	15 (**9e**)	10 (**9e**)

- Procedure: H_2O_2 (10-20 mmol) was added to a solution of ketone **8a** (10 mmol) in ethyl lactate (12 ml, 10:1 by wt.) at 55°C. **in parenthesis the molar ratio pTSA to ketone.

The results of table 5.12 indicate that BV oxidation of acetophenones occurs with limited excess of H_2O_2 and moderate to good yield in 16-24 h at 25°C when methoxy electron-releasing substituents on *ortho* and *para* position in the phenyl ring are present, whereas only traces of acetate ester was observed with electron-withdrawing substituents (i.e. *p*-nitroacetophenone). The yields are generally improved in the presence of pTSA, but the improvement is quite small with nitro derivative whereas with

acetophenone and 4-methyl derivative the improvement is significant. Still the yield remains under 80% with near stoichiometric amount of H_2O_2. The overall trend is similar to one observed with p-X-substituted phenyl sulfides but with a clear decrease of rate and yield.

In order to better characterize this BV oxidation of arylketones by the system ethyl lactate/H_2O_2, the model substrate 2,4-dimethoxyacetophenone was further investigated and the results compared with the analogous reaction of *meta*-chloroperbenzoic acid (*m*-CPBA).



The kinetic dependence of the rate on initial H_2O_2 concentration was investigated at constant pTSA (3%) and 25 °C. For similar oxidation by using *m*CPBA, DCM was used as solvent without *p*TSA. The progress of reaction was monitored by GC-MS following the decay of **8d** and formation of **9d**, after addition of an internal standard (2-methoxynaphthalene).

In Figure 5.15 are reported the results of decay of ketone **8d** against time for its oxidation by ethyl-lactate/H_2O_2 system under a wide range of relative ratios R = H_2O_2/**8d** (20-1:1). The related experimental condition used and the analytical data collected are reported in table 5.13.

The good linear correlation observed in Figure 5.15 was used to evaluate the initial rate and to deduce the order of reaction for substituted acetophenone **8d**. As evidenced by the good linear plot in Figure 5.16, the reaction is clearly first order in ketone. Moreover, the good correlation between 1/[**8d**] against time for reaction at 1:1 ratio of ketone to H_2O_2 indicates that the reaction is also first order in hydrogen peroxide. Even better correlations of all data were deduced if the change in concentration of ethyl lactate is also taken into consideration.

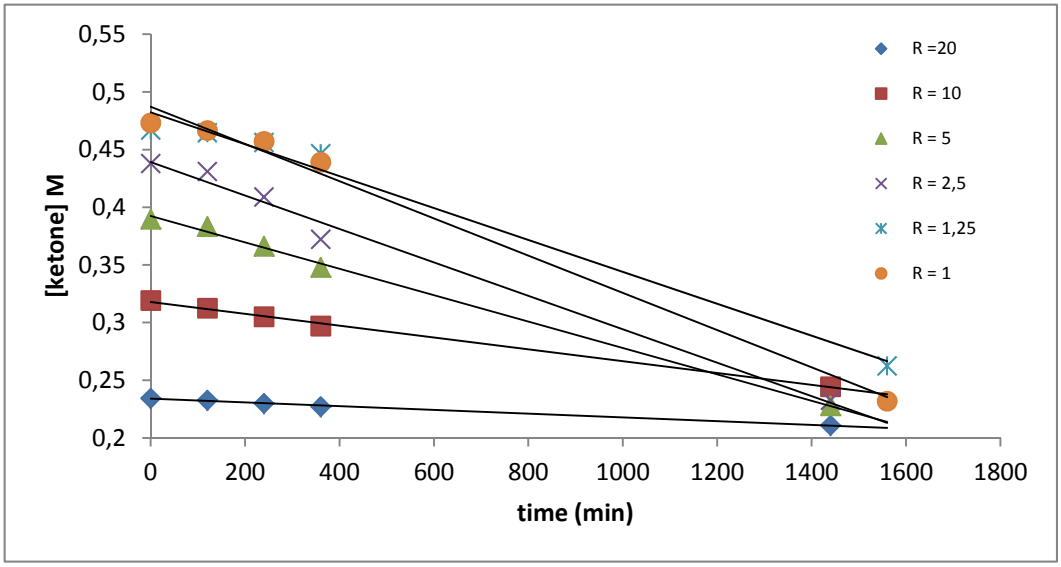
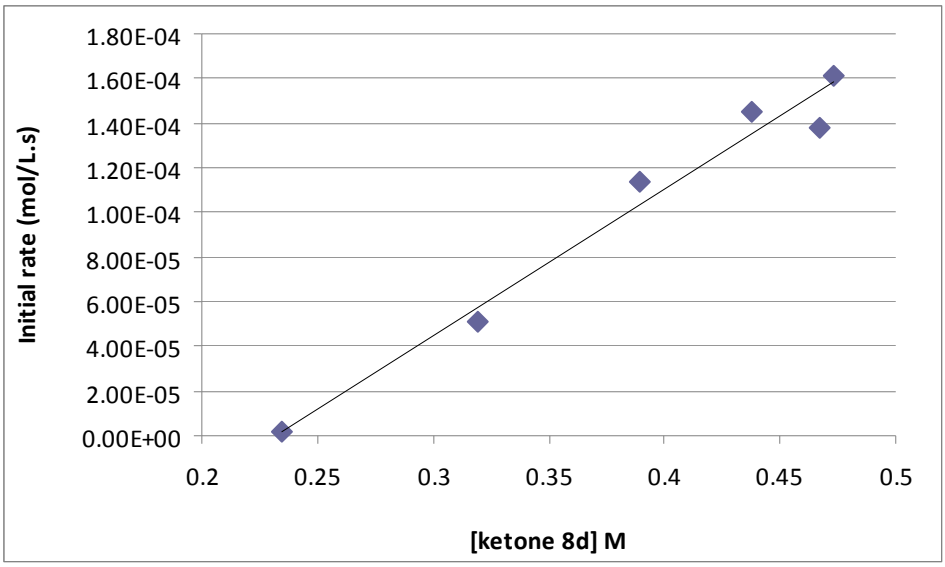


Figure 5.15 – Rate of disappearance of **8d** against time for different ratios H_2O_2/**8d** in EL (25°C).



[**8d**]	Initial rate
0.234375	1.62E-06
0.319149	5.13E-05
0.38961	1.14E-04
0.437956	1.45E-04
0.466926	1.38E-04
0.473186	1.61E-04

Figure 5.16 – Linear dependence of the initial rate of oxidation of **8d** by H_2O_2/EL from initial concentration of ketone **8d** (25°C).

With *m*CPBA in solvent DCM the oxidation of **8a** was faster than the reaction with the system ethyl lactate/H_2O_2. Figure 5.17 reports the plot of 1/[**8a**] against time for two different concentrations of **8a** and H_2O_2 (0.20:0.20 M and 0.10:0.20 M). The reaction shows a clear second order kinetic, first order in ketone **8a** and first order in hydrogen peroxide, as deduced from the 2:1 ratio of slope in the linear plots proportional to the ratio of concentration of reagents.

$$v = k\cdot[\text{ketone}]\cdot[H_2O_2]$$

At higher time remarkable deviation were observed from simple second order kinetics suggesting that water and ethyl lactate itself can play relevant roles in these oxidations.

As concern water, when initially added to the DMC solution of **8d** to form a heterogeneous system, the reaction, after an initial slow oxidation of **8d**, stops at about 20% conversion and does not proceeds further also after 24-48 h. The effect of water was even more dramatic with the system EL/H_2O_2 because only traces of oxidation product were observed after 24 h.

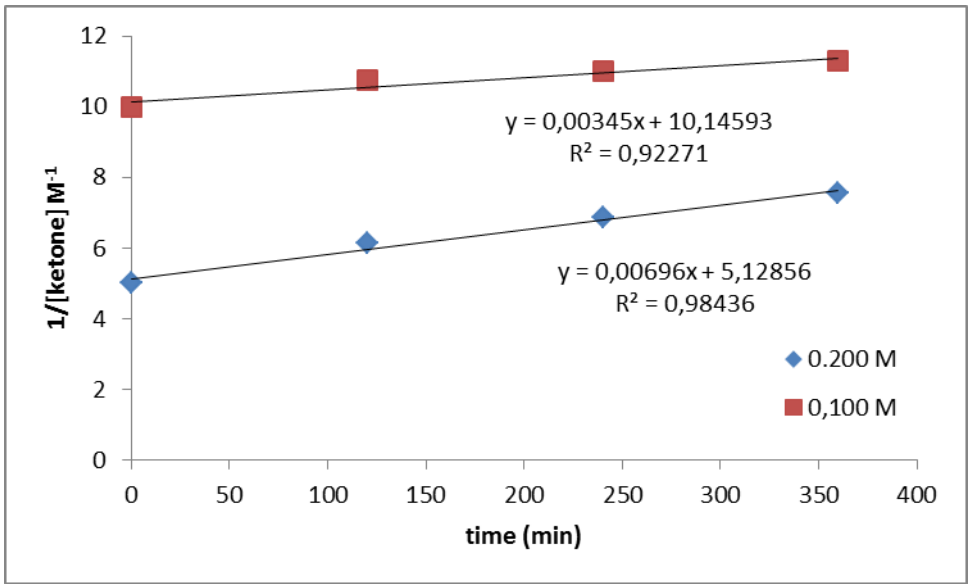


Figure 5.17 – Linear dependence of 1/[**8d**] against time in the oxidation of **8d** by mCPBA (25°C).

To evaluate these aspects some experiments of oxidation of **8d** by EL/H_2O_2 system were carried out in which the amount of ethyl lactate solvent and water product was varied. Representative results are reported in Figure 5.18 for the effect of ethyl lactate concentration as initial rate against time. The good correlation between the initial rate and ketone concentration (Fig. 5.19) is indicative of the fact that ethyl lactate has a limited influence in the first instants of the reaction because present always in large excess.

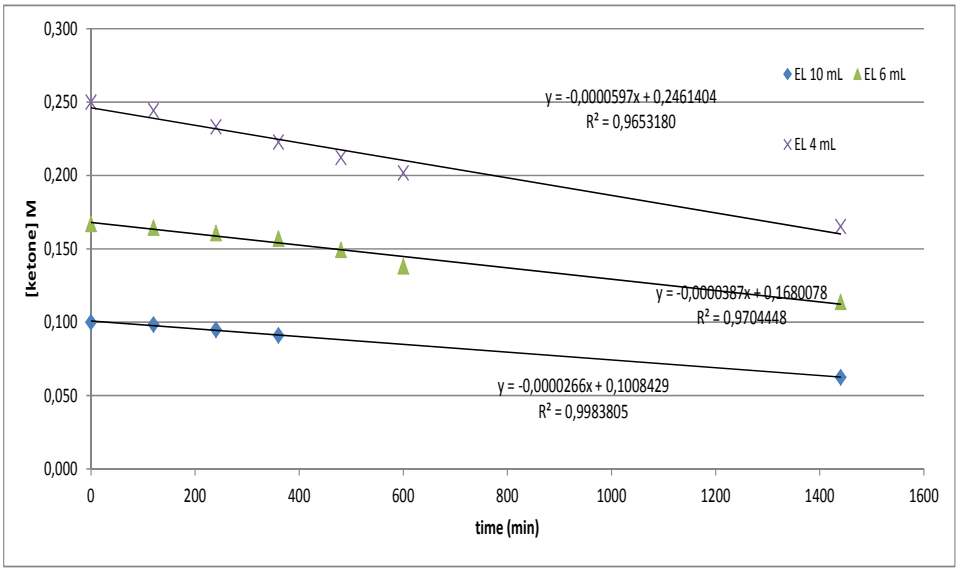


Figure 5.18 – Decay of [**8d**] against time in the oxidation of **8d** by EL/H_2O_2 system (25°C, volume of ethyl lactate in the legend).

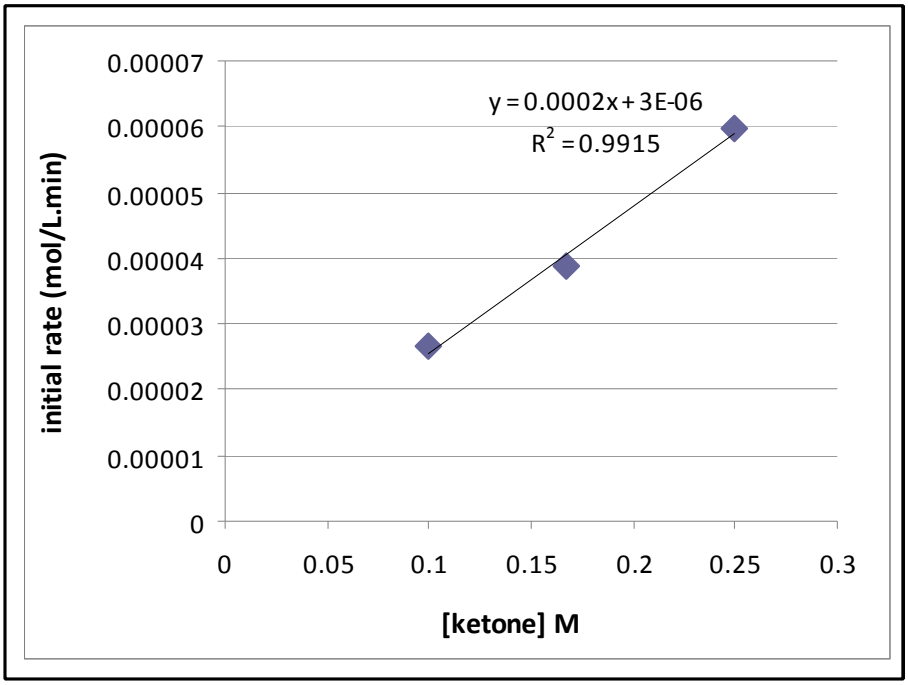


Figure 5.19 – Linear dependence of the initial rate of oxidation of **8d** by H_2O_2/EL from initial concentration of ketone **8d** (25°C, from Fig. 5.16).

Finally the effect of temperature was determined in experiments collected in Table 5.18 at three temperatures, 298, 313 and 333 K. Owing to the close, but not equal, amount of reagents, the data were elaborated as reported in Table 5.19 as a second order plot of $\ln([H_2O_2]/[\mathbf{8d}]) = \ln(A/B)$ against time (min.). A good linear plot was obtained (figure 5.20) confirming the second order kinetics also at higher temperature.

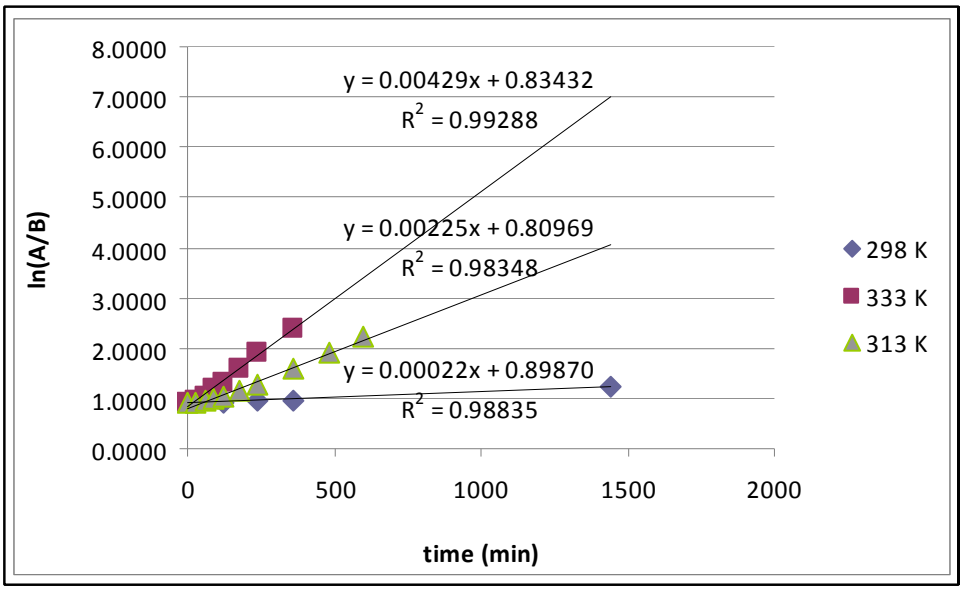


Figure 5.20 – Second order plot of ln([H_2O_2]/[**8d**]) = ln(A/B) against time at three different temperature for the oxidation of **8d** by H_2O_2/EL system (25-60°C).

The rate constants so deduced were plotted against 1/T to deduce the value of activation energy in an Arrhenius plot (Fig. 5.21). The few data are affected by significant errors and a moderate correlation coefficient was obtained.

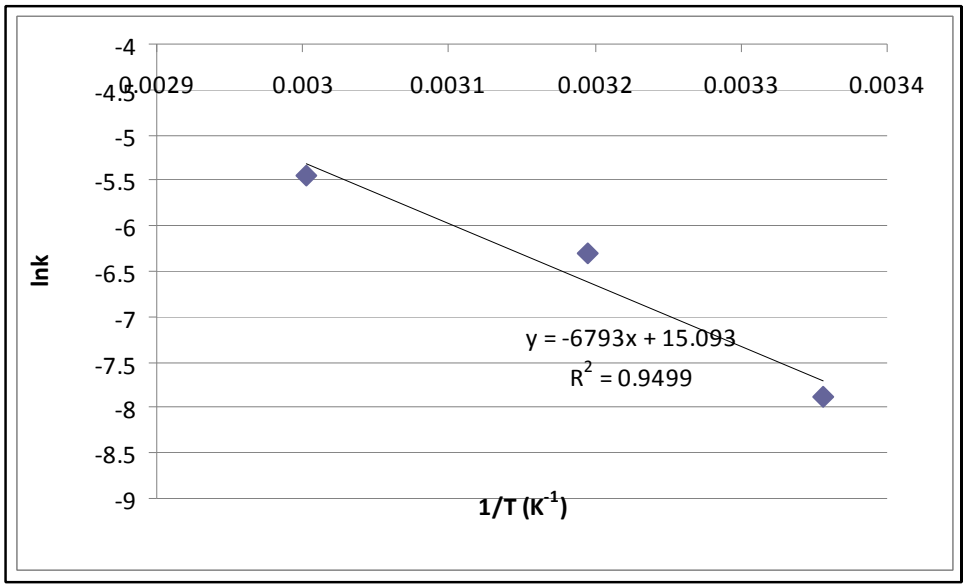


Figure 5.21 – The rate constants so deduced were plotted against 1/T to deduce the value of activation energy in an Arrhenius plot

From the slope of plot in figure 5.21 a value of activation energy of 56,2 kJoule/mol was deduced with a negative entropy (-125 J mol^{-1} K^{-1}) as expected for a peroxyacids intermediate in a strong hydrogen bonding environment.

The kinetic data obtained confirm that the EL/H_2O_2 system is effective as oxidant of electron-rich carbonyl compounds and that it can used safely also at higher temperatures. The second order kinetic confirm also that BV reaction under these conditions must involve an activated source of electrophilic oxygen non coincident with hydrogen peroxide (our peroxylactic acid) and a Criegee intermediate strongly engaged in hydrogen bonds.

EXPERIMENTAL

Starting 4'-X-acetophenones (acetophenone bp 202°C, 4'-methylacetophenone mp 22-24°C, 4'-methoxyacetophenone 36-38°C, 2',4'-dimethoxyacetophenone mp 38-40°C, 4'-nitroacetophenone mp 75-78°C) were obtained from Aldrich and used without purification. The products **phenyl acetate** (**9a**) bp 196°C. d = 1.073 $g \cdot L^{-1}$, **(4-methylphenyl)acetate** (**9b**) bp 208-210°C, d = 1.035 $g \cdot L^{-1}$, **(4-methoxyphenyl)acetate** (**9c**) bp 246°C, d = 1.099 $g \cdot L^{-1}$, and (4-nitrophenyl)acetate (**9e**) mp 75-77°C were available from Aldrich. **(2,4-dimethoxyphenyl)acetate** (**9d**) mp 46-48°C was isolated from the reaction mixture of the BV reaction with H_2O_2/EL and found identical with a sample prepared according to literature.[263]

Representative procedure for the BV oxidation of substituted acetophenones 8a-8a by ethyl lactate/hydrogen peroxide couple.

For each oxidation the same procedure was applied. A solution of X-substituted acetophenone **8a-8e** (5.0 mmol) in ethyl lactate (11.8 g, 100 mmol) was made at r.t., then inserted in a thermostatic bath at 25 °C for 15 min. In some experiments pTSA (0.15-2.5 mol based on the acetophenone) was added. To this solution, the 70% aqueous H_2O_2 solution (5-100 mmol) was once added under stirring at 25 °C and, after a predetermined time, an aliquot of the mixture was treated with trimethyl phosphine 1 M solution in THF (5-100 mmol) until all oxidant was destroyed. The system was then analyzed by GC-MS against internal standard (2-methoxynaphthalene) for determination of **8a-e** conversion and **9a-e** yield. The results obtained are reported in Table 5.12.

Determination of kinetics of oxidation of 2,4-dimethoxyacetophenone (8d) by H_2O_2/EL.

Oxidation of compound **8d** (180.2 mg, 1.0 mmol) was carried out by using ethyl lactate (10 ml) and hydrogen peroxide (1-20 eq) in the presence of catalytic amount (5%) of p-toluenesulfonic acid (pTSA), at

25 °C. The results obtained by GC-MS analysis are reported in Table 5.13 and elaborated in Table 5.14 for the initial rate determination reported in Figure 5.13.

Table 5.13 – Conversion of ketone **8d** against time for the its oxidation by H_2O_2/EL at different ratios [H_2O_2]/[**8d**]

Run	**Oxidant (eq.)**	**% Conversion vs. time (h)**				
		2 h	**4 h**	**6 h**	**24 h**	**26 h**
S-45	H_2O_2 (20)	0.7	1.9	3.1	10.0	
S-44	H_2O_2 (10)	2.1	4.4	6.9	23.4	
S-47	H_2O_2 (5)	1.6	6.0	10.7	41.4	
S-48	H_2O_2 (2.5)	1.6	5.1	9.0	37.5	
S-50	H_2O_2 (1.25)	0.5	2.3	4.4		43.8
S-51	H_2O_2 (1.0)	1.4	3.4	7.2		51.0

Table 5.14 – Data of table 5.13 elaborated as concentration of **8d** against time (min.)

Ratio R↓	Time→ 0	120	240	360	1440	1560
20	0.234375	0.232734375	0.2299219	0.227109	0.2109375	
10	0.319149	0.312446809	0.3051064	0.297128	0.24446809	
5	0.38961	0.383376623	0.3662338	0.347922	0.22792208	
2,5	0.437956	0.430948905	0.4089705	0.372163	0.23260198	
1.25	0.466926	0.46459144	0.4561868	0.446381		0.262412
1	0.473186	0.466561514	0.4570978	0.439117		0.231861

Kinetics of oxidation of 2,4-dimethoxyacetophenone by *m*-CPBA/AN.

Acetophenone (1.00 mmol) was dissolved in CH_3CN (5.0 mL) followed by addition of mCPBA (1.00 or 0.500 mmol). The reaction mixture was then leaved under stirring for 24 h at 25 °C. Another portion (1.0 mmol) of the oxidant mCPBA was then added and the reaction mixture was then left 1 h under stirring at 80°C. The progress of reaction was monitored by GC-MS and the results are reported in Table 5.15 and elaborated in Table 5.16 for II order rate determination.

Table 5.15 – Kinetic of oxidation of compound **8d** by *m*-CPBA/DCM

Run	**Oxidant (eq.)**	**% Conversion vs. time (h) at 25°C**				
		2 h	**4 h**	**6 h**	**24 h**	**25 h (80°C)**
S-46	mCPBA (1.0)	18.4	27.1	33.7	42.3	92
S-49	mCPBA (0.5)	7.1	9.1	9.5	20.0	44

Table 5.16 – Data elaborated from Table 5.13 for rate constant determination

Time (min)	0	120	240	360	1440
[**8d**] M	0.200	0.163	0.146	0.133	0.115
1/[**8d**]	5	6.127	6.859	7.541	8.666
[**8d**] M	0.100	0.093	0.091	0.089	0.080
1/[**8d**]	10	10.764	11.001	11.299	12.500

Kinetics of oxidation of 2,4-dimethoxyacetophenone (8e) by H_2O_2/EL on ethyl acetate amount.

2,4-dimethoxyacetophenone (1 mmol) was dissolved in ethyl lactate (in the amount reported in table 5.17) and to the solution a catalytic amount (3%) of p-toluenesulfonic acid (*p*TSA) was added at room temperature. Then, hydrogen peroxide (30% aqueous solution, 2.5 mol based on **8e**) was added once under stirring and the reaction was allowed to proceed for the time indicated in Table 5.17. The progress of reaction was monitored by GC-MS.

Table 5.17 – Dependence of kinetic of oxidation of compound **8d** (1 mmol) by H_2O_2/EL or m-CPBA/DCM from ethyl lactate concentration

Run	Ethyl lactate (mL)	% Conversion vs. time (h)						
		0	**2**	**4**	**6**	**8**	**10**	**24**
S-48	10	0.0	1.6	5.1	9.0			37.5
S-56	8	0.0						
S-57	6	0.0	1.5	3.7	6.0	10.6	17.3	31.8
S-58	4	0.0	2.3	6.7	10.9	15.1	19.3	33.9

Temperature dependence of kinetics of oxidation of 2,4-dimethoxyacetophenone (8d) by H_2O_2/EL and effect of added water.

2,4-dimethoxyacetophenone **8d** (1 mmol) was dissolved in ethyl lactate (10 mL) at room temperature. The flash was introduced in a thermostatic bath at a fixed temperature (25, 40 and 60±1 °C), and the solution thermostated for 15 minutes, then hydrogen peroxide (30% aqueous solution, 2.5 mmol based on **8d**) was added once under stirring and the reaction was allowed to proceed at the bath temperature for the time indicated in Table 5.18, withdrawing samples at a determined time for GC-MS analysis. The quantified conversion of **8d** are reported in Table 5.18.

Table 5.18 – Temperature dependence of oxidation of compound **8d** (1 mmol) by H_2O_2/EL (10 ml) or m-CPBA/DCM and effect of water in the starting medium.

Run	H_2O_2 eq.	H_2O	Temp. (K)	% Conversion vs. time (h)									
				0.5	**1.0**	**1.5**	**2.0**	**3.0**	**4.0**	**6.0**	**8.0**	**10**	**24**
S-48	2.5	-	298				2.1		4.4	6.9			37.5
S-52	2.5	-	333	4.2	16.7	35.9	45.7	62.6	73.7	84.6			
S-54	2.5	-	313	2.2	5.0	9.5	17.3	31.5	42.6	60.8	74.2	81.8	
S-53	2.5	(H_2O)	298	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5
S-55	1.0*	(H_2O)	298				20.3		15.7	21.7	18.2	22.1	18.7

* mCPBA

Table 5.19 – Elaboration of Table 5.18 data as ln([H_2O_2]/[ketone] vs. time (Figure 5.18)

tempo	0	30	60	90	120	180	240	360	480	600	1440
[ketone] B	0,1				0,0979		0,0956	0,0931			0,0625
	0,1	0,0958	0,0833	0,0641	0,0543	0,0374	0,0263	0,0154			
	0,1	0,0978	0,095	0,0905	0,0827	0,0685	0,0574	0,0392	0,0258	0,0182	
[H_2O_2] A	0,25				0,2479		0,2456	0,2431			0,2125
	0,25	0,2458	0,2333	0,2141	0,2043	0,1874	0,1763	0,1654			
	0,25	0,2478	0,245	0,2405	0,2327	0,2185	0,2074	0,1892	0,1758	0,1682	
tempo	0	30	60	90	120	180	240	360	480	600	1440
ln (A/B)	0,9163				0,9291		0,9435	0,9598			1,2238
	0,9163	0,9423	1,0299	1,2060	1,3251	1,6116	1,9026	2,3740			
	0,9163	0,9297	0,9474	0,9774	1,0345	1,1600	1,2846	1,5741	1,9190	2,2237	

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