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Exploring the self-assembly of 2,4,6-tris(4-pyridyl)benzene ligand in metal-organic cages

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ABSTRACT

The thesis presented here is the result of the work done in the past three years over the PhD project focused on the synthesis, characterisation and application of Metal-Organic Frameworks (MOFs) and Metal-Organic Cages (MOCs). This project starts from the tridentate organic ligand 2,4,6-tris(4-pyridyl)benzene (TPB) and investigates its coordination chemistry and self-assembly with metal subunits into complex metal-organic architectures. The primary focus of the research is the combination of TPB with zinc metal salts ZnX_2 ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) to obtain icosahedral MOCs that interlock into a poly- $[n]$ -catenane structure. These materials have been synthesised via both solution-based (instant synthesis or slow crystallisation) and solvent-free (mechanochemical grinding) synthesis and then characterised with instrumental techniques like single-crystal and powder X-ray diffraction (SC-XRD/P-XRD) and liquid- and solid-state NMR spectroscopy. The study of the dynamic behaviour allowed the trapping of molecules for molecular recognition, drug release and gas capture applications. Beyond the polycatenane, the research explored the coordination of TPB with Pd-based end-capping groups into MOCs despite the challenges in crystallisation. These cages are water-soluble and allow the transport of hydrophobic molecules in aqueous media. Furthermore, the project investigated structural diversification by functionalization of the TPB ligand. Using Suzuki-Miyaura coupling reactions, new forms of tridentate ligands were obtained, such as a methylated or an extended-arm derivative. These new organic ligands were tested with zinc salts, and a novel two-dimensional coordination polymer was obtained and fully characterised.

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1 *Introduction*

This chapter is written to provide a general overview of the topics that will be covered in the following chapters. The fundamental skeleton of this PhD programme is the development of organometallic compounds, specifically Metal-Organic Cages (MOCs), isolated or interlocked. After the definition of the aim of the work, a first section is given to describe the importance of metal-organic materials in the current scientific landscape. The synthesis of the said compounds will be carried out both in solution and in the solid state, to obtain products under different reaction conditions. The second section will focus on the definitions of kinetic and thermodynamic control for the synthesis of stable and metastable products. The third section will finally be focused on the reaction conditions and the instrument in the solid-state synthetic approaches.

1.1 Aim of the work

The work presented here is based on the synthesis, characterisation, and application of a variety of metal-organic compounds, specifically in the world of MOCs. Metal-Organic compounds have always drawn the attention of scientist given their interesting tunability. The possibility to precisely design the organic ligands and metal centres allows to obtain a coordination product with the desired features for specific applications.

The metal-organic compounds studied are all based on a specific exotridentate ligand that is the 2,4,6-tris(4-pyridyl)benzene (TPB). Triangular-shaped ligands are involved in many coordination assemblies reported in the literature. This particular ligand showed the potential to coordinate into interesting topological assemblies with a cage-like nature.

The aim of this work is to explore its self-assembly into interlocked $M_{12}L_8$ and discrete M_6L_4 MOCs. The synthesis of these compounds can be done in solution and in the solid state, so it is important to investigate both approaches to define the

differences and take the most out of the two. The characterisation part is performed with a variety of spectroscopic and diffractometric techniques to fully elucidate the structural topology and dynamic behaviour of these supramolecular objects.

A key part of the work is establishing the link between the microscopic environment (synthetic conditions and topological structure) and the resulting macroscopic properties. Once the material is completely described, it is important to design a range of applications, tailored to its characteristics, so that it can be exploited for a practical and useful purpose. For this reason, in this work, particular attention was dedicated to proposing and investigating potential applications in various fields (molecular recognition, drug delivery, gas storage).

Small changes in the building blocks can lead to drastic variations in the coordination and thus in the final assembly. Applying functionalization to the main structure of the TPB ligand can completely change the product. This is important for the design of new materials and applications. To further explore this field, the final part of the PhD project delved into the synthesis of new functionalized TPB and studied their self-assembly and the influence of the diversification on the final products.

1.2 Metal-Organic Cages

Metal-Organic compounds are attracting increasing attention for their interesting topological features and for their extremely broad versatility in a wide range of applications. Much progress has been made in research, from the very first mention of metal-ligand coordination^[1] to the most recent and important 2025 Chemistry Nobel Prize recognition to Metal-Organic Frameworks (MOFs), awarded to Professors Susumu Kitagawa, Richard Robson and Omar Yaghi^[2].

MOCs can be considered as part of the big family of metal-organic coordination compounds.^[3] MOCs can be defined as hollow (0D) supramolecular compounds that arise from the coordination self-assembly of organic ligands and metal ion clusters to form geometrical polyhedra with a specific pore size. These architectural objects have nanoscale dimensions and, given their hollow nature, can find many applications, ranging from molecular trapping to nanoreactors. MOCs can be synthesised in the

solid state or in the liquid state. In the solid state, the cages can be stabilised thanks to intermolecular interactions to form reticular structures to give crystalline materials. If the cages have an overall ionic nature, they can be dispersed in a solvent to be present in the liquid state. Moreover, there are cases reported in literature where single cages are connected by molecular linkers to form a reticular network that is macroscopically present as gels but can also be solid.^[4-6] MOCs can be isolated, defined as discrete zero-dimensional (0D) assemblies, or can be interlocked via mechanical bonds, where the cages form one-dimensional (1D) or three-dimensional (3D) catenated structures. Such structures will be presented in this section.

1.2.1 Discrete 0D MOCs

The possibility of designing and synthesising hollow molecular complexes is of fundamental importance for the development of new materials to be used in a variety of applications. MOCs are the product of the self-assembly of metal units and organic ligands, usually via coordination bonds and often in the presence of templating guest molecules. Using highly symmetric ligands often yields polyhedral structures that are classified as Platonic or Archimedean solids. But over the years, scientists tried to manipulate these two building blocks to obtain the desired assemblies of any size, shape or function.^[7]

The approaches used in the synthesis of these supramolecular compounds are different. Molecular panning or directional bonding are some of the methods on which the MOCs synthesis is based.^[8-12] The desired final product comes from a clear idea of the functionalities and dimensions that one wants to define. For this reason, the starting point, that is, the choice of the building blocks, is of fundamental importance. Small variations in the geometry and chemical nature of the organic ligand or metal unit can lead to drastic changes in the final architecture and size of the assembly (Figure 1.1).^[13] For example, if one looks for a particular complex to host a large guest, the cage must be designed to have a large internal void. If the cage is not big enough, the guest cannot be hosted, but if the cage is too big, the host-guest interactions will be too weak to allow guest inclusion. Therefore, the MOC must be designed to be of the right size. In the literature, there are several reports on the construction of big assemblies to imitate hollow structures present in nature to host big molecular complexes.^[14,15] The size is controlled by the dimensions of the linkers;

longer ligands can lead to larger cages because bigger will be the faces of the polyhedra generated by those linkers. But this is not the only factor that determines the size of a cage. Geometrical restraints apply, and the assembly of vertices (metal units, M) and edges (organic ligands, L) into big polyhedral objects can be mathematically predicted, also considering the curvature of the ligands as demonstrated by Fujita and coworkers (Figure 1.1).

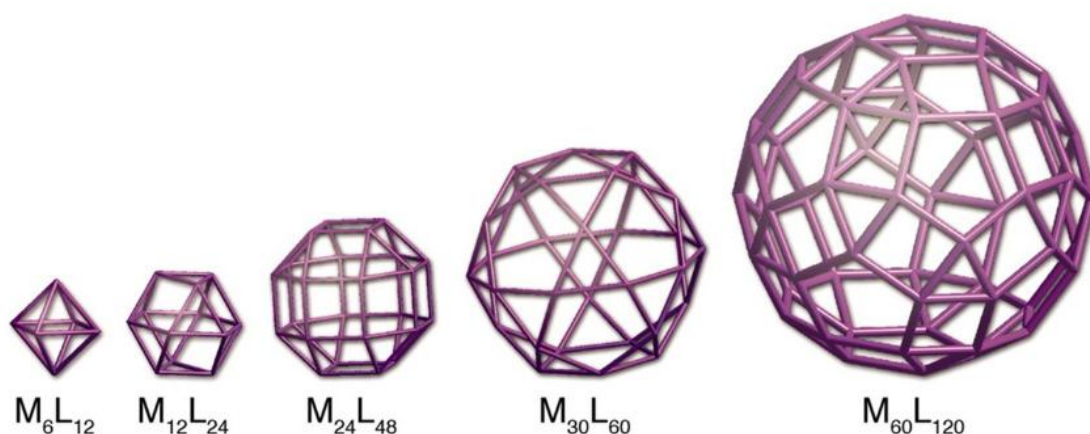


Figure 1.1 — Family of $M_n L_{2n}$ polyhedra.^[13]

As taught by the lock and key model, used to represent the enzyme-substrate system, even the shape and internal environment are fundamental for guest inclusion. Particularly shaped guests can be nicely fitted inside (*i.e.* induced fit) complementary shaped host structures. The chemical nature of the internal void (*e.g.* hydrophobic or hydrophilic) also plays a role in capturing guests with affinity. The design of MOCs with specific shapes can lead to the encapsulation of some guests that would be otherwise not trapped (*i.e.* shape-specific guest inclusion).^[16] The internal environment of a cage is determined by the functional groups present on the starting building blocks. The ligands can be functionalized by adding specific moieties that will end up being binding sites for guest molecules. The moieties will bring an environment depending on their chemical nature, for example, there can be a hydrogen bond acceptor site or a specific high reactivity site. Even if this concept can be quite straightforward, the practical self-assembly outcome can be difficult to predict. Introducing a small or large chemical moiety on the ligand can have dramatic effects on the geometry and coordination of the units, resulting in a different shape and size of the final self-assembled MOC.

Given the high tunability and possibility to tailor the shape, size and functionalization of MOCs, researchers have tried to exploit these features to develop new smart materials in applications like molecular recognition, catalysis, and gas storage. Three examples will now be presented to give an idea of the importance of these supramolecular assemblies, not only for a synthetic and topological interest, but also for their role as functional molecular flasks.^[17]

The first example presented is on the synthesis of a series of Metal-Organic Polyhedra (MOPs) and their gas sorption studies reported by *Yaghi et al.*^[18] The metal centres of these MOPs are trinuclear clusters of $\text{Fe}_3\text{O}(\text{CO}_2)_6$, which is common in the synthesis of MOPs. This cluster has been modified with sulphate bridging groups to occupy three of the six binding points. The resulting triangular secondary building unit (SBU) is reacted with organic ditopic or tritopic linkers that coordinate into porous anionic truncated tetrahedra (denoted IRMOP, using ditopic benzenedicarboxylate-based ligands) or truncated heterocubane (denoted MOP, using the tritopic 1,3,5-tris(4-carboxyphenyl)benzene) (Figure 1.2). The cages are anionic with eight negative charges and form an overall neutral system in the presence of the dimethylammonium guest, trapped during the reaction in DMF. The structures can be considered as biporous, as there is one type of pore that is given by the internal void of the cage, and there is a second type of open space generated by the voids present in between adjacent polyhedra. The volume of the pores between polyhedra is much larger than the volume of the pores in the cages, giving a very important total void volume (sum of the two contributions) with values of 46-70% of the total crystal volume (depending on the type of MOP). Gas adsorption isotherm studies were performed to obtain information on the structural behaviour of the MOPs. The gases studied in these tests were N_2 (78 K), CO_2 (196 K), Ar (78 K), and benzene (298 K). IRMOP-51, IRMOP-53 and MOP-54 presented reversible type I isotherms in all cases with apparent surface area of 480, 387, and 424 m^2/g . These values can be comparable to zeolites and some MOFs, and this type of isotherm gives insights into the structural rigidity and permanent porosity of the MOPs. Then the MOPs were exposed to high-pressure CH_4 (298 K) with the aim of studying the possibility of gas fuel storage. The results showed that the MOPs were capable of trapping methane with 5.6, 5.9, and 7.3 molecules per cage, respectively, for IRMOP-51, IRMOP-53, and MOP-54. IRMOP-51 was also exposed to H_2 , resulting in 12.5 (78 K) and 3.1 (87 K) molecules per unit, values comparable to those of MOF-5. These studies demonstrated that it is possible

to design MOPs with high surface area and with sorption abilities to be used in gas storage applications.

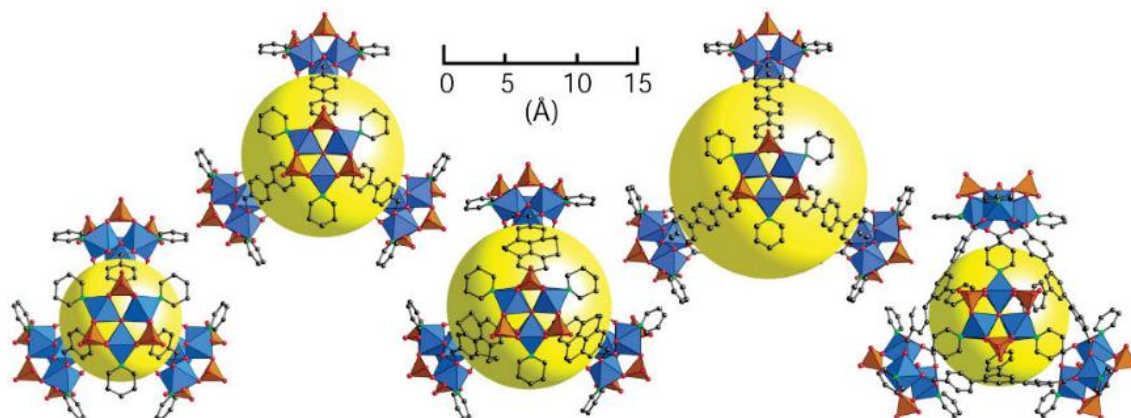


Figure 1.2 — XRD models of IRMOP-50,-51,-52,-53 and MOP-54 where the yellow sphere represents the accessible space.^[18]

The second example is on the stabilisation of an air-sensitive compound trapped in tetrahedral assemblies reported by *Nitschke et al.*^[19] In this study, the authors try to solve the problem of the high reactivity of tetrahedral phosphorus (P_4) with oxygen, leading to oxidising species that spontaneously combust. The idea behind the work is to confine the P_4 (white phosphorus) into MOCs so that there would not be enough space for the molecule to react with oxygen and prevent the formation of combustible products (the intermediate combustible products would be too large to fit in the cages). A tetrahedral cage (Figure 1.3) was synthesised in aqueous solution and put in contact with solid white phosphorus. The formation of the complex is confirmed by ^1H NMR with a shift of the host peak and by ^{13}P NMR, which presented just one peak (only one environment for the P). Single crystals were obtained by vapour diffusion of 1,4-dioxane in the complex solution, and single crystal X-ray diffraction (SC-XRD) analysis confirmed the crystal structure and confirmed the presence of a hydrophobic internal environment, ideal for the trapping of P_4 (Figure 1.3). The crystals resulted unchanged even after months of exposure to the atmosphere, meaning that the cage is stable and can stabilise the dangerous P_4 . The removal of the guest from the tetrahedral cages is done by adding a benzene solution to the aqueous solution of the complex. Benzene is a competitor and is more favoured to be trapped in the cages, pushing out P_4 , which is released into the benzene solution. P_4 will further react with oxygen to produce phosphoric acid dispersed in the aqueous

solution. Thus, MOCs, like the one presented here, are also capable of trapping and stabilising highly reactive molecules. Also, with the design of an ionic cage with an internal hydrophobic environment, it is possible to bring water-insoluble compounds to be dispersed in solution by trapping them in the cages.

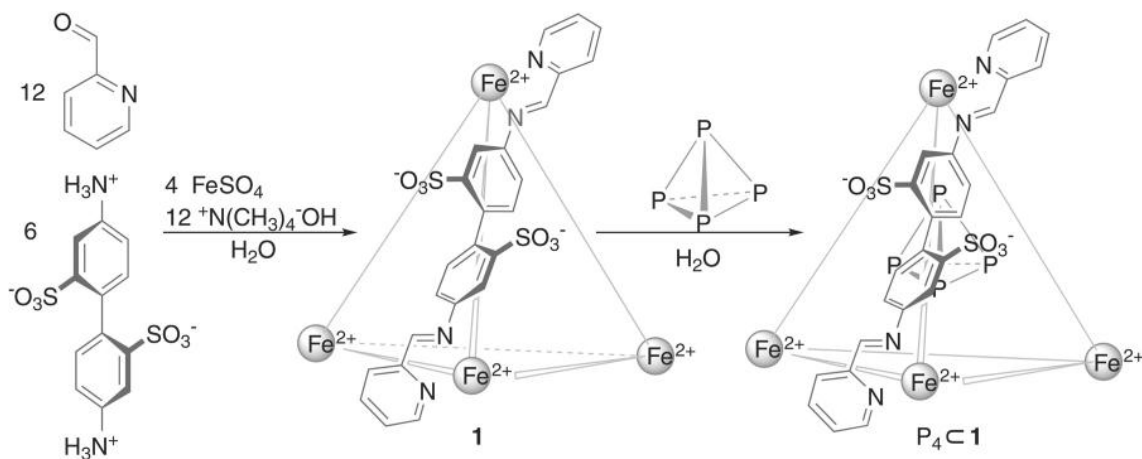


Figure 1.3 — Synthetic scheme of tetrahedral cage and P_4 trapping.^[19]

The third example is the famous crystalline sponge method, where an octahedral complex network is used for guest inclusion and molecular recognition purposes, reported by *Fujita et al.*^[20] This method was largely investigated and optimised by the same group, but the very first paper on this topic reports the use of a coordination network built on large MOCs that would act as a “crystalline molecular sponge”, able to recognise and absorb guests, even in very small quantities. The cages reported here are octahedral complexes (M_6L_4) coordinating six $Co(NCS)$ metal units (M), with four 2,4,6-tris(4-pyridyl)-1,3,5-triazine (TPT) ligands (L). In the solid state, the cages are disposed as an array, where the metal units are shared by adjacent cages, to form a porous crystalline network. This structure can be considered as biporous, as there are the voids of the M_6L_4 cages and the interstitial voids in between the cages. This network of cages acts as a host in the presence of big guests. In this case, the crystalline sponge was soaked in a toluene solution of fullerene, and it was able to trap the big C_{60} or C_{70} assemblies. But the crystalline sponges are not only used for molecular recognition. More recently, Fujita and coworkers reported that crystalline sponges can be used to incorporate nanogram/microgram quantities of liquids that can hardly be obtained as single crystals.^[21] The crystalline sponge is left in a vial containing the liquid guest (*e.g.* guaiazulene) that would penetrate the network’s

cavities (Figure 1.4). The guest interacts with the host and will occupy specific binding sites in an ordered manner. In this way, the 3D structural elucidation of these compounds in the solid state can be obtained, which would not be possible otherwise. MOCs prove to be also useful in analytical chemistry for determining crystal structures in compounds that are normally liquid or products that are obtained in very small quantities (*e.g.* natural products).

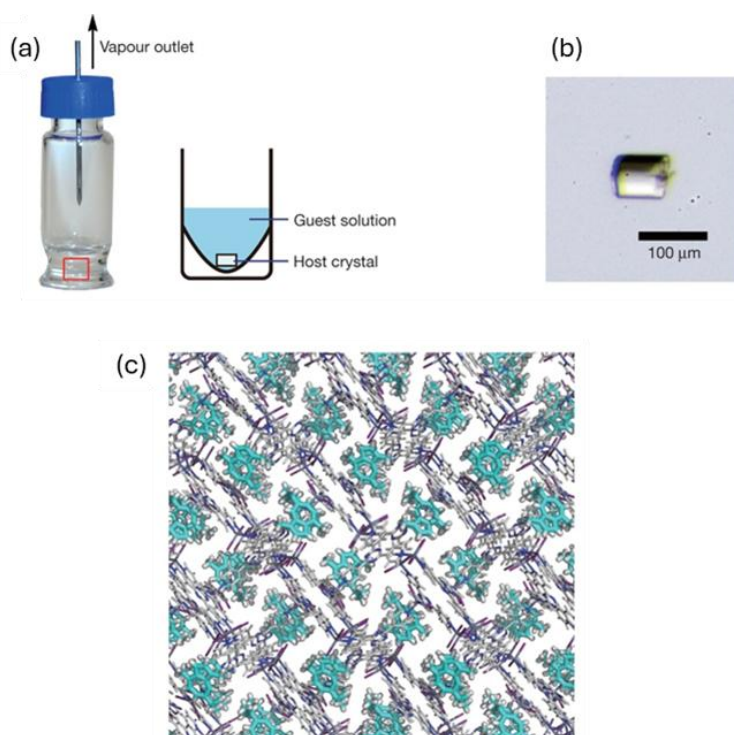


Figure 1.4 — a) Vial containing the crystalline sponge and the guest solution; b) Magnification of the microcrystal; c) Networked structure of the crystalline sponges containing the guest.^[21]

1.2.1.1 M₆L₄ cages

One of the first and most notable cases of isolated MOC discovered was reported by Fujita's group following their supramolecular self-assembling studies.^[22] The intention to produce polyhedral self-assembled systems for host-guest studies for molecular trapping purposes led them to obtain hollow octahedral assemblies from a square planar end-capping Pd group (M) and a rigid tridentate ligand (L). Six units of an ethylenediamine palladium metal salt ($\text{enPd}(\text{NO}_3)_2$, enPd) coordinate in water with four molecules of TPT (L), to obtain single M₆L₄ octahedral cages with the ability to encapsulate large guests (Figure 1.5).^[23–26]

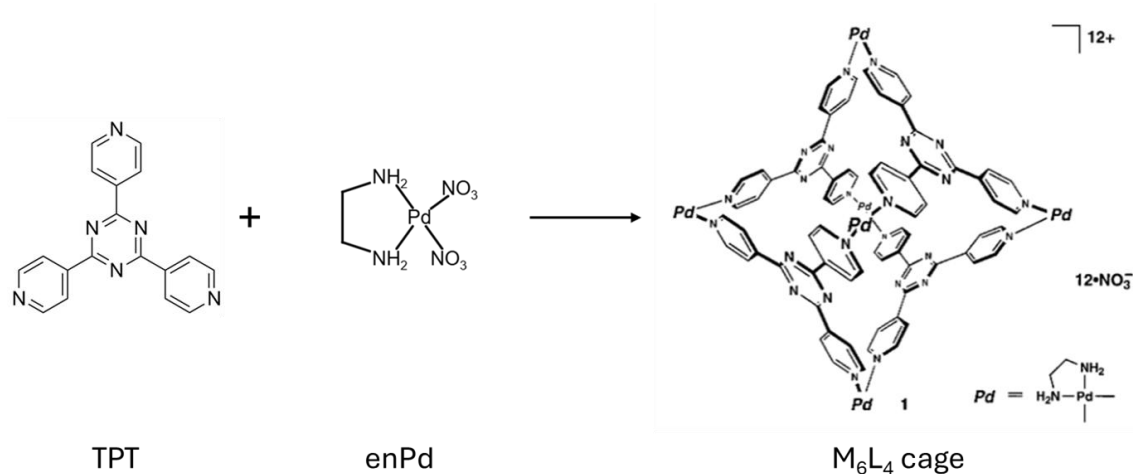


Figure 1.5 — Reaction and structural model of $(enPd)_6(TPT)_4$ octahedral coordination cage.^[25]

The cages have a 12+ ionic nature and a diameter of about 1 nm. The formation of the assembly could be corroborated and quantified through ^1H NMR spectroscopy, observing the chemical shift variation between the peaks of pure components and the peaks of the M_6L_4 cage. Interestingly, even if an excess of metal is added in the self-assembly process, the M_6L_4 cages are still the main product, with the excess of metal clearly visible at the NMR. This denotes the thermodynamic stability of the cage. The crystallisation of the cages was possible, by evaporation, in the presence of a guest, sodium adamantane carboxylate (in a ratio 4:1 with respect to the cage). SC-XRD analysis could clarify the geometry of the host-guest interactions. The adamantane guest has an amphoteric nature, with the carboxylic group being hydrophilic and the adamantane carbon core being hydrophobic. The cage is ionic, so it is soluble in water, but the inner core of the cage is hydrophobic due to the presence of the environment generated by the aromatic ligand TPT. The guest in the crystalline solid-state places itself at the open windows of the cages with the adamantane core pointing toward the internal part (hydrophobic) and the carboxylic moiety pointing outwards (hydrophilic).

The guest inclusion is also observed in the liquid state. The titration of the cage complex with stoichiometric amounts of guest clearly shows the inclusion of the guest, having a different chemical shift in the ^1H NMR spectrum. If fewer than four molecules per cage are present in solution, three sets of peaks appear in the spectrum, one for the complexed host-guest system, one for the uncomplexed host and one for the complexed guest molecules. In excess, if more than four molecules per cage are added to the solution, three sets of peaks are also present, but different from the

previous case. One corresponds to the complexed host-guest system, one to the free uncomplexed guest and the last to the uncomplexed guest.

Other types of large molecules were subjected to test to explore the host-guest behaviour of these M_6L_4 cages, confirming the placement and orientation seen with the adamantane guests. These assemblies are perfect candidates for guest trapping purposes and to bring in aqueous solution hydrophobic molecules. This ability for guest inclusion was subsequently used, and the M_6L_4 cages were also optimised for the development of crystalline sponges.^[20,21]

1.2.2 Interlocked MOCs

MOCs are not only present as isolated structures but can also assemble in what are called Mechanically Interlocked Molecules (MIMs). MIMs have recently attracted attention in the scientific world because they are central in the studies that earned Prof. Sauvage, Prof. Stoddart and Prof. Feringa the Nobel Prize in Chemistry in 2016.^[27–29] These compounds are molecules formed by the interconnection of two or more subunits via a mechanical bond.^[30,31] The mechanical bond can be described as a physical bond that allows the entanglements of two or more units thanks to their reciprocal attractive/repulsive forces. The separation of the mechanically interlocked units is possible only if there is the cleavage of one of their own chemical bonds.

One of the best examples of MIMs is catenanes.^[32,33] Catenanes (Latin for chains) are defined by IUPAC as: “Hydrocarbons having two or more rings connected in the manner of links of a chain, without a covalent bond. More generally, the class catena compounds embraces functional derivatives and hetero analogues”.^[34] As clearly provided by the definition, catenanes can have two or more rings, or macrocycles, and the name of these molecules can better be addressed as $[n]$ -catenanes, with n equal to the number of rings participating in the chain. When the number of rings is high enough (infinitely extended), the structure is defined as poly- $[n]$ -catenane (PC).

There is a restricted class of MIMs that is a subset of poly- $[n]$ -catenanes concerning MOCs. Organic macrocycles are not the only units that can compose PCs, because polycatenanes can also be self-assembled from MOCs (PC-MOCs).^[35,36] MOCs can interlock one another to give 1D, 2D or 3D structures (up to now, only 1D and 3D have been reported), which give restricted relative motions (translation, rotation and twisting) with respect to the free isolated cages (Figure 1.6). Importantly, PC-MOCs

combine, at the same time, the properties of host-guest assemblies (MOCs) with the properties of polymeric materials (PCs). The concatenation is achieved thanks to non-covalent interactions that help stabilise the cages and the final interlocked molecule. Despite the MOCs interlocking, which tends to decrease the available volume in the cages, there is the simultaneous formation of hierarchical porosities in the structure. In such cases, the presence of more than one type of pore could help the interaction and adsorption of guest molecules. This section will focus on the origins of PC-MOCs and some interesting case studies.

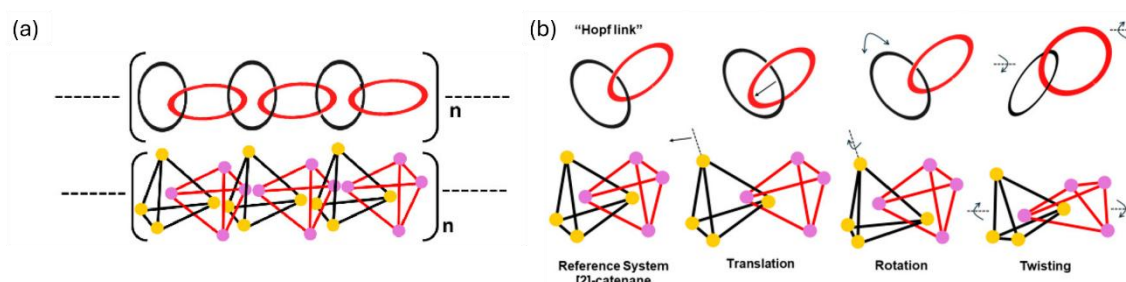


Figure 1.6 — a) Cartoon of 1D poly-[n]-catenane and multiple mechanically interlocked MOCs; b) Relative motions of Hopf Links and between two interlocked MOCs.^[36]

The first report of an $[n]$ -catenane composed of MOCs is a $[2]$ -catenane self-assembled of M_3L_2 MOCs reported by Fujita *et al.*^[37] The MOCs composing the catenane are made from the self-assembly of 3 units of ethylenediamine palladium metal salt ($enPd(NO_3)_2$, $enPd$), one molecule of TPT, and one molecule of 2,4,6-tris(4-(pyridin-4-methyl)phenyl)-1,3,5-triazine in water. The thermodynamic product is formed at high temperatures (100 °C, after 3 days) and corresponds to two interlocked MOCs thanks to the interactions among the aromatic rings in the ligands that form a quadruple π - π stacking (Figure 1.7).

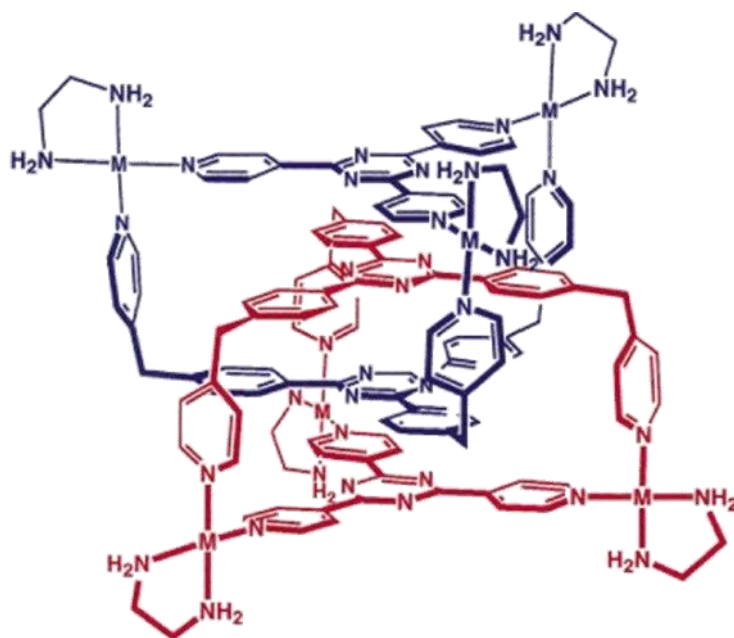


Figure 1.7 — Structure formula of the first MOCs-based [2]-catenane.^[37]

This case study opened the path for further studies and development of interlocked MOCs with some reported cases of [2]-catenanes.^[38–41] Alongside the discovery of [2]-catenanes, scientists wanted to go beyond the two interlocked cages and tried to expand the interlocking to reach infinitely extended 1D, 2D or 3D poly-[*n*]-catenanes. There are many examples of poly-[*n*]-catenanes self-assembled from MOCs^[42–45] In this chapter, some of the most relevant cases will be presented.

The first documented case of poly-[*n*]-catenanes self-assembled from MOCs was published by *Lu et al.*^[46] The structure is a 3D poly-[*n*]-catenane of adamantane-like polyhedral cages. The cages are formed by the coordination of 6 silver Keggin anion structures with 4 molecules of 1,2,4-triazole and have an octahedral shape with sextuple self-interpenetration topology. Each silver ion is coordinated to two triazoles that, applying the symmetry operators, give octahedral-shaped cages which have open windows that allow the mechanical bonds to establish between all the vertices of each cage and form a 0D→3D extended polycatenated structure. The mechanical bonds are stabilised by the aromatic-aromatic interactions established between the triazole aromatic rings. The 3D concatenation creates nanometric voids in which the templating polyoxometalate anions are placed and do not allow the entrance of any other guest. Up to that point the formation of infinitely catenated polyhedral cages

was only assumed but not reported in literature; this was the very first published case of PC-MOCs.

The second case study presented here is an interesting work on the application of PC-MOCs for the adsorption/desorption of alcohols.^[47] This PC-MOCs is formed by the assembly of four tri(4-carboxy-benzyl)amine anions with six $[\text{NiL}]^{2+}$ ($\text{L} = 1,4,8,11$ -tetraazaundecane) cations (Figure 1.8) to give discrete tetrahedral cages that interlock at their vertices with four adjacent cages into a 3D network. The activated material can be used for adsorption/desorption of a series of alcohols (methanol, ethanol, *iso*-propanol and *tert*-butyl alcohol). The recorded isotherms show hysteresis loops for each alcohol, which get larger as the size of the alcohol molecule increases. The dynamic behaviour of the pores provides an interesting feature for the use of the material in applications such as guest separation and sensing.

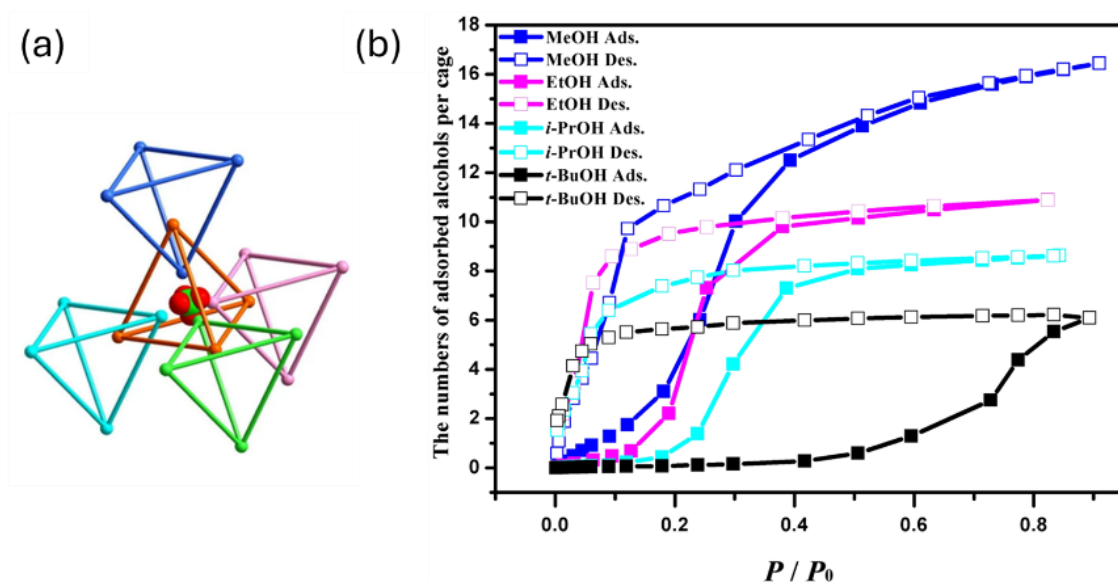


Figure 1.8 — a) Polycatenane of discrete tetrahedral cages; b) sorption isotherms of MeOH, EtOH, *i*-PrOH, *t*-BuOH.^[47]

The third work presented here is another application study where a semiconductive 3D PC-MOCs is demonstrated to possess a high X-ray attenuation efficiency and could be used as an X-ray detector.^[48] This PC-MOCs is obtained by reaction of 4,4',4''-((1,3,5-triazine-2,4,6-triyl)tris(sulfanediyl))tribenzoic acid (H_3L_1) and uranyl nitrate hexahydrate. H_3L_1 reacts *in-situ* to form a new ligand (L_2) which

coordinates with the uranyl cluster to form octahedron-like M_4L_6 MOCs that interlock by mechanical bonding with six adjacent cages into what was defined as a “superoctahedral architecture” generating an infinite 3D network (SCU-14). Given the unique structural feature of multiple π - π stacking interactions, there is a charge transfer pathway (Figure 1.9). The bandgap was estimated to be 2.61 eV, which is a reasonable value for semiconducting materials and falls within the range of values for materials used in the application field of X-ray detection. The presence of Uranium as a metal node allows a high X-ray attenuation efficiency. SCU-14 demonstrates to be a valid example of how PC-MOCs are not only intriguing for their challenging synthesis and topological interest, but they can also find applications in various fields, like, in this case, X-ray detection and photoelectronics.

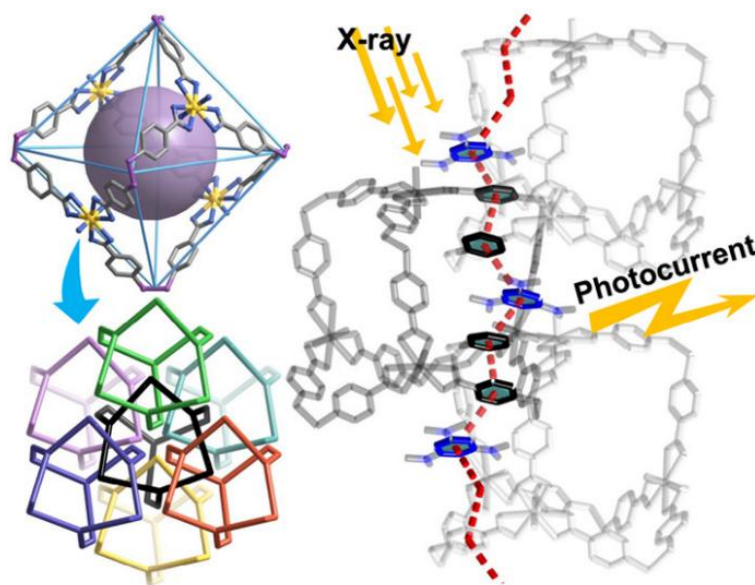


Figure 1.9 — Polycatenation of octahedral MOCs and its charge transfer structural pathway.^[48]

1.2.2.1 $M_{12}L_8$ poly-[n]-catenanes

An interesting case study in the PC-MOCs topic, which is also the foundation of this PhD programme, is the family of the poly-[n]-catenanes self-assembled from $M_{12}L_8$ icosahedral MOCs. This type of PC-MOCs was first reported by *Dehnen et al.*^[49] and *Constable et al.*^[50] in 2011. Starting with the famous crystalline sponges by Fujita *et al.*, using the coordination network formed from the assembly of TPT with $ZnCl_2$, the authors investigated the effects that small variations in these building blocks would have on the final product. Changing the core of the ligand from a triazine to a

pyridine, the authors discovered that the 2,4,6-tris(4-pyridyl)pyridine (TPP) ligand self-assembles with ZnCl_2 into icosahedral MOCs with formula $[(\text{ZnCl}_2)_{12}(\text{pytpy})_8]_n \cdot 3\text{CHCl}_3$. By slow crystallisation, using the three-layer method, it is possible to get single crystals suitable for SC-XRD and thus elucidate the topology of the new PC-MOCs (Figure 1.10).

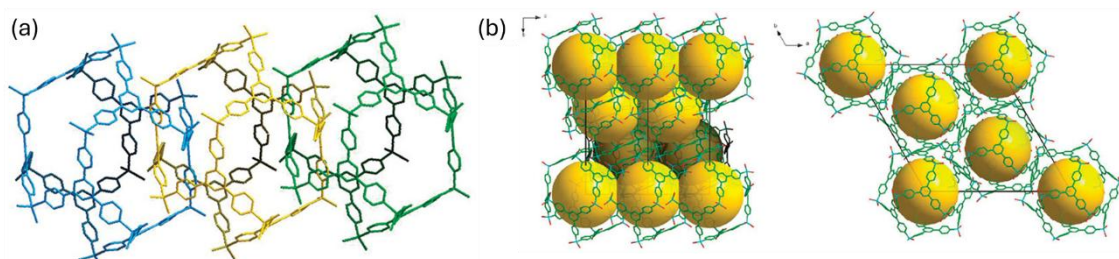


Figure 1.10 — a) Structural model of 1D interlocked icosahedral cages; b) Packing view of the polycatenanes along the *a*-axis and *c*-axis.^[49]

The cages have a volume of approximately $2700 \text{ \AA}^3$ and have 20 faces, eight occupied by TPP, while the other are open windows, and at the vertices of the polyhedra are the metal ions. These cages are not isolated, but they interlock together into a 1D poly- $[n]$ -catenane that extends along the crystallographic *c*-axis and pack together in the rhombohedral unit cell. The mechanical bond is established between the M_{12}L_8 cages thanks to the open windows and is stabilised by the π - π interactions among the ligand aromatic rings. In the voids of the cages, there is enough space for guest molecules to be hosted, and the volume is so large that the solvent molecules are disordered and form a nanodroplet of liquid guest.

This was the first case of icosahedral M_{12}L_8 MOCs that self-assemble into a PC. Later in 2020, *Martí-Rujas et al.* further investigated the structural arrangements under slight ligand variations.^[51] Using 2,4,6-tris(4-pyridyl)benzene (TPB), instead of TPT, and coordinating it with ZnCl_2 , the authors reported the formation of a PC-MOCs with formula $[(\text{ZnCl}_2)_{12}(\text{TPB})_8]_n \cdot 9(\text{C}_6\text{H}_5\text{NO}_2)$ that resulted in being isostructural to the material reported by Dehnen et al.^[49] (Figure 1.11). This study not only proved that changing the ligand core from a pyridine to a benzene yields an isostructural material, but the point was that this product could be obtained under kinetic control. While the previous structure (TPP and ZnCl_2) was obtained only by slow crystallisation, this new isostructural PC-MOC could also be obtained by fast crystallisation, which allows the formation of the $\text{TPB}_8(\text{ZnCl}_2)_{12}$ catenane selectively and in short periods of time.

This is possible because, in the slow crystallisation, there is the error-checking process, which is a process that consists of the constant rearrangement of the intermediates to finally obtain the most stable thermodynamic product. On the other side, with the fast synthesis, the reaction is under kinetic control (Section 1.2.1), and it makes it possible to isolate a metastable product. The synthesis of the $M_{12}L_8$ poly- $[n]$ -catenane was investigated using different aromatic solvents (nitrobenzene, *o*-nitrotoluene, chlorobenzene, toluene, *p*-chlorotoluene, 1-bromo-4-fluorobenzene) that are included as nanodroplets in the cages. The possibility of trapping guests makes this material a good candidate for molecular recognition and storage, and the possibility of having it in the form of bulk powders makes it more available and open to scale-up opportunities.

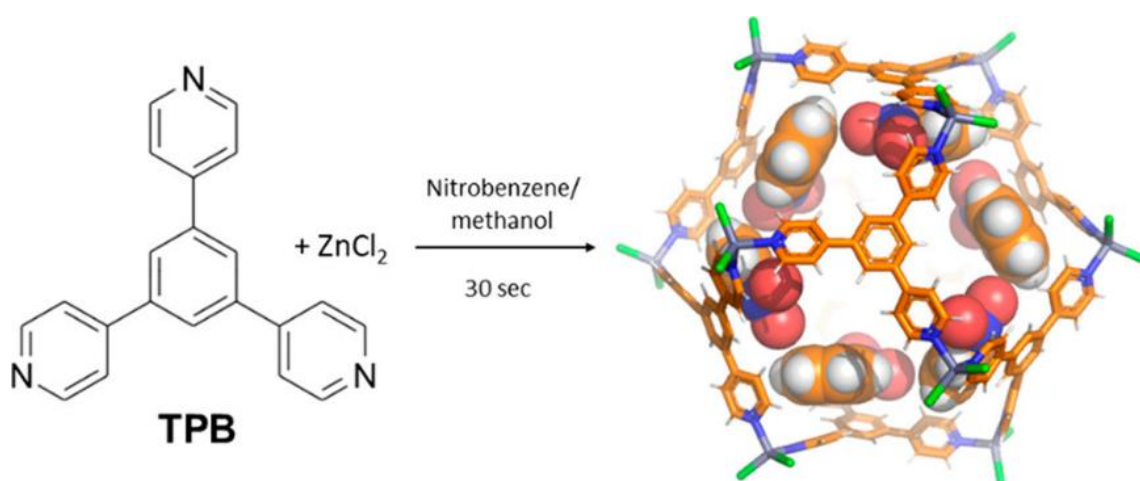


Figure 1.11 — Synthesis of $M_{12}L_8$ interlocked MOCs. A single $M_{12}L_8$ cage is shown^[51]

1.3 Kinetic vs thermodynamic control in self-assembly

In the self-assembly of Zn^{2+} ions and TPB ligand in the presence of solvent guest molecules, there are two main key factors in the reaction development. The first aspect to consider is the stability of the intermediates and products; the second is the rate of formation of these products. These parameters have a direct influence on the progress and result of a reaction. All the reactions are characterised by the reactants (the starting materials), the intermediates (depending on the mechanism of reaction) and the products (stable or metastable depending on the conditions of reaction). The final products can be different and can compete by following different reaction pathways.

In the presence of an equilibrium, at a given temperature, the reaction can proceed under kinetic or thermodynamic control. Kinetic control is characterised by short reaction times and occurs when the forward reaction is significantly faster than the backward reaction (which happens at the start of every reaction), leading to the production and isolation of metastable products (*i.e.* one of the local minima of the Gibbs free energy). In general, with time, the equilibrium is established, and the most stable product (*i.e.* the one with the lowest energy, global minimum) will form. Changing the temperature will affect the control of the reaction, increasing temperature going toward the thermodynamic products, while decreasing temperature will favour the kinetic control.

Kinetic and thermodynamic control is fundamental when dealing with self-assembling systems. MOCs are self-assembled, usually with thermodynamic control, for example, with slow crystallisation methods (*e.g.* three-layer method). This is because these complexes are held together by coordination bonds and electrostatic interactions, weaker with respect to covalent bonds, which can be easily cleaved and formed again (*i.e.* low activation energy). An equilibrium is established where this “error-checking” process allows, with time, to constantly rearrange the metastable intermediates and finally form the most stable product. On the other side, at low temperatures, high concentrations and fast reaction times, the reaction can be driven toward a defined kinetically trapped state that leads to kinetic metastable products that could not be achieved in the thermodynamic conditions (Figure 1.12). A kinetically trapped state can be achieved with several approaches: host-guest chemistry, ionic interactions, and coordination chemistry.^[52] Kinetic and thermodynamic control can lead to the formation of new undiscovered materials.

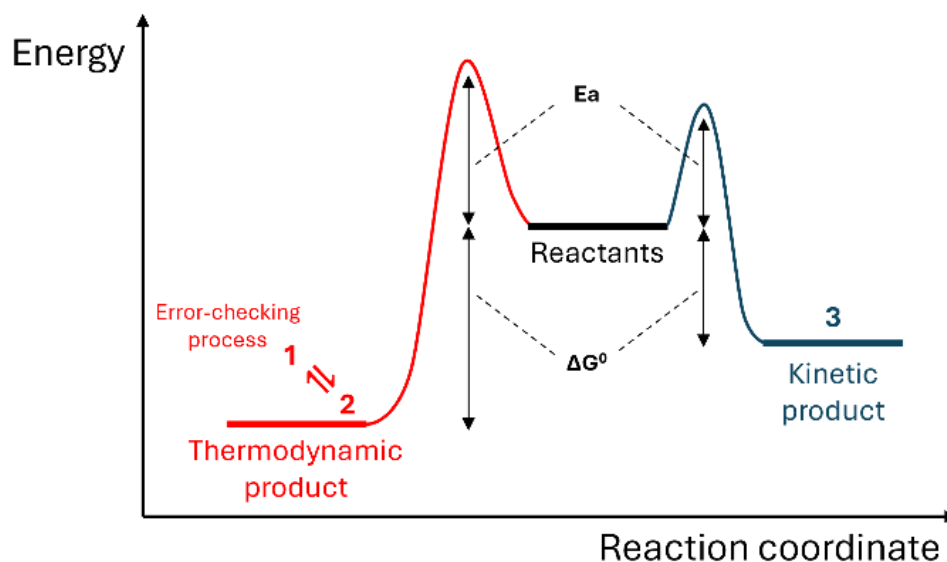


Figure 1.12 — Scheme of kinetic and thermodynamic control in self-assembly.

1.4 Solid-state for green chemistry

The most common approach for MOCs self-assembly is the reaction in the liquid state. In this state, the solvent plays a fundamental role, aiding the formation of the molecular assembly and potentially absorbing heat released from the reaction. High temperature and the presence of the solvent allow a high number of molecular collisions, higher than what could happen in the solid-state. The amount of solvent (*i.e.* the concentration of reactants) directly influences the molecular motion and the number of collisions, thus influencing the rate and control of the reaction (kinetic vs thermodynamic).

Despite the positive aspects in the presence of solvents, there are some drawbacks that have drawn attention toward other synthetic approaches. Over the past few decades, the tendency toward more “green” approaches that would avoid the use of solvents was not only an opportunity to investigate new unexplored fields of chemistry and save money at the industrial level, but also a chance to prevent waste production, to increase energy efficiency and to overall limit the environmental pollution. The importance of decreasing the use of solvents is such that it has been assigned a place in the 12 principles of green chemistry: “*The use of auxiliary substances*

(e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used".^[53]

With the aim of optimising the use of solvents as imposed by current targets, new approaches started to gain ground in the scientific area. In contrast to reactions in solution, where the presence of solvent is required, solvent-free solid-state reactions are chemical reactions that occur between solids without any presence of liquids.^[54] In the field of investigation of new nanomaterials, in their synthesis but also in their application, a valid solution is found in solid-state reactions.^[55] When dealing with solid-state, the driving forces of the reaction can be mechanical forces, temperature or light.

This field of chemistry that uses mechanical forces to achieve chemical reactions is referred to as mechanochemistry.^[56–58] Mixing and grinding or milling the reagents, it is possible to react them, breaking and forming bonds thanks to mechanical action. The absence of solvent (or presence in very small amounts, which is referred to as liquid-assisted grinding (LAG)) makes the process efficient as the purification step is drastically reduced, and there is no need for removal and recycle of the solvent that is used in the solution-state reactions. In mechanochemistry, the reactions occur faster and with less energy requirement with respect to liquid phase reactions. It also provides a quite simple approach for the scale-up at an industrial level and a more precise approach for controlling the stoichiometry of the reaction. Mechanochemistry allows the synthesis of molecules and the discovery of new reactions that are challenging or even not possible in the solution state. This solid-state approach is not only used for organic reactions, but it is also being explored in the synthesis of metal-organic materials.^[59] Few are the drawbacks with this approach, like the heat management (the solvent absorbs and regulates the heat released from the exothermic reactions) or the handling of solid materials at an industrial scale, but new instrumentation is always under study to solve these problems. Nevertheless, when designing new protocols for mechanochemical reactions, every aspect must be considered and every contribution weighted with respect to the solution state for the least energetic consumption, having clear in mind the objective of the work.

If at the lab scale using small quantities, a mortar and pestle can do the work, when increasing the mass and volumes of reagents, mills come to the assistance for a reproducible and industrially feasible solution. There are several mechanochemical techniques and systems, from the oldest mortar and pestle useful for grinding to more recent ball millers (Figure 1.13). Ball mills are characterised by the presence of balls

that impact with the reagents inside jars and differ from each other in the motion given to the jar, planetary or vibratory. Extruders work based on a screw that mixes the reactants and simultaneously extracts the product. There are also mechanochemical systems based on acoustic devices.

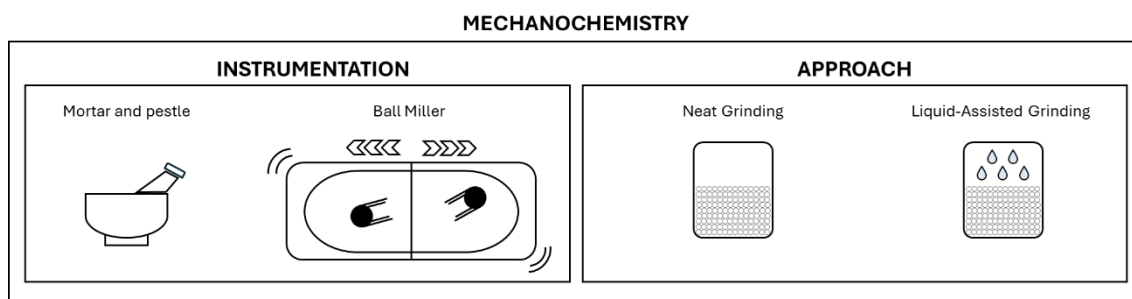


Figure 1.13 — Classification of mechanochemical techniques with their representation and picture.

The use of millers opens up a series of experimental conditions that can influence the final outcome of the reactions. The size and material of the jar and of the balls, the number of balls, and the temperature controls are some of these influencing factors. Also, the jars of the millers provide a closed system for the reaction, making it hard to monitor in real time, and when the jar is opened, the system is exposed to the external environment, having consequences on the products. New technologies were recently developed to manage and analyse the reaction occurring *in-situ*. One example is the development of new methods and equipment for the *in-situ* monitoring by synchrotron X-ray powder diffraction of mechanochemical reactions occurring in ball mills.^[60,61] For example, the study reported by *Dinnebier et al.* focuses on the mechanochemical synthesis of a Zeolitic Imidazolate Framework (ZIF) directly monitored with a high-energy synchrotron X-ray source.^[60] The mechanosynthesis, neat grinding or liquid assisted, is performed in a plastic jar with stainless steel balls, which is placed on the miller and hit by the high-energy X-ray incident beam. In this way, it is possible to *in-situ* monitor the evolution over the course of the milling and identify all the formed species, intermediates and products.

Exploring the solid state is interesting not only in the synthetic approach, exploiting the mechanochemistry, but also for the structural features that such a state can hold. Considering the solid state, one immediately thinks of an overall static condition, but at the molecular level, there can be motion due to molecular thermal displacements or due to structural dynamics like molecular rotors. Metal-organic

compounds can have interesting dynamic behaviours that give them functional properties to make them smart, responsive materials.^[62–64] Merging the mechanical and structural properties of porous solids with the flexible properties of molecular motions can establish dynamic environments for applicative purposes.^[65–67] Molecular rotors are molecular elements that exhibit rotary motion spinning on a molecular axis. This dynamic motion gives several interesting properties, from regulating the dielectric response of the material to regulating the access of guest molecules in porous materials, acting as “gates”. The rate of motion of the molecular rotors can differ depending on the environment and can reach high regimes even at low temperatures.^[68,69] In these fields, some of the most interesting cases reported in literature are about the design of porous materials with molecular rotors for the storage of CO₂.^[70,71]

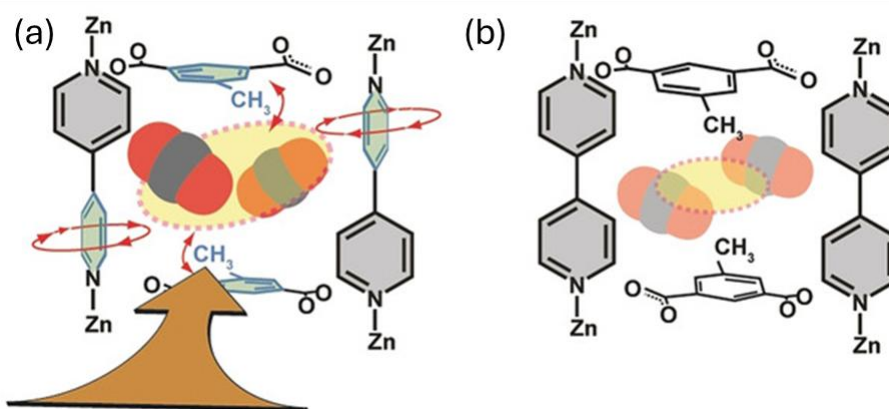


Figure 1.14 — Cartoon of the CO₂ adsorption mechanism by rotational rotor behaviour at room temperature (a) and at 195 K in vacuum by steric hindrance (b).^[72]

One interesting case of study, as example, is the design of a porous coordination polymer with a mechanism to trap and store CO₂ thanks to molecular rotors that spin at different frequencies based on the temperature (Figure 1.14).^[72] In this paper, Zn²⁺, 4,4'-bipyridine (bpy), and 5-methylisophthalic acid are reacted to form a 2D coordination polymer ([Zn(5-Meip)(bpy)]_n) with cavities surrounded by pyridines and methyl benzene rings. These aromatic moieties have rotational motion along their axes, and the frequency of the spin is temperature dependent. The rotational motion was studied with ²H solid-state NMR, a common technique for the quantification of the motional molecular frequencies. While at low temperature (195 K) the pyridines and the methyl benzene rings are static, at higher temperatures (273

K, 298 K) there is partial motion (Figure 1.14). At these temperatures, one pyridine is static while the other flips on its axis with a frequency of 400 kHz at 273 K and 600 kHz at 298 K. The methylbenzene group wobbles around its position. While the size of the pores at 195 K is not large enough to host CO₂ molecules, the adsorption tests showed that at 296 K, there is physisorption. This means that while at low temperature CO₂ cannot be trapped, at high temperatures the aromatic rings rotate, there is a slight expansion of the pores, and the guests are facilitated to enter the pores. If the temperature is decreased after the adsorption, the structure goes back to the static regime and prevents the desorption of the CO₂, making the material a good candidate for CO₂ storage. In this work, the authors provided a great case for the use of dynamic rotors in porous materials for the storage of gases as an example of the value that the study of the solid state can contribute to scientific knowledge.

2 *Experimental techniques*

2.1 Introduction

When dealing with the characterisation of materials, there are many methodologies that can be applied depending on what is being sought. The instrumental techniques to be used for a complete chemical and physical description can be divided into three main classes. These three techniques are: microscopic techniques, diffraction techniques and spectroscopic techniques. Each of these is based on the interaction of an electromagnetic wave, with a specific wavelength, with the matter, and each is used for the determination of material characteristics and properties. Microscopic techniques can be optical, where the use of visible light helps the structural investigation of the material in the micrometric scale (up to around 5 μm), or electronic (*e.g.* SEM or TEM techniques), in which electrons interacting with matter can achieve a much higher resolution (a few nanometers), producing pictures with detailed structural insights in the nanometric scale. Diffraction techniques are multiple and can use electrons, neutrons or X-rays as primary beams. X-ray diffraction (XRD) is the principal method used to analyse crystalline materials both as single crystals and powders, a powerful technique to obtain structural, qualitative and quantitative descriptions of crystalline materials. Spectroscopic techniques give an average and local information of the chemical and molecular environment. All these three techniques are complementary to each other and can provide a full elucidation of the short- and long-range environment of the investigated material.

This chapter is an introduction to the main diffraction and spectroscopic techniques used in this work during this PhD programme. Giving a full, detailed description of these techniques would be too long and never exhaustive in a single chapter and can be found in appropriate textbooks for XRD^[73–84] and NMR^[85–93]. This introduction aims to give an idea of the basic principles and how important these methods and instruments are in the research field. First, diffraction techniques with single crystal (SC-XRD) and powder (P-XRD) diffraction will shortly be presented to underline their importance in solid-state chemistry. Then, with a short summary, it will be illustrated how liquid-state and solid-state Nuclear Magnetic Resonance

(NMR) techniques are used for the study of molecular arrangement, dynamics and host-guest systems. Following, there will be a brief explanation of the CLASSIC NMR technique used for the *in-situ* investigation of crystallisation and guest exchange experiments.^[94]

2.2 Diffraction by crystals

The study of the solid state is of fundamental importance for the description of the chemical and physical properties of the materials and, of course, of MOCs and MOFs, which is the main topic of this thesis. A great part of all the solids present on the Earth consists of crystals. Crystals are present in everyday life in the form of minerals, salts, ice and so on. They can be molecular or non-molecular solids, but all have in common the structural feature of being crystalline. The crystalline state is identified by the ordered arrangement of atoms, ions or molecules into a unit, periodically repeated in three directions to obtain the overall crystal lattice. The smallest asymmetric portion is the asymmetric unit and is subjected to the symmetry operation generating the unit cell, which is the smallest volume that is then regularly repeated in the directions to form the crystal lattice. There are seven 3D crystal systems (triclinic, monoclinic, orthorhombic, trigonal, tetragonal, hexagonal and cubic), which can be primitive or centred, and generate the fourteen independent crystal lattices called Bravais lattices and geometrically represented by the unit cell. The unit cell is described by the cell axes defined by their length (a , b , c) and by the angles established between these three vectors (α , β , γ) as shown in Figure 2.1. These six elements are called cell parameters. Combining the symmetry elements with the Bravais lattices, 230 space groups are obtained that specifically define all the crystalline materials.

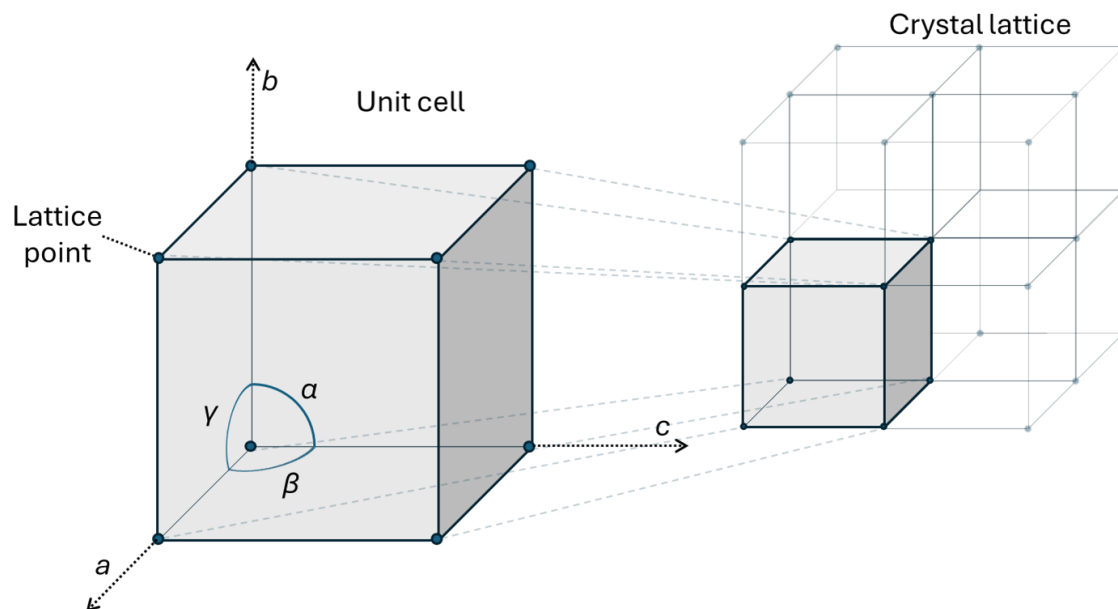


Figure 2.1 — Unit cell representation with indication of the parameters.

From the birth of X-rays and the discovery of X-ray diffraction, crystallography made a huge step forward in the description of the crystalline state, thanks to its highly ordered nature. The use of X-ray diffraction, both as single crystal and powder, in the field of MOFs and MOCs is of primary importance. The ordered nature of these compounds makes this technique crucial for the precise investigation of the atomic arrangement of the atoms. Not only the structural topology, but XRD can be used for applicative studies. The porous structure of these materials can be studied to investigate the host-guest chemistry and pore occupancy. A change in the XRD pattern can give insights into framework expansions or contractions and thus dynamic behaviours in the presence of guests. Determining the position and orientation of the guests is important to comprehend the behaviour at the nanoscale level for further applications of the bulk material. With modern technologies, it is also possible to perform *in-situ/in-operando* studies to understand chemical stability, phase transitions or particular behaviours in real time when subjected to external stimuli.

X-ray radiation sources

X-rays were accidentally discovered in 1895 by Wilhelm C. Roentgen (Nobel Prize in Physics in 1901^[95]). X-rays are electromagnetic waves with a wavelength in the order of 0.1-100 Å and interact with atoms because the bond distances are in the order of Å. The most common and first way to generate X-rays in a lab is to use a

system consisting of a glass tube kept under constant vacuum and with two electrodes that generate a high voltage (X-ray tube, Figure 2.2). The cathode, a tungsten filament, is heated and emits electrons, which are accelerated by the electric field toward a metal target (anode). In the impact, a lot of heat is generated, and the immediately decelerated electrons generate X-rays which exit from the Beryllium windows (almost transparent to X-rays) at the sides of the tube. To control the temperature of the anode, the system must have a cooling system, which can be a cooling water flux or, in most modern systems, the anode is kept spinning to dissipate the heat (rotating anode tube).

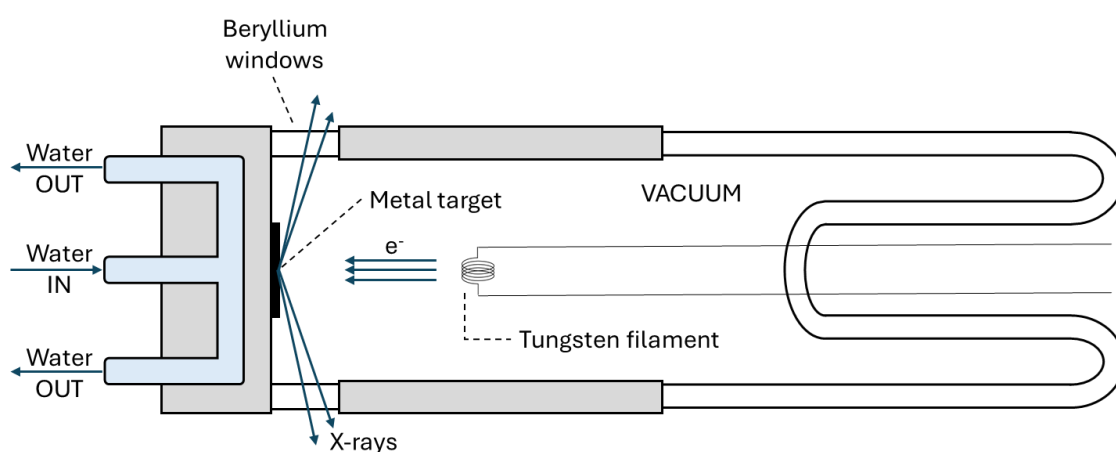


Figure 2.2 — Schematic cross-section of a traditional X-ray tube.

X-rays generated by this system are polychromatic, having two spectral components. First, a “continuous” background (*bremsstrahlung*) due to the instant deceleration of the electrons, and with an intensity that increases with the applied voltage. The second is the “characteristic” component observed if the electrons have enough energy to impact the atoms of the metal target and ionise and put them in the excited state. To take back the atom into the equilibrium state, the electrons of the outer levels transition into the inner orbitals to saturate the vacancy. With these transitions, there is a corresponding emission of radiation (e.g. K_α , K_β , L_α ...) that is characteristic of the atom and of the energy difference between the energetic levels, thus having a specific wavelength. Taking as an example copper (commonly used for lab XRD experiments), the transition from the L level to the K level ($L \rightarrow K$ transition) generates the K_α emission lines, which are two and have slightly different wavelengths, $K_{\alpha 1} = 1.5405 \text{ \AA}$ and $K_{\alpha 2} = 1.5443 \text{ \AA}$. The $M \rightarrow K$ transition generates the K_β with a value of $1.3922 \text{ \AA}$, which is also split into two close peaks. Other elements

(e.g. Mo, Ag, ...) can be used, which give different K_α values for the choice of the best X-ray wavelength based on the experiment. The emitted X-rays are then filtered through monochromators and collimators to isolate the K_α radiation into point-like parallel beams, which will be directed toward the material of study. At this point, the radiation interacts with the electrons of the material and produces both an incoherent diffusion (Compton effect) and a coherent diffusion (Rayleigh effect). The incoherent diffusion is due to the scattering of the photons impacting with free electrons, and having different energies, they do not interact together. On the other side, photons that elastically scatter have equal energies and interact coherently into diffracting phenomena.

Another method for the generation of X-rays is the synchrotron source.^[96,97] When charged particles are accelerated close to the speed of light and deflected by a magnetic field, there is emission of a radiation cone. Synchrotron facilities are built based on this principle (Figure 2.3). The electrons are accelerated in a linear accelerator, then inserted in a circular storage ring thanks to properly placed magnets, where they keep running close to the speed of light. The presence of alternating magnets, undulators and wigglers generates opposed magnetic fields to let the electrons wiggle and generate the radiation. At some points in the storage ring, there are bending magnets that deflect the electrons and direct the radiation in beamlines tangential to the ring. In the beamlines, there is a monochromator and the optics to focus the X-rays in the experimental hutch. The most important advantage that a synchrotron source brings over a laboratory instrument is the high brightness (*photons per second per 0.1% bandwidth per mrad² per mm²*). The X-ray beam coming out of the ring is particularly intense and highly collimated due to the high energy of the circulating electrons ($\gamma = E/mc^2$, $m = 9.109 \times 10^{-31}$ kg). This characteristic made the synchrotron facilities appealing for the scientific community to be used in a wide variety of experiments ranging from single crystal diffraction, small angle scattering, spectroscopies, to High-resolution Powder Diffraction and many more.

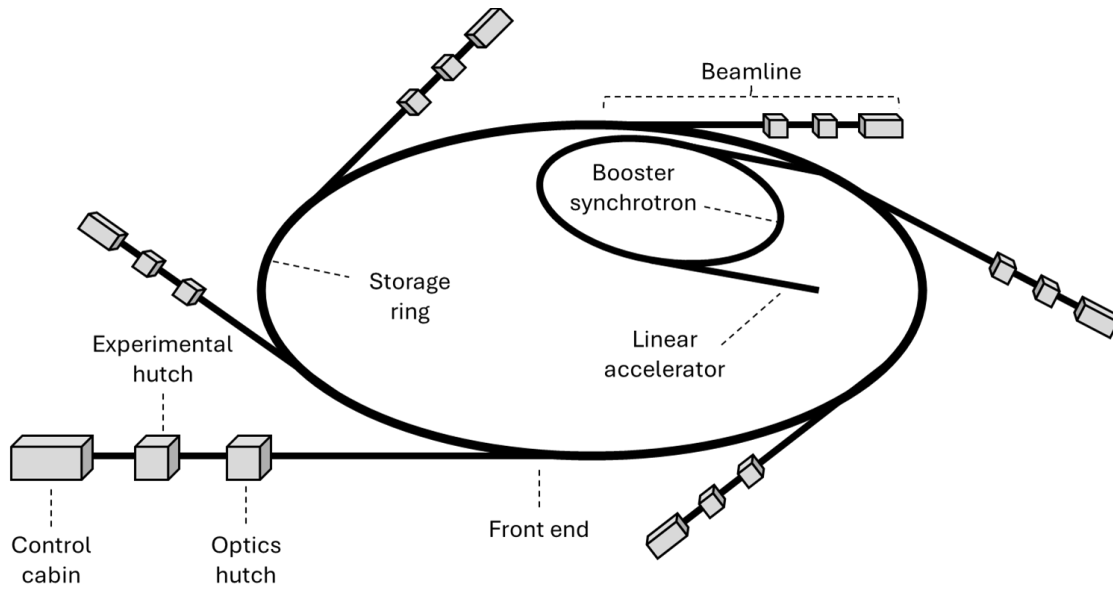


Figure 2.3 — Synchrotron scheme.

X-ray diffraction

The diffraction of X-rays was first discovered in 1912 by Friedrich, Knipping and von Laue, and later developed by William Henry and William Lawrence Bragg in 1913 with the definition of the fundamental law of diffraction.^[98,99] This law is described as the interaction of a monochromatic X-ray beam with a regular arrangement of atoms that, in a crystal structure, lie on virtual planes.^[100] When the X-ray photons interact with the electron cloud of an atom in the array of the crystal lattice, the atom acts as an X-ray source, releasing a beam with the same wavelength as the incident one (Thomson scattering). The scattered X-rays combine into a wavefront (Huygens principle), and, for a specific angle (θ , Bragg angle), these wavefronts are in phase, giving constructive interference and an intensity maximum.

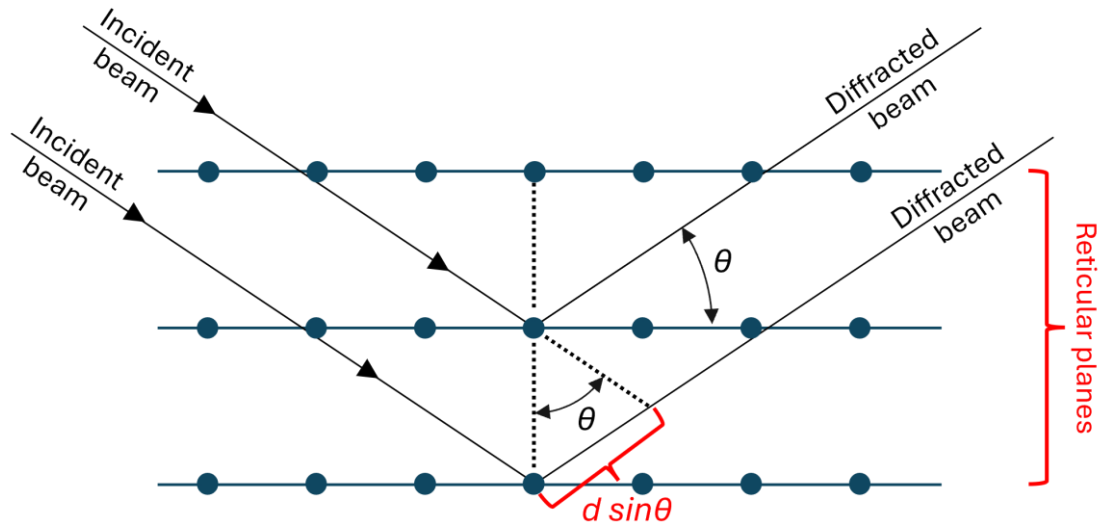


Figure 2.4 — 2D geometric construction for the Bragg diffraction of X-rays in a crystal lattice.

This law gives rise to the geometrical demonstration and formula underlying the entire theory of diffraction and modern diffraction techniques.^[101] It is the Bragg's Law and relates the wavelength of the beam with its angle of incidence and the spacing between the atomic planes (Figure 2.4), and can be demonstrated to be:

Equation 1 — Bragg's Law.

$$n\lambda = 2d_{hkl}\sin\theta$$

where n is an integer, λ is the wavelength of the incident radiation, d_{hkl} is the interplanar spacing between the planes of Miller indices h, k, l , and θ is the Bragg angle. This equation provides the condition under which the diffraction is obtained. For the visualisation in the 3D space of Bragg's Law and predicting the directions of the diffracted beams, there is a geometrical construction known as Ewald's sphere (Figure 2.5).

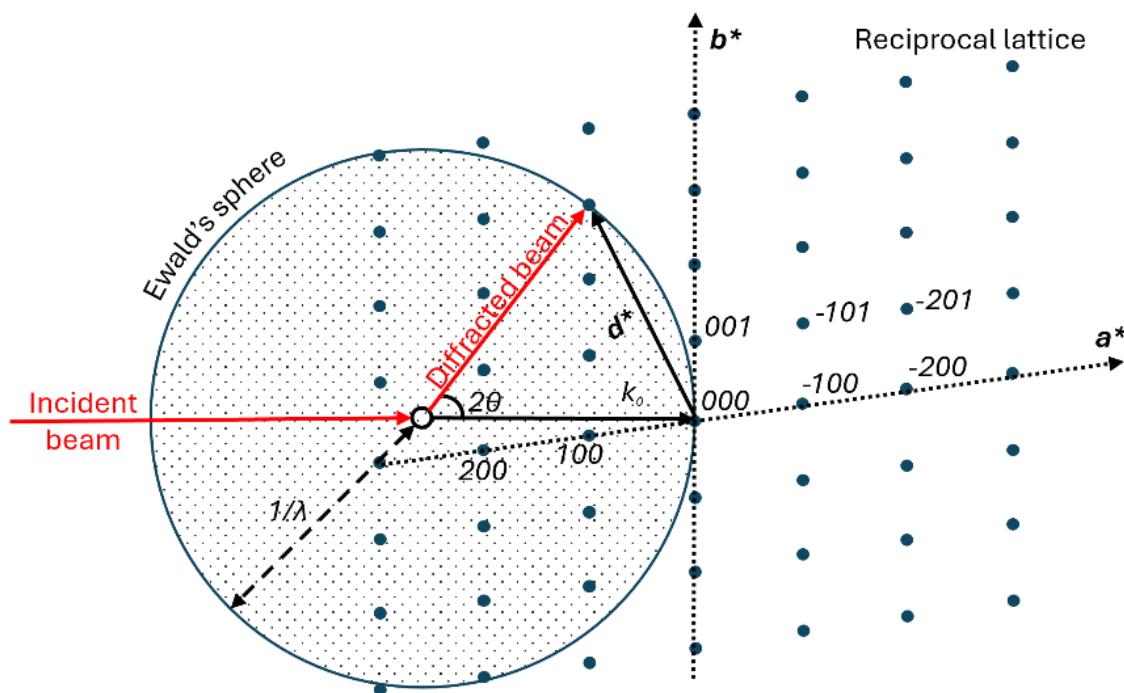


Figure 2.5 — 2D geometric construction of the Ewald's sphere.

This construction is based on the reciprocal space of a crystal. The direct space is the crystal lattice where the atoms are placed, defined by the lattice vectors a , b , and c . The reciprocal space is the lattice with vector reciprocal to the direct space vectors and defined as a^* , b^* , c^* and the interplanar spacing defined as $d^* = \lambda/d$. Ewald's sphere is a virtual sphere of radius $1/\lambda$ and centred in the crystal, where the incident beam is diffracted. The surface of this sphere is formed of all the points that satisfy Bragg's Law, so that when the reciprocal lattice is rotated, and a point of the lattice passes through the surface, the diffraction condition is satisfied, so that it is possible to predict which lattice points will be in a reflecting position. Because the sphere is designed on a radius $1/\lambda$, a small wavelength gives rise to large spheres, and thus, high resolution can be achieved because more points satisfy the condition. On the other side, large wavelengths produce a small sphere, and so lower resolution is obtained. This construction is applied in experiments where the instruments are built so that the crystal (or the detector) is rotated.

The X-rays are scattered by the electronic density component of the atoms. The electronic distribution in a crystal can be reconstructed by means of the Fourier synthesis, which combines each Fourier contribution obtained by the scattering of the electrons in the atoms. Each electron contributes to the scattering amplitude, which is summed over all the electrons in the atom to get the atomic scattering factor f . This

factor is dependent on the atom (number of electrons per atom, Z) and on the scattering angle (expressed as $\sin\theta/\lambda$), starting with a value equal to the number of electrons in the atom at $\theta = 0^\circ$. Increasing the angle, the single scattering contributions produce destructive interference (phase difference), and thus the value of f decreases. Summing all the contributions of the f factor in the atoms of the unit cell (with the respective phase differences), the result is the structure factor $F(hkl)$ representing the scattering of a plane defined by the Miller indices h, k, l . This factor is given by the product of an amplitude $|F(hkl)|$ and a phase factor $e^{i\phi(hkl)}$. Using the Fourier synthesis (Reverse Fourier Transform), it is possible to determine the electronic density as a function of the position x, y, z :

Equation 2 — Reverse Fourier Transform equation for the electron density distribution.

$$\rho(xyz) = \frac{1}{V} \sum_h \sum_k \sum_l |F(hkl)| e^{i\phi(hkl)} e^{-2\pi i(hx+ky+lz)}$$

where V is the volume of the unit cell. The detector can measure the intensity of the diffracted beams, which is proportional to the square of the amplitude $|F(hkl)|$, and this factor can be calculated in this way. Instead, the lack of lenses able to focus the X-rays causes the loss of the phase information, making it impossible to directly determine the $\phi(hkl)$ (this is known as the “phase problem”), but there are methods that get around this problem and help the reconstruction of the electron density and thus model the crystal structure.

When the material must be analysed by XRD, there must be a distinction on the macroscopical nature of the sample. If a sample is a single crystal or a microcrystalline powder, the instrumentation, procedure and outcome of the analysis will be different.

2.3 Single-crystal X-ray diffraction

Single crystals are mounted on a pin on a goniometer, illuminated by the X-ray beam, which will rotate to guarantee all the possible orientations. The reflections are received by a detector (Figure 2.6), and then the analysis of the recorded data is evaluated to produce an average structure with the electron distribution and then its representation with a model.^[102] The sample treatment and the selection of a single crystal out of the synthetic batch are fundamental as they determine the experimental conditions that will influence the result of the analysis. Even the collection parameters (e.g. X-ray source, exposure time, cryogenic conditions...) are determined by the final result, depending on what is looked for in a single crystal XRD experiment. The structural model is just the final step of the procedure, but the amount of information that one can obtain from the reflections, if the data are properly treated, in the reciprocal space is multiple. Crystal system, space group and unit cell are just some of the parameters that contribute to the final representation. Mosaicity, disorder and defects have a big contribution and help define the most subtle aspects of the crystal.

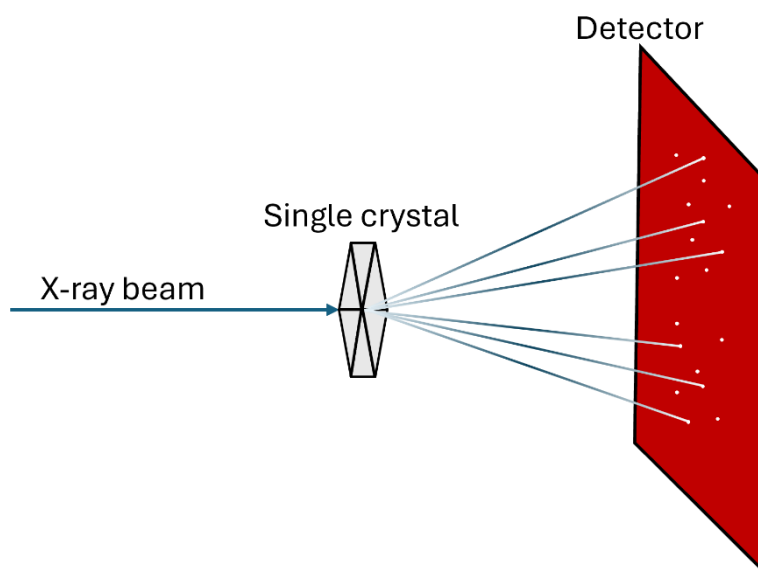


Figure 2.6 — Scheme of single-crystal X-ray diffraction experiment.

Single-crystal structure determination

But how is the process that leads to the representation of the crystal structure starting from the reflections measured by the detector?

After the data collection, there are three main steps in the crystal structure determination: data reduction, structure solution and structure refinement (Figure 2.7).

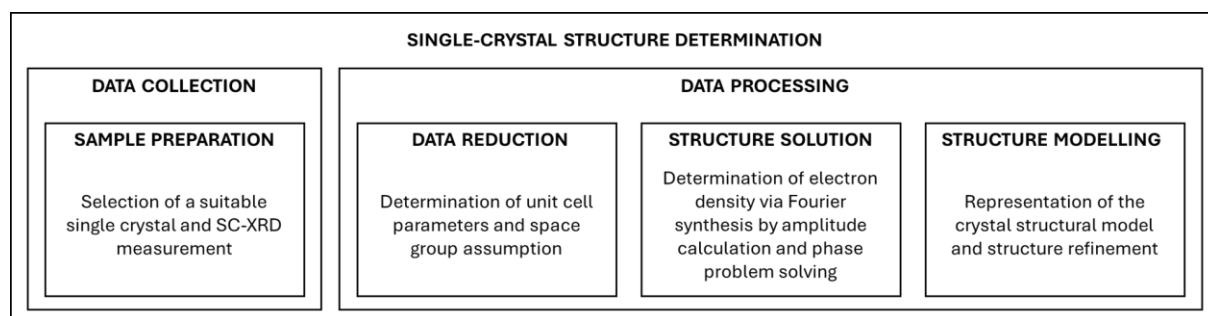


Figure 2.7 — Schematic representation of the procedure for SC-XRD data collection and data processing.^[102]

The first step is the data reduction, which consists of the determination of the unit cell parameters (a , b , c , α , β , γ). These can be deduced from the angles of the diffraction beams because the geometrical disposition of the diffraction maxima can be directly related to the dimensions of the crystal lattice and its spatial orientation. The symmetry elements that describe the crystal lattice can lead to destructive interference for given (hkl) planes, which means that specific reflections will be missing from the diffraction pattern (systematic absences). From the study of these systematic absences, there are some rules (selection rules) that allow the determination of the space group and thus the symmetry present in the crystal.

The second step is the determination of the crystal structure by calculation of the electron density, which is, as explained previously, prevented by the phase problem. First, the amplitude must be retrieved from the intensity of the diffraction peak. This process is called integration and allows us to calculate the number of photons measured by the detector in correspondence with each diffracting maximum for the specific (hkl). From the measured intensity, one can calculate the amplitude of the structure factor because:

Equation 3 — Relation between structure factor and intensity of diffracted beam.

$$|F(hkl)| \propto \sqrt{I(hkl)}$$

The phase $\phi(hkl)$ is the only parameter missing from Equation 3 to be able to calculate the electron density distribution. To get around this problem, there are different methods, some of which will be presented here. The first method presented is the Patterson method^[103] which is based on the construction of a vector map derived by the Patterson equation. Patterson developed an equation, based on the Reverse Fourier Transform, which is a function of the atomic coordinates differences that depends only on the square of the corrected structure factor amplitudes, not on the phases. From this equation, a vector map can be constructed where each point represents an atom and where the distances between the points are faithful to the distance between atoms in the crystalline structure. Based on this method, one can use the heavy atoms or the isomorphous replacement technique to build the actual electron density map. The replacement of some atoms of the structure under analysis with heavy atoms that possess strong recognisable peaks allows for the location and assignment of their position in the map and then deriving the remaining part of the structure. Another approach is the one of the direct methods. It is a statistical approach based on the relationship between the phases of different reflections. For small molecules, it is possible to use specific probabilistic equations to determine the phases directly from the amplitudes. The structure determination process brings to an electron density distribution map, which can be used to build a structural model representative of the measured crystal. This model is based on the average x, y, z coordinates of the atoms, but there are factors like the thermal displacement parameters and the atomic occupancy factor, which can be adjusted for each atom for the optimal structural model.

To get the best model possible, the last step of the process is the refinement. The model parameters are constantly changed, using the least square method to minimise the difference between the measured amplitudes and the calculated ones in the structure factors. If the number of parameters is too large, geometrical or chemical restrictions can be applied to simplify the refinement. To evaluate the goodness of the refinement, there are two factors that measure the difference between the observed and calculated amplitude structure factors. The reliability R-factor (R , Equation 4) and the weighted R-factor (wR , Equation 5), which considers a weighting factor based on the standard deviation of the observed values. Minimising these two factors can lead

to a better model, but the geometrical and chemical features must be considered independently of the low value or the R-factors, as these are just mathematical parameters and can lead to structural faults.

Equation 4 – R-factor

$$R = \frac{\sum_{hkl} |F_{hkl}^{obs}| - |F_{hkl}^{calc}|}{\sum_{hkl} F_{hkl}^{obs}}$$

Equation 5 – Weighted R-factor

$$wR = \frac{\sum_{hkl} w_{hkl} |F_{hkl}^{obs}| - |F_{hkl}^{calc}|}{\sum_{hkl} w_{hkl} |F_{hkl}^{obs}|}$$

2.4 Powder X-ray diffraction

When the sample is not a single crystal but a collection of microcrystals in powder form, the system and procedure for the structure solution change. The powder method was first developed by Debye and Scherrer in 1916. There are different geometries and methods, and the diffraction pattern obtained from a powder is different from the one obtained from a single crystal. The reflections from a single crystal produce single spots with specific intensity and orientation. The powder is nothing more than a collection of very small single crystals, all oriented differently in space. Each crystallite will have the same reflection from the same set of planes, but given the different orientation, the reflection will produce a set of cones, each with constant intensity. The concentric set of rings is then integrated along the scattering angle to produce a one-dimensional diffracting pattern of the intensity as a function of the 2θ angle (Figure 2.8).

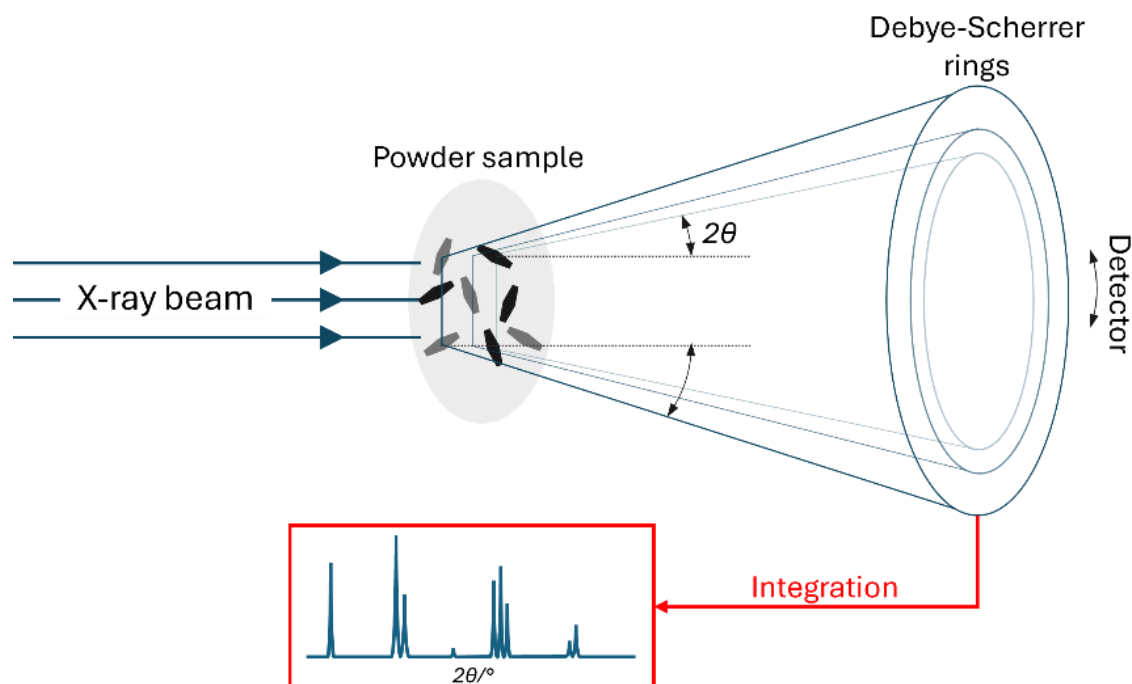


Figure 2.8— Scheme of powder X-ray diffraction experiment.

Every P-XRD pattern is characteristic of the sample and of the experimental condition used. The analysis of the pattern can meet obstacles like low resolution of high peak overlap, but nevertheless, the recent developments in the technological field allow to obtain a complete qualitative and quantitative analysis. In the qualitative aspect, the P-XRD pattern can be used as a fingerprint so that other samples can be compared to that phase/material based on the peak position and relative intensity. The quantitative aspect is granted by the large amount of information present in a P-XRD pattern. The properties and characteristics in the micro and nanoscale are reflected in the P-XRD pattern in the peak position, intensity, profile and in the background (Figure 2.9). The background is generated by the non-Bragg scattering, which means the scattering from the sample holder or from the air, the Compton scattering and the diffuse scattering. The peak position gives an indication of the unit cells, as it corresponds to the diffracting angle. Each (hkl) plane can be assigned to each peak corresponding to a specific 2θ value, and from this, the lattice parameters and space group can be deduced. The intensity of the peak gives information on the atoms present in the unit cell with all its parameters (thermal displacement, occupancy factor, preferential orientation...). The profile of the P-XRD pattern is influenced by the instrument parameters (geometry, optics, detector, collimators...) and by the macroscopic characteristics of the material (particle size, shape, strain...).

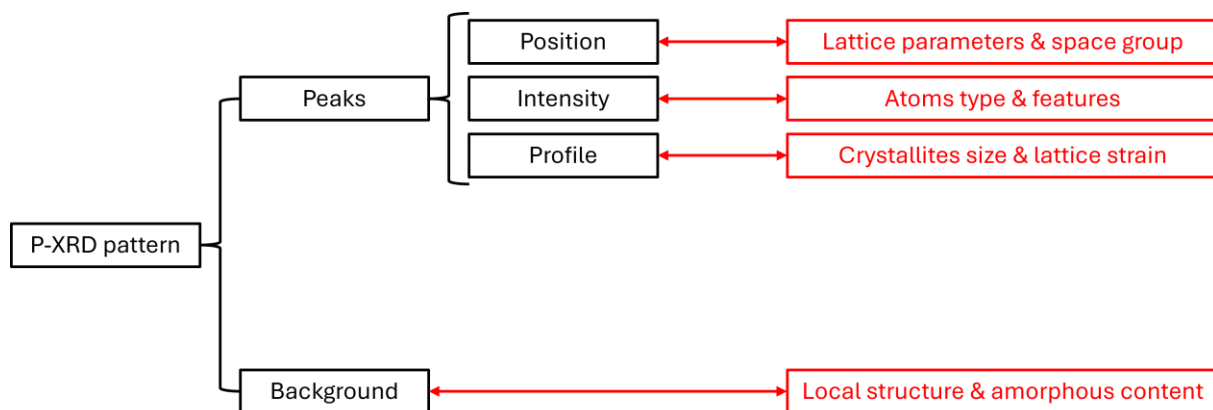


Figure 2.9 — Powder diffraction pattern information.

Ab initio structure determination from P-XRD data

The structure determination from P-XRD data without any starting information on the possible crystal structure is called *ab initio* structure determination.^[104–106] The process presents some similarities to one from SC-XRD data presented in the previous section. Although the main steps are the same (indexing and space group identification, structure solution, structure refinement), the outcome of the measurement is different, as it is the way to treat the data. SC-XRD measurements give reflections in the three dimensions characterised by the intensity and angle. The same information is given by P-XRD data, but in a monodimensional representation by integration of the diffraction cones. The structure determination process is based on the extraction of any possible information out of the peak position, intensity, profile and background feature with all the limitations that can be entailed (low resolution, peak overlap, large background...).

The first step is the indexing and space group determination. The name “indexing” refers to the assignment of the Miller indices (h, k, l) to each peak position. This can be done by a number of indexing programs (*e.g.* ITO^[107], TREOR^[108], DICVOL^[109], CRYSFIRE^[110]...) which, from the values of 2θ , calculate the clear fractions of the normalised $\sin^2\theta$ and from the selection rules determine the crystal lattice. From the (hkl) values, the lattice parameters ($a, b, c, \alpha, \beta, \gamma$) are determined and the space group assigned. The proposed parameters and space groups are confirmed by the Pawley^[111] or by the Le Bail^[112] fit. These techniques allow us to refine the experimental pattern, changing the variables of the peak shape, intensity, position and

background without any structural basis. By fitting these parameters, it is possible to confirm the unit cell and proceed to the next step.

The second step is the structure solution. In this second phase, the intensities of the peaks are taken into account. There are two families of approaches for structure solution: *traditional* and *direct-space* methods. The traditional approach is based on the extraction of the intensity of the reflections from the P-XRD pattern and then, like for single-crystal structure determination, uses the Patterson or direct methods to solve the structure. The direct-space approach, starting from a structural fragment (representing the asymmetric unit), generates a set of crystal structures and calculates their P-XRD pattern. This pattern is then fitted to the experimental one and, like in the SC-XRD structure determination, there are two figures of merit to describe the goodness of the fit, which are the R-factor (R_p , Equation 6) and the weighted R-factor (R_{wp} , Equation 7). The set of variables that defines the P-XRD pattern which better matches the experimental one represents the global optimum with the lowest R-factor.

Equation 6 – R-factor

$$R_p = \frac{\sum_i |y_i^{obs}| - |y_i^{calc}|}{\sum_i y_i^{obs}}$$

Equation 7 – Weighted R-factor

$$R_{wp} = \sqrt{\frac{\sum_i w_i (|y_i^{obs}| - |y_i^{calc}|)^2}{\sum_i w_i |y_i^{obs}|^2}}$$

The third and last step in the structure determination process is the structure refinement by the Rietveld method (Hugo Rietveld, 1969).^[113,114] The P-XRD pattern calculated from the best structure obtained in the structure solution step is refined to the experimental one. Each parameter (background, peak position, intensity and profile) is adjusted to make the calculated pattern ever so similar to the experimental one. Minimising the error (least-squares approach) between the two patterns, the R_{wp} factor will reach a reasonably low value when the model structure represents the correct one well. Like in the SC-XRD structure determination, some geometrical restraints (*e.g.* lengths and angles of chemical bonds) can be applied to secure a more reliable Rietveld refinement. From a good model, one can infer deep structural

features like strain or dynamics and information on the bulk material (not only on the single crystal itself), which is useful for the application and scale-up purposes.

2.5 Brief overview of Nuclear Magnetic Resonance

Nuclear Magnetic Resonance (NMR) is a fundamental technique in the field of analytical chemistry as it is a direct way to gain information on the number, nature and environment of the atoms present in a molecule. From these insights, one can deduce the molecular skeleton, molecular dynamics, host-guest interactions, kinetics and so on.

Every nucleus has a mass and a charge, and the ones that have odd mass number or odd atomic number, or both, possess an intrinsic spin and thus an intrinsic angular momentum (*e.g.* ^1H , ^2H , ^{13}C , ^{14}N , $^{17}\text{O}\dots$). Every one of these nuclei can be studied by means of NMR. The NMR technique is based on the energetic differences between the energy states of these atomic nuclei. The energy gap between these two states is very small, and there is a small excess of the population in the low-energy state, generating a macroscopic magnetisation.

Applying an external magnetic field (B_0), there is a splitting of the energy levels, the so-called Zeeman Effect.^[115] For the energy difference between these states, ΔE is given a Larmor frequency ν (Equation 9). Thus, the Larmor frequency is directly related to the magnetisation; the bigger the magnetisation is, the bigger the Larmor frequency and thus the higher the signal. The exact energy transition is not only a function of B_0 but also depends on the chemical environment around the nuclei. Thus, the magnetic field to be considered is an effective field B_{eff} function of a shielding constant (σ) that depends on the number and distribution of electrons around the nucleus that will themselves apply a magnetic field ($B_{\text{eff}} = B_0(1-\sigma)$).

Equation 8 — Energy difference between the two levels.

$$\Delta E = \hbar\gamma B_{\text{eff}} = h\nu$$

Equation 9 – Larmor frequency.

$$\nu = \frac{\gamma B_0(1 - \sigma)}{2\pi}$$

When the sample is in the magnetic field, a radiofrequency at Larmor's frequency is applied, and the magnetisation is rotated by an angle α . When the radiofrequency is removed, the system, out of equilibrium, goes back to the original orientation. This oscillation signal induces a current in a coil, and the Free Induction Decay (time domain) is recorded, which will then be transformed into the spectra (frequency domain) by Fast Fourier Transform. The peak intensity (area under the curve) is proportional to the number of directly excited nuclei. Figure 2.10 represents a scheme of the NMR instrumentation.

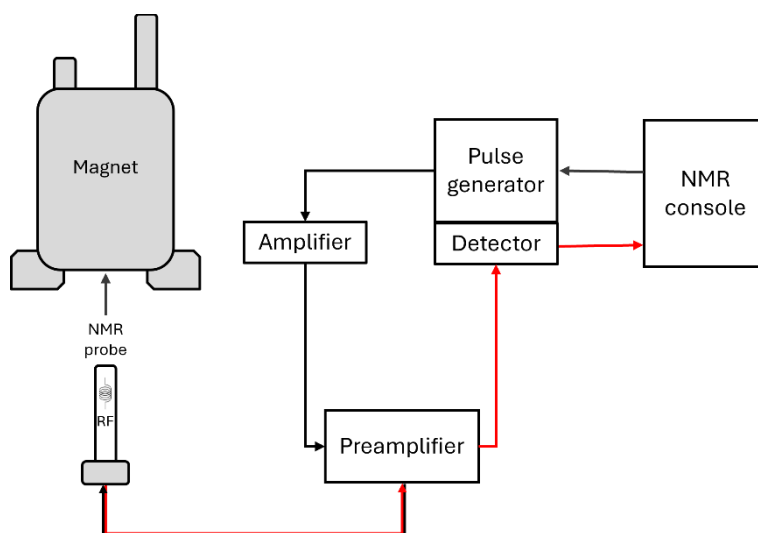


Figure 2.10 – NMR instrument scheme.

Anisotropic interactions

The NMR measurement is affected not only by the magnetic field applied, but there are four types of anisotropic interactions that depend on the orientation of the molecules with respect to the magnetic field and are described using tensors that relate two magnetic moments considered. These four anisotropic interactions are: shielding effect, indirect dipolar-dipolar interactions, direct dipolar-dipolar interactions and quadrupolar interactions.

The shielding effect is due to the electronic environment around the nuclei. The electrons create a magnetic field contributing to the energy levels splitting. The nuclei are said to be shielded or unshielded from the applied magnetic field, creating a chemical shift in the peaks in the NMR spectrum. The chemical shift varies based on the orientation of the molecule with respect to the external field and is described by the shielding tensor $\bar{\sigma}$. The effective magnetic field is influenced by $\sigma(\theta)$, and the Larmor frequency can be calculated according to the expression above (Equation 9). From the position of the peaks, depending on B_0 , one can understand the electronic environment around the nuclei, and from the shape of the peak, one can identify the symmetry of the molecule.

The direct dipole-dipole interaction is the interaction between two nuclei close in space (tensor $\bar{D}$). The interaction can happen between two identical nuclei (homonuclear interaction) or between two different nuclei (heteronuclear interaction). These interactions cause a splitting of the energy levels and cause the spectrum peaks to split into two identical peaks with frequencies around the isotropic value. Like in the case of the shielding effect, the direct dipole-dipole interaction is affected by the angle θ between B_0 and the internuclear axis but is independent of B_0 .

Indirect dipole-dipole interactions (J coupling, tensor $\bar{J}$) are the interactions between the magnetic dipole moments (parallel or anti-parallel) transferred by the covalent bond electrons (Fermi contact interactions). The nuclei of distances of up to three bonds are subjected to this effect. This effect is usually covered by the direct dipole-dipole interactions, and in the solid-state, it does not have a relevant contribution.

Quadrupolar interactions are relevant only for $I \geq 1$. In this case, the nuclei also possess an electric quadrupole moment due to the anisotropic distribution of charges. The distribution of charges in the nuclei generates an electric field. The distribution of charges in the molecules is described by the electric field gradient (tensor $\bar{q}$). The interaction between the electric field and the electric field gradient generates the quadrupolar interactions. With the increase of B_0 , there is a decrease in the effect of the quadrupolar interactions. The difference in the energy levels is a function of the spin quantum number, of the quadrupolar constant χ (which depends on the components of the electric field tensor $\bar{q}$) as well as the orientation θ with respect to B_0 . The quadrupolar interactions cause a complicated broadening of the peaks, which in the isotropic case is reduced to the central value.

This is a very general overview of the main interactions present in a molecule and relevant for the NMR technique. But this is mainly valid when performing Solid-state NMR because solids have an anisotropic environment with respect to the applied magnetic field, having almost steady molecules (only restricted motion around the molecular site). All the previous equations and considerations are valid except for the cases of high symmetry. Solid-state NMR can be done on a single crystal (for specific orientations) or on powders (the resulting spectra are the sum of the components of each crystallite in every possible orientation).

When dealing with liquids, these considerations simplify significantly. The molecules in the liquid state have a high degree of motion, experiencing all possible orientations and achieving an isotropic condition. Since all these interactions are dependent on the orientation θ with respect to B_0 , the contributions in the liquid state are cut down. The direct dipole-dipole interactions and the quadrupolar effect are cancelled by the rapid molecular tumbling. The shielding effect and the indirect dipole-dipole interactions are reduced to their isotropic value as the contribution due to the anisotropy (θ is averaged) goes to zero. This makes the liquid state NMR spectra simpler to examine, but some studies can only be done in the solid state.

Magic Angle Spinning

The direct analysis of solid-state NMR spectra can give a lot of information about the structure and dynamics of the sample, but it can be complicated due to the broadening due to anisotropic interactions. To reduce this effect and simplify the patterns typical of powders to the isotropic spectra, there is a practical solution. This technique is called Magic Angle Spinning (MAS) and is based on the assumption that if the solid sample is oriented at a particular angle θ , and spun at a high frequency, the anisotropic interactions are reduced to their isotropic value.^[116,117] The high spinning is required to average the molecular motion as the rotor is tilted around an angle of 54.74° (this value mathematically nullifies the component that makes the anisotropic effects dependent on the orientation). The frequency of the spinning is also an important factor because if the frequency is too low, broad peaks are simply decomposed into a number of equally spaced peaks around the isotropic peak. These peaks around the central value are called spinning sidebands and are spaced by the spinning frequency. At high enough frequencies, the spinning sidebands disappear to leave only the isotropic component. The effect of the MAS frequency depends on the dominant anisotropic interactions in the sample, usually shielding and dipole-

dipole interactions are averaged to the isotropic values, but if the quadrupolar interactions are predominant, MAS will not have enough effect to completely remove the broadening.

Decoupling

One other important technique used to obtain high-resolution NMR spectra is decoupling. Decoupling allows for the elimination of the heteronuclear dipolar interactions. This is achieved by recording the spectra of a nucleus X (*e.g.* ^{13}C) while irradiating the sample with the radiofrequency of the nucleus A (*e.g.* ^1H). This is also used in the liquid state, where the predominant interactions are indirect dipole-dipole interactions (J coupling). In this case, the multiplets that would be generated by the carbons attached to protons are simplified to singlets with a higher signal-to-noise ratio.

High-power decoupling

High-Power Decoupling (HPDEC) is used in solid-state NMR to remove the anisotropic contribution of the heteronuclear direct dipolar interactions that can't be eliminated by MAS. In this case, a high radiofrequency power is used to directly excite the nucleus and contributes to removing the dipolar coupling effect and increasing the signal-to-noise ratio.

Cross Polarization

Another strategy to increase the signal-to-noise ratio of the spectra is to use a technique called Cross Polarisation (CP). Because the magnetisation of ^{13}C is lower than that of ^1H (which is more naturally abundant), Larmor's frequency of ^{13}C will be lower, and thus the signal will be lower. Lower magnetisation atoms require longer experiments or the isotopic enrichment of such a sample. Another solution is the use of CP. In this technique, the magnetisation of abundant atoms like ^1H is transferred to low magnetisation atoms like ^{13}C by imposing the same rate of precession of the two nuclei. This is done by applying pulses on both nuclei with specific radiofrequency (Hartmann-Hahn condition^[118]) that can be repeated after the relaxation time of ^1H is passed (Figure 2.11). In this way, there is a much stronger sensitivity due to the magnetisation of ^{13}C by ^1H and the measurement can be repeated

faster due to the shorter relaxation time of ^1H with respect to ^{13}C . The CP experiment is always paired with the decoupling to detect the carbon signal while applying the radiofrequency of ^1H to have a higher signal-to-noise.

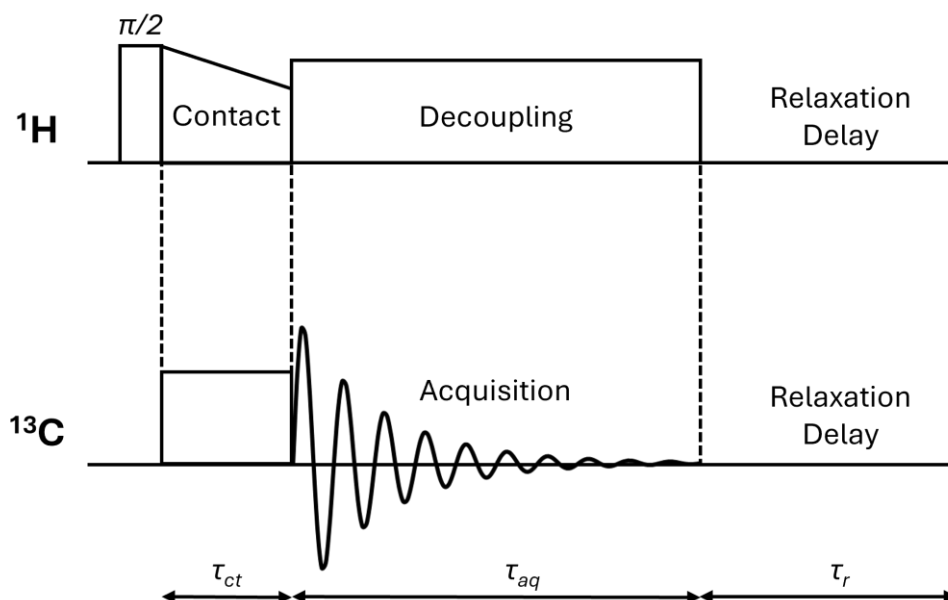


Figure 2.11 — CP pulse sequence scheme.

Other than these common practices for obtaining high-resolution spectra, there are many more solutions to be able to investigate the sample in different conditions and with different parameters to get the most out of it. For example, 2D correlation experiments to map the interactions between nuclei to investigate the vicinity or coupling of the atoms. This is very important for the study of host-guest systems or in the study of large molecules like proteins.

Host-guest investigation by ^1H NMR titration system

The NMR technique is a powerful tool for the investigation of host-guest systems. NMR monitoring of the titration of the host system with gradual amounts of guests can give information on the kinetics of the association, stoichiometry and, using an appropriate binding model, the association constant can be calculated.^[119,120] One example of the use of the NMR titration technique on MOCs study is reported by Nitschke et al.^[121] The authors report the synthesis of a complex cuboctahedron MOC,

which is used to trap guest molecules like pyrene. Titration of the cage with the increasing equivalents of guest affects the ^1H NMR spectra, where the peaks of the cage present a regular shift because of the interactions that cause shielding/de-shielding effect (Figure 2.12). Job plot and Hill function were used to determine the association ratio and binding constant. The mole ratio method provides the plot of the chemical shifts as a function of the host/guest ratio. Above a given quantity of guests added, there is a tendency to a plateau, and it is possible to determine the exact maximum number of guest molecules per cage. In this case, the host can accommodate eight pyrene molecules (Figure 2.12). The Hill function, rearranged into the Hill plot, allows to determine the Hill coefficient (n), a direct indicator of the type of host-guest cooperation, the affinity of the two counterparts after binding.^[122] In this case, the Hill coefficient was 1.02, which is assigned to the non-cooperative binding, indicating the independence between MOC and pyrene. Using a 1:8 binding model and a Hill coefficient equal to 1, the association constant K_a is $1.17 \times 10^{-2} \text{ M}^{-1}$.

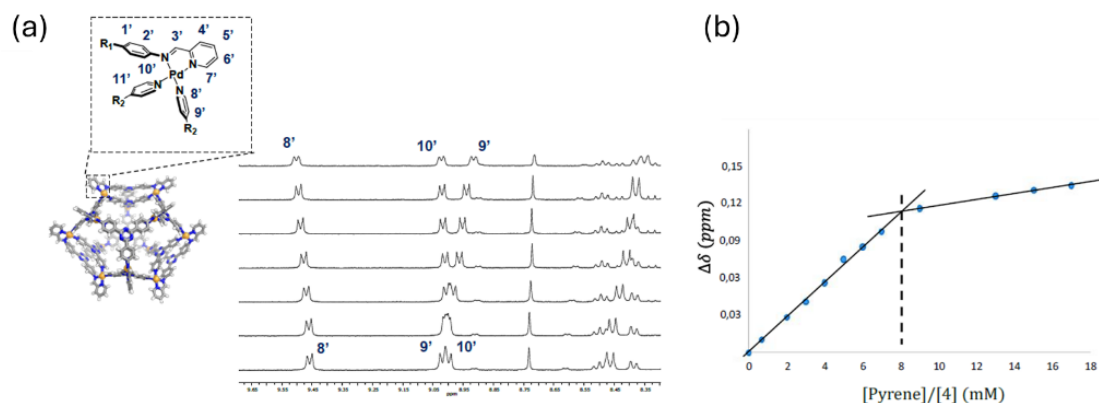


Figure 2.12 — a) ^1H NMR spectra of the titration of the MOC with pyrene;
b) mole ratio method for stoichiometry determination.^[121]

2.5.1 CLASSIC NMR technique

One of the limitations of the NMR holds is the possibility to record liquid-state or solid-state samples, but not both at the same time. This prevents, for example, the *in-situ* investigation of phase transformation processes like crystallisations. An interesting new strategy recently developed to overcome this problem is the

Combined Liquid- and Solid-State *In-situ* Crystallisation (CLASSIC) NMR technique.^[94,123,124] It is possible to investigate the evolution of crystallisation processes from the initial liquid phase, passing from the first crystallite particle up to the formation of eventual polymorphs. This is done by alternating different pulse sequences during an NMR measurement to acquire time-resolved liquid- and solid-state NMR spectra without interfering with each other. Having recorded the alternated spectra, the data is processed by splitting it into a set of each pulse to have the evolution over time of the different spectra. As an example, the first experiment was developed on the crystallisation of the different forms of *m*-aminobenzoic acid (*m*-ABA). In that case, the sequence was set up to alternate 1) $^1\text{H} \rightarrow ^{13}\text{C}$ CP with HPDEC and 2) direct-excitation ^{13}C NMR. Combining all the sets of data for each time of pulse, there is a clear evolution plot of the liquid component and solid phase (Figure 2.13). Analysing the solid-state spectra evolution, it is clear that after 2 hours the peaks assigned to form I of *m*-ABA start to appear and are constant for the entire duration of the experiment, indicating no phase transformation.

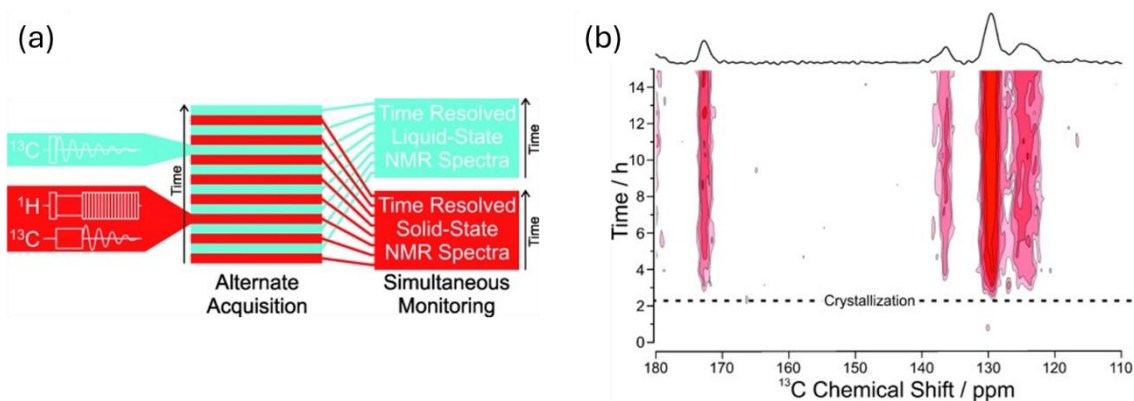


Figure 2.13 — a) CLASSIC NMR scheme; b) solid-state $^1\text{H} \rightarrow ^{13}\text{C}$ CPMAS evolution spectra.^[94]

The innovation that this technique brings is evident and can be very important for the *in-situ* study of the formation of new polymorphs, new MOFs and even studies on host-guest systems. The repeating sequence can be tailored to the experiment, optimising the acquisition parameters and adding more pulses to the sequence to get the most information with the best time resolution.

3 TPB *and* Zn-based metal salts

This chapter describes the investigation of the synthesis, characterisation, and application of $M_{12}L_8$ interlocked icosahedral nanocages. Section 3.1 explores the synthesis of the $M_{12}L_8$ poly- $[n]$ -catenanes starting from TPB and ZnI_2 in every aspect, both in the solution state (instant synthesis or slow crystallisation) and in the solid-state (mechanochemical approach, liquid-assisted grinding or neat grinding). Using the slow crystallisation two types of single crystals. One, the kinetic product, is the interlocked MOCs that are also present as a precipitate at the bottom of the test tube. The second, thanks to the error-checking process that allows the rearrangement of the coordination bonds, is the thermodynamic product. With the instant synthesis, it is possible to trap the kinetic product into an amorphous phase that can then be transformed into a crystalline phase and confirm the formation of the catenane with a rapid approach in the powder state. In the absence of solvent, the solid-state approach is explored by means of grinding the two reactants. Again, the product is amorphous, but thanks to the templating effect of a solvent, it is possible to obtain the crystalline phase. In this way, it is possible to obtain the catenane in a fast and easy way, with good yields in a scalable approach and without using a solvent.

Section 3.2 describes the study of the dynamic behaviour of the material, experimenting with the aromatic guest exchange using single crystals of $M_{12}L_8$ poly- $[n]$ -catenane. Single crystals of the catenane are exposed to vapours of different guests to check any preferential inclusion and study the binding sites of the cage. To test the robustness of the structure and further explore the dynamic motion of the framework, multiple guest exchanges on the very same crystals are carried out. Finally, thanks to a combination of SC-XRD, DFT calculations and solid-state NMR, it was possible to propose a mechanism for the guest molecules to enter/exit the cages and stabilise the overall structure.

The last part of this chapter, in Section 3.3, illustrates the next step in the guest inclusion in $M_{12}L_8$ interlocked MOCs. While in the previous sections the guests would mainly be aromatics, here the focus is on the trapping of small molecules. In this way,

it is possible to define the interactions of such small molecules with the cages and check if the template effect is efficient or leads to the collapse of the structure. The cages show different adaptations and responses when exposed to the trapping of aromatics or non-aromatics.

3.1 Kinetic trapping of TPB and ZnI_2 into M_{12}L_8 poly-[n]-catenane

The self-assembly of TPB and ZnI_2 using solution and solid-state processes will be presented in this chapter (Figure 3.1). Using the instant synthesis method, it is possible to rapidly and selectively coordinate the reactants into the M_{12}L_8 poly-[n]-catenane by kinetic trapping.^[125] The structure, obtained also in the form of single crystals, is investigated by SC-XRD. The slow crystallisation also led to the thermodynamic product, which is a coordination polymer as a result of the structure solution. An amorphous phase of the M_{12}L_8 poly-[n]-catenane can also be selectively obtained using mechanochemical approaches (*i.e.* NG). This product presents dynamic behaviour because it is subjected to amorphous-to-crystalline transformation when exposed to aromatic compounds (*e.g.* xylenes). Combining SC-XRD and DFT calculations allowed us to describe the interaction energies present in the host structure and with the guest molecules.

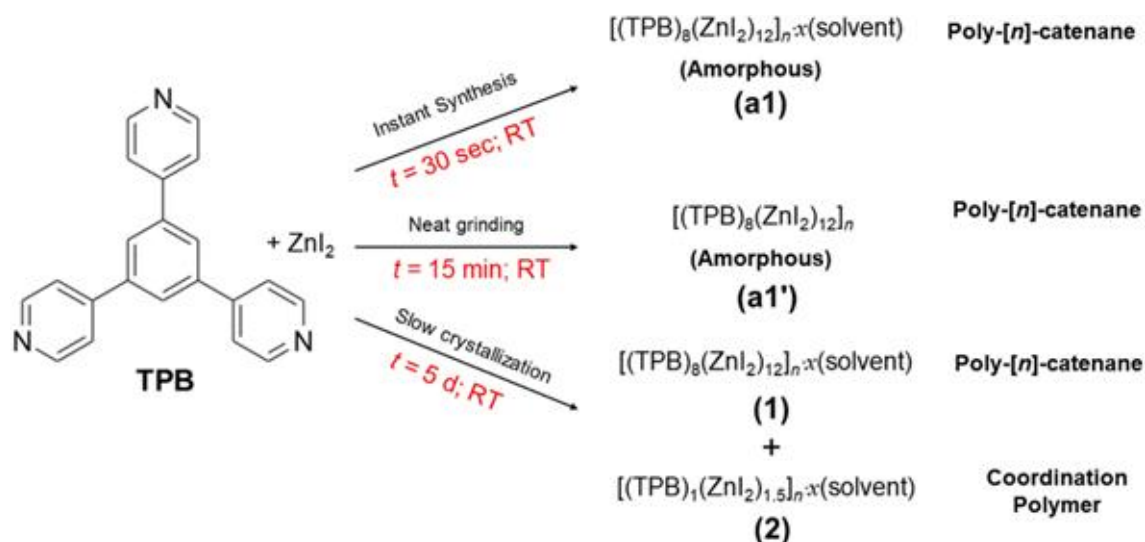


Figure 3.1 — Reaction scheme of TPB and ZnI_2 by instant synthesis, neat grinding and slow crystallisation.^[125]

3.1.1 Instant synthesis of TPB and ZnI_2 using aromatic solvents

Applying extremely fast crystallisation methods, the instant synthesis, at room temperature conditions, in the preparation of mechanically interlocked large M_{12}L_8 cages is rare. The instant synthesis method allows the selective synthesis using kinetic control, with which it is possible to obtain the poly-[n]-catenane of interlocked M_{12}L_8 nanocages as a homogeneous phase. While the instant synthesis of M_{12}L_8 poly-[n]-catenanes using ligand TPB and ZnCl_2 or ZnBr_2 has already been done^[51,126], using ZnI_2 has not been reported. Changing one of the building blocks in the self-assembling components can have a drastic effect on the final products. For example, it can form different and unexpected structures, particularly in self-assembling systems where the building blocks are more than twenty components, as is in the poly-[n]-catenanes self-assembled of M_{12}L_8 icosahedral nanocages using templating solvents.

Addition of a methanolic solution of ZnI_2 into a vigorous stirring light-yellow nitrobenzene solution of TPB instantaneously formed a suspension, which was left to stir for 5 mins (Figure 3.2a). The solid was very difficult to dry using pump filtration. Therefore, the sample was dried by flowing dry N_2 for 30 minutes. P-XRD analysis revealed that the new product is amorphous (hereafter named **a1**) with a very large bump covering the 10-30 range in $2\theta/^\circ$ Bragg diffraction angles and with the absence of sharp Bragg reflections (Figure 3.2b). The diffuse scattering shows that there is short-range ordering that is different from the starting crystalline materials. This

differs from what was observed in the chloride and bromide versions of poly-[*n*]-catenanes, which, upon instant synthesis using the same solvents, always gave crystalline materials. Importantly, the amorphous phase structure is not known, but it can be inferred via an amorphous-to-crystalline phase transition if **a1** uptakes aromatic guest molecules, producing the M₁₂L₈ poly-[*n*]-catenane periodic structure.

Therefore, **a1** was immersed in a methanol/toluene (1 ml : 4 ml) solution in a round-bottom flask and stirred (12 h). Then, the suspension was filtered and the solid analysed by P-XRD. The diffractogram showed that **a1** transformed to a crystalline material, as sharp Bragg reflections are observed (Figure 3.2c). The experimental P-XRD pattern corresponds to that of a M₁₂L₈ poly-[*n*]-catenane (see below). This indicates that the instant synthesis product is the poly-[*n*]-catenane of interlocked M₁₂L₈ cages in the amorphous state. It is important to recall that amorphous **a1** does not dissolve into toluene/methanol, followed by a recrystallisation yielding the polycatenane, but includes the solvent in the M₁₂L₈ cages, rearranging in an ordered manner.

Using TG analysis, the guest molecules were quantified to 1.3 guest molecules in the asymmetric unit (considering only toluene) (13.8 % weight loss) and 7.8 guests per M₁₂L₈ nanocage (Figure 3.2d). ¹H NMR of the sample analysed by TGA did not show any presence of methanol, thus corroborating that the weight loss corresponds to toluene (Appendix 13.1). The TG is also informing about the stability of the structure because from 250 to 400 °C there is no weight loss, indicating that the M₁₂L₈ poly-[*n*]-catenane is fully evacuated and after *ca.* 400 °C the material decomposes. Therefore, using nitrobenzene as a templating solvent does not lead to a crystalline poly-[*n*]-catenane nor to another crystalline phase using the instant synthesis method, as observed by the repetition of three experiments. This behaviour is different to that observed using ZnCl₂ and ZnBr₂, which, under the same experimental procedure, formed the M₁₂L₈ poly-[*n*]-catenane in the crystalline form.

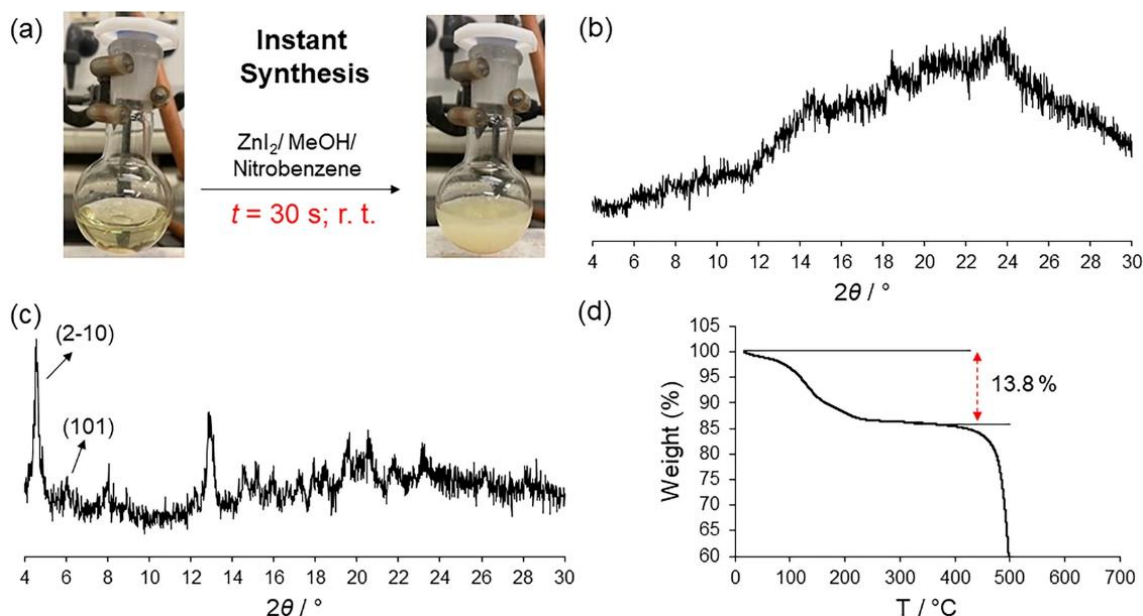


Figure 3.2 — a) Picture of the instant synthesis process before and after addition of ZnI₂; b) P-XRD pattern of **a1**; c) P-XRD pattern of **1**; d) TGA of **a1** after contact with Tol/MeOH.^[125]

The instant synthesis has also been carried out using chlorobenzene and toluene as templating solvents following the same protocol as in the nitrobenzene synthesis (see Materials and methods). The obtained product is in both cases crystalline, but the quantity of product is small (low yields). Interestingly, the sample obtained with chlorobenzene remained crystalline after one month of being synthesised (Appendix 13.2), with 19% of weight loss of guest molecules included as shown by TG (Appendix 13.3). However, the sample obtained using toluene as a template, after one month, became amorphous and included very few guests (6% of weight loss with a not well-defined weight loss release step from TG). Clearly, these two examples of TPB-ZnI₂ poly-[*n*]-catenanes have different stabilities depending on the solvent. Single crystals of the TPB-ZnI₂ catenane were grown to investigate the structure by SC-XRD.

3.1.2 Slow crystallisation of TPB and ZnI₂ using nitrobenzene

The proof that the poly-[*n*]-catenane can be formed using TPB and ZnI₂ using slow crystallisation experiments, has been carried out by preparing single crystals by self-assembling TPB and ZnI₂ using a templating guest. Pristine single crystals of TPB-ZnI₂ poly-[*n*]-catenane were obtained by layering diffusion of Zn(II) to a solution of

TPB in nitrobenzene. In a crystallisation tube, as a bottom layer, TPB was dissolved in a nitrobenzene/MeOH mixture, then as a middle layer, methanol was added (dropwise to avoid rapid mixing of the phases) until a clear biphasic solution was formed (Figure 3.3). As the upper layer, a methanolic solution of ZnI_2 was added dropwise in such a way that no precipitate was observed during the layering. The crystallisation tube was left standing, and after *ca.* 5 days, large crystals attached in the middle layer of the tube were obtained. A single crystal of good quality was selected and mounted for SC-XRD analysis. Importantly, the crystals covered in the mineral oil used to mount in the loop did not crack even after being in contact with the atmosphere for more than one hour, making possible structure solution at room temperature.

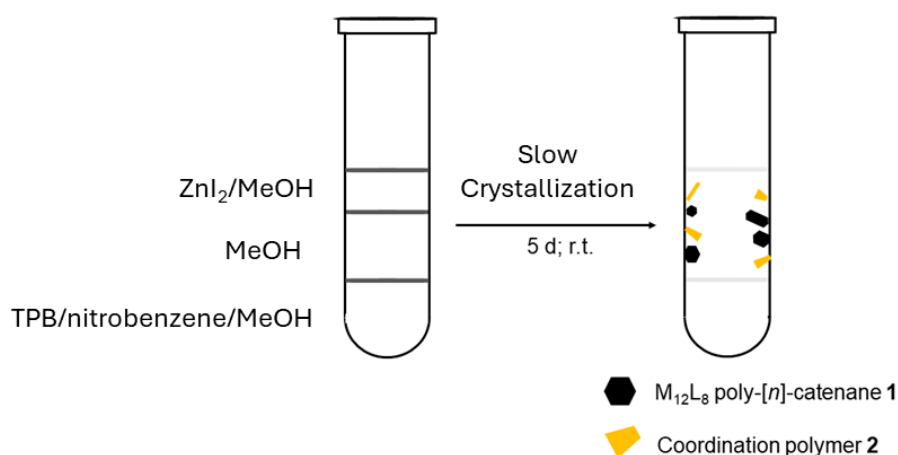


Figure 3.3 — Cartoon of the slow crystallisation method using TPB, ZnI_2 , nitrobenzene and MeOH.^[125]

The single crystal X-ray structure (300 K) was solved in the trigonal space group $R\bar{3}$ with the following unit cell parameters: $a = 38.6805(7) \text{ \AA}$; $b = 38.6805(7) \text{ \AA}$; $c = 16.0202(3) \text{ \AA}$; $\alpha = \beta = 90^\circ$ and $\gamma = 120^\circ$; $V = 20758 \text{ \AA}^3$. Crystallographic analysis reveals the formula $[(\text{ZnI}_2)_{12}(\text{TPB})_8] \cdot 6(\text{C}_6\text{H}_5\text{NO}_2)$ (all the crystalline structures corresponding to the M_{12}L_8 poly- $[n]$ -catenane with aromatic solvent will be hereafter named **1**) with one ZnI_2 , one TPB ligand and one third of a second TPB ligand in the asymmetric unit (Figure 3.3b). The structure of **1** corresponds to a poly- $[n]$ -catenane with interlocked M_{12}L_8 icosahedral cages. The large M_{12}L_8 cages include one nitrobenzene in the asymmetric unit that can be solved by X-ray crystallography (Figure 3.3b). Reports of guest inclusion in small voids are widely reported due to efficient host-guest

interactions, but the binding and precise three-dimensional (3D) resolution of guests in large cavities is very challenging due to the lack of good host-guest and/or guest-guest non-covalent interactions. The simulated P-XRD pattern matches well with the reported $M_{12}L_8$ poly- $[n]$ -catenane structures, indicating that the sample is isostructural (Appendix 13.4).

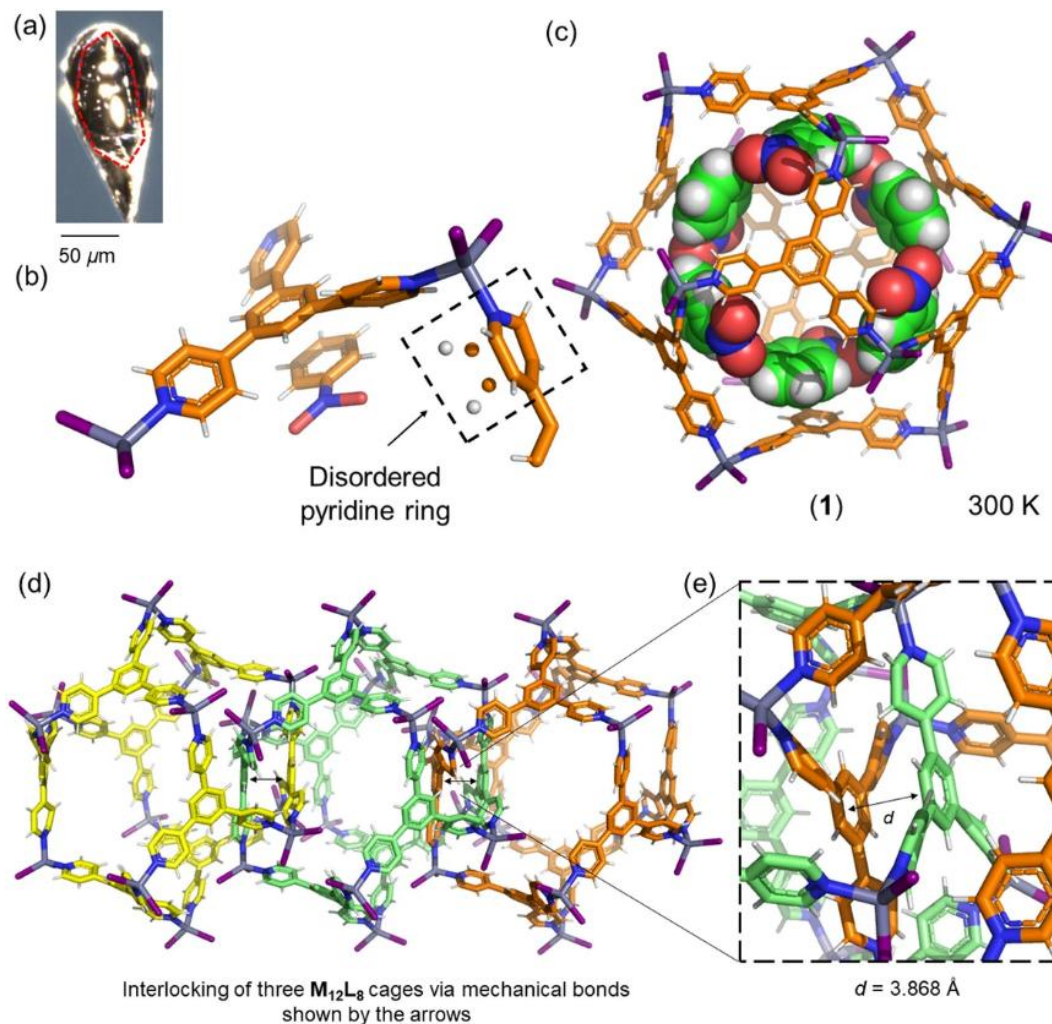


Figure 3.4 — a) Photo of the single-crystal used for the structure solution of **1**; b) asymmetric unit of **1**; c) single $M_{12}L_8$ nanocage with six ordered nitrobenzene molecules; d) three interlocked $M_{12}L_8$ nanocages; e) zoom on the mechanical bond between the cages.^[125]

Regarding the $M_{12}L_8$ cage-framework, it is formed of twelve Zn(II) metal centres at the vertices of the icosahedron with a tetrahedral geometry. In the asymmetric unit, the Zn takes part in two types of bonds with three Zn-N bonds (2.046 $\text{\AA}$, 2.058 $\text{\AA}$, and 2.052 $\text{\AA}$) and four Zn-I bonds (ranging from 2.523 to 2.563 $\text{\AA}$) (Figure 3.4b). The icosahedron is defined as “opened icosahedra” due to the large windows formed by

the absence of twelve of the twenty TPB ligands forming the triangular faces of the “closed” icosahedron. These large windows allow a good interpenetration of $M_{12}L_8$ cages and thus the mechanical bond formation, resulting in 1D chains of interlocked icosahedral cages. The 1D chains extend along the crystallographic c -axis and pack in the crystalline state in such a way that the interactions among the rods are through weak $C-H\cdots I-Zn$ electrostatic interactions.

The mechanical bond among the cages takes place because of the efficient π -stacking among the benzenic core of the TPB ligand ($d = 3.868 \text{ \AA}$) of adjacent cages. The good benzene-benzene interactions among TPB ligands are one of the key factors contributing to the formation, under kinetic control^[51], of the poly- $[n]$ -catenanes of interlocked $M_{12}L_8$ nanocages through the mechanical bond. This aspect is favourable from the enthalpic point of view. It is known that switching from benzene to triazine core in the exotridentate ligand TPT, the outcome of the self-assembly is a completely different structure that does not form the $M_{12}L_8$ interlocked cages but a 3D coordination polymer with doubly interpenetrated networks.^[127]

The packing of the 1D chains of interlocked $M_{12}L_8$ cages does not lead to a porous structure but an array of isolated cages with large internal volumes of *ca.* $2600 \text{ \AA}^3$ (Figure 3.5). The volume occupied by the solvent molecules corresponds to 36 % of the total cell volume ($7553 \text{ \AA}^3$), being similar to the other reported isostructural structures.^[51,128,129] Interestingly, the inter-chain interactions for the zinc iodide catenane have an important role in the structure stabilisation. In fact, the terminal ligand I in the Zn metal interacts with the aromatic rings of TPB via $C-H\cdots I$ interactions with $3.169 \text{ \AA}$ and $3.145 \text{ \AA}$ distances from adjacent chains.

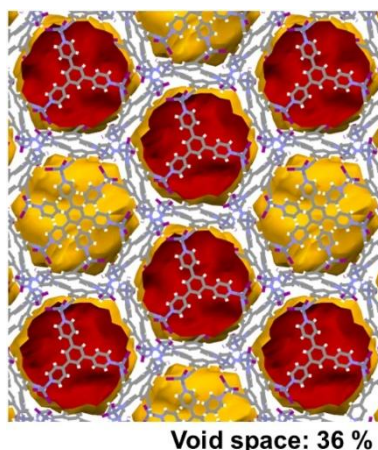


Figure 3.5 — Picture of the isolated voids in **1**.^[125]

Even though the crystal structure has been solved at room temperature, the $M_{12}L_8$ cages can be solved with reasonably small atomic thermal parameters. Interestingly, one of the four pyridine rings in the asymmetric unit is disordered over two positions, which is important to explain the guest replacement reactions despite not having continuous channels (Figure 3.5). The pyridine ring motion, along with the dynamic behaviour of the 1D chains of interlocked $M_{12}L_8$ cages, has been proposed to facilitate the guest exchange and the dynamic behaviour of the $M_{12}L_8$ poly-[n]-catenane systems (Section 3.2.5).

The nitrobenzene guest interacts with the TPB host framework via aromatic-aromatic interactions. The host-guest distance among the centroids of the ring in the nitrobenzene and the benzene ring of TPB is 4.135 Å (Figure 3.6a). The nitrobenzene is oriented with the part of the guest molecule that is more electropositive towards the more electronegative part of the coordinated TPB ligand, according to the maps of electrostatic potential (MEPs) for nitrobenzene guest and TPB host.

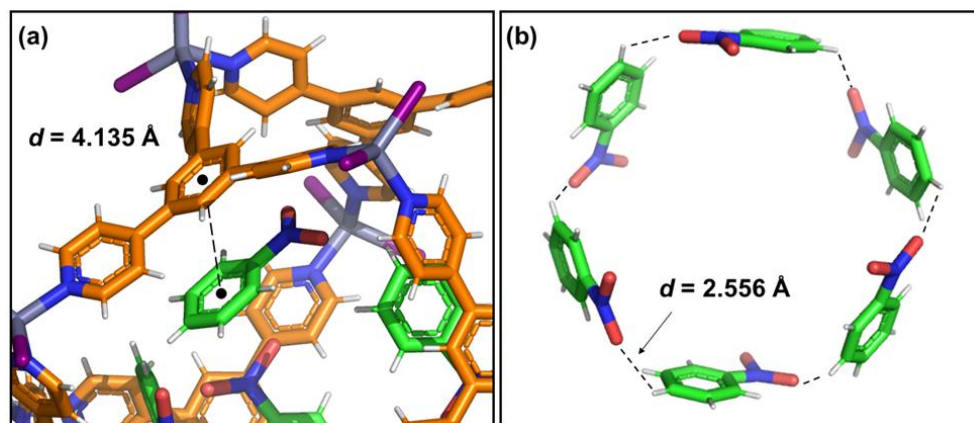


Figure 3.6 — Crystal structure of the $M_{12}L_8$ poly-[n]-catenane (1): a) benzene-nitrobenzene host-guest interactions; b) guest-guest nitrobenzene interactions.^[125]

There are additional electrostatic interactions involving the nitrobenzene guests, which are among the aromatic C-H and one oxygen atom from the $-NO_2$ group. The C-H $\cdots$ O distance is 2.556 Å, which, from an enthalpic point of view, is contributing to the stabilisation of the $M_{12}L_8$ cage (Figure 3.6b). The oxygen engaged in the electrostatic interaction is shorter in the $-NO_2$ group, indicating its involvement in the stabilisation of the guests within the $M_{12}L_8$ nanocage.

Screening of single crystals of self-assembling TPB and ZnI₂ in various aromatic solvents

To gauge more structural information in the self-assembly of TPB and ZnI₂ and to compare the results from instant synthesis, several slow crystallisation experiments were carried out with TPB and ZnI₂ with various aromatic solvents acting as templating agents (Figure 3.3). The solvents screened were: *o*-dichlorobenzene (*o*-DCB), toluene (Tol) and chlorobenzene (Cl-Benz). Interestingly, in all the crystallisation tubes, the M₁₂L₈ poly-[*n*]-catenanes are formed (as indicated by the unit cells obtained, which were all trigonal with lattice parameters like those of **1**), but in all cases, different crystalline structures were identified as evidenced by the diverse lattice parameters.

Slow crystallisation by layering diffusion method using chlorobenzene as templating solvent, gave, after 5 days, a mixture of two macroscopically different crystals: i) the M₁₂L₈ poly-[*n*]-catenane, which was confirmed by the unit cell parameters as block-like crystals, and ii) a new colourless crystalline phase (hereafter named **2**) easily distinguishable due to their thin-plate habit. Crystals of **2** (covered with mineral oil) are stable at room temperature for several hours; therefore, due to their thermal stability, the SC-XRD was recorded at room temperature (300 K). The thin plates (Figure 3.7a) have different lattice parameters and space group symmetry from those of **1**: $a = 24.1055(4) \text{ \AA}$, $b = 14.4843(2) \text{ \AA}$, $c = 18.2201(2) \text{ \AA}$, $\beta = 100.8630(10)$, $V = 6247.58 \text{ \AA}^3$, crystallising in the monoclinic system (*C2/c* space group).

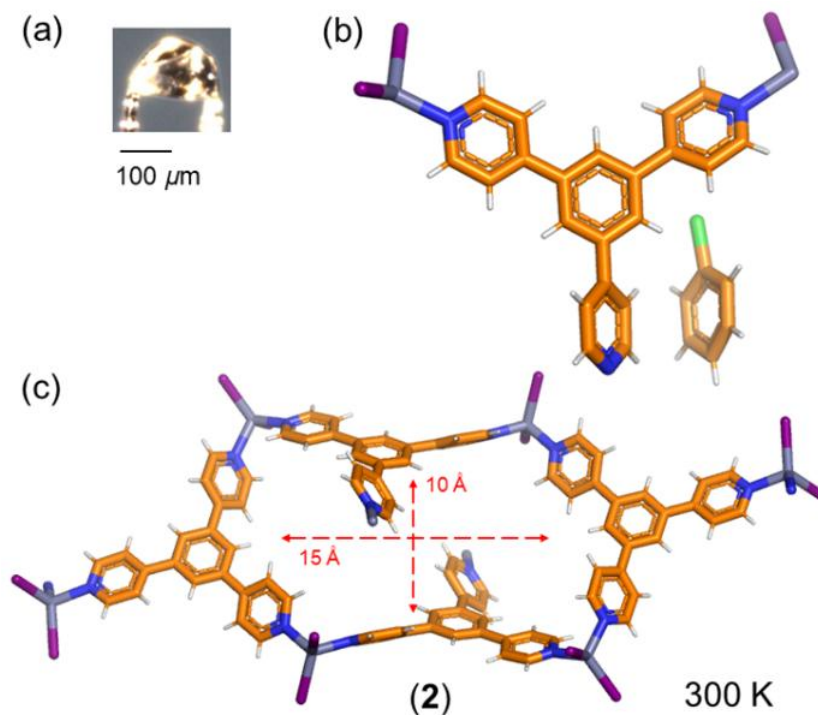


Figure 3.7 — a) Photo of the single crystal used for the structure solution of **2**; b) asymmetric unit of **2**; c) minimum circuit of **2** composed of four TPB and four metal centres.^[125]

In the asymmetric unit, there is one TPB ligand and one and a half ZnI_2 , as one of the Zn atoms sits at a special position on a 2-fold axis. One chlorobenzene guest molecule is also included in the asymmetric unit (Figure 3.7b). The chemical formula, according to the SC-XRD data, is $[(\text{TPB})_1(\text{ZnI}_2)_{1.5}]_n \cdot (\text{C}_6\text{H}_5\text{Cl})$ (**2**). The minimum metal-ligand circuit is formed by four TPB ligands and four Zn(II) metal centres expanding along the c -axis, which form infinite 1D channels including chlorobenzene. The smallest TPB- ZnI_2 circuits form rectangular pockets with windows of *ca.* $10 \text{ \AA} \times 15 \text{ \AA}$ dimensions (Figure 3.7c).

In **2**, the minimum circuits expand through the other two Zn-N coordination bonds to give a tubular structure expanding along the c -axis (Figure 3.8a and 3.8b). The tubes form 1D channels of dimensions *ca.* $16 \text{ \AA} \times 6 \text{ \AA}$. Adjacent 1D chains expand along the a - and b -axis via aromatic (pyridine) $\text{C-H} \cdots \text{I}$ interactions ($d = 3.045 \text{ \AA}$). The included guest does not interact with the host structure, but guest-guest interactions through π - π electrostatic contacts with distances among the centroids of each chlorobenzene of $3.743 \text{ \AA}$ (Figure 3.8c and 3.8d). The close guest-guest interactions are contributing to the stabilisation of the whole structure. Thus, **2** can be regarded as a coordination polymer with a 1D channel structure with void space (void volumes

are calculated using a spherical probe of 1.2 Å diameter), corresponding to the 30% of the total unit cell volume (Appendix 13.5).

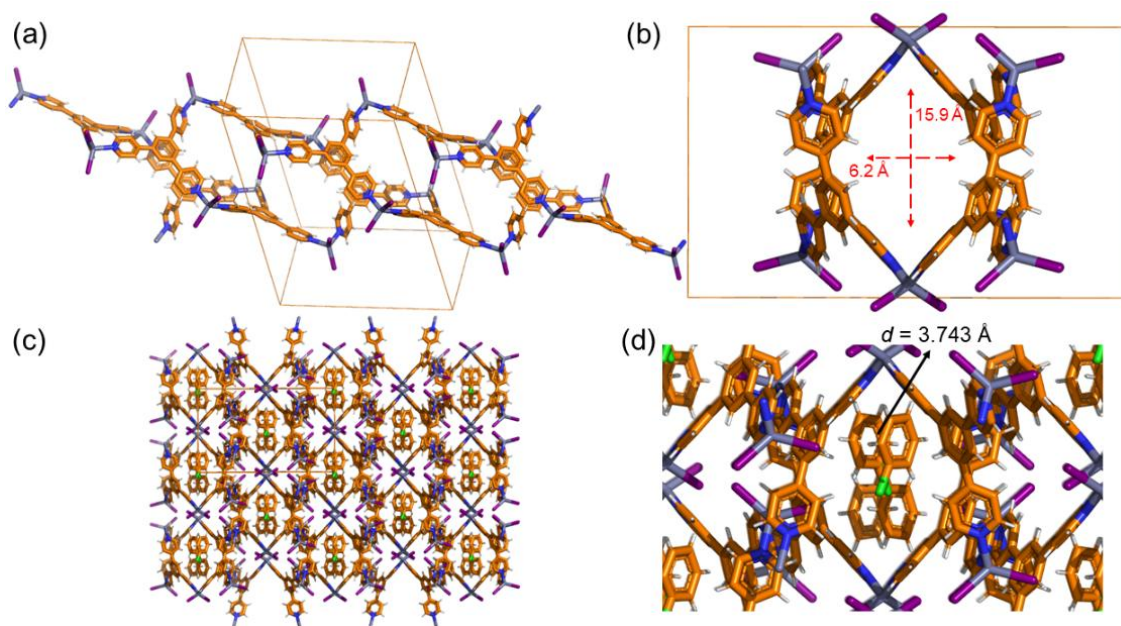


Figure 3.8 — Single crystal X-ray structure of **2**: a) propagation of the minimum circuit; b) view of the tubular structure along *c*-axis; c) packing of the tubular structure along *c*-axis with guest molecules; d) expanded view of the tubular structure including guest solvent.^[125]

When toluene is used as aromatic templating solvent, also a mixture of crystals is obtained where the $M_{12}L_8$ poly- $[n]$ -catenane (large and stable blocks) co-exist with a coordination polymer (thin plates) with unit cell parameters similar to the those of **2**: $a = 29.721(4)$ Å, $b = 13.3437(15)$ Å, $c = 17.2043(15)$ Å, $\beta = 99.804(17)$, $V = 6723$ Å³.

3.1.3 Kinetic control in the synthesis of $M_{12}L_8$ poly- $[n]$ -catenane

Attempts to obtain the coordination polymer **2** or any of the other coordination polymers observed, by instant synthesis, were unsuccessful, as $M_{12}L_8$ poly- $[n]$ -catenanes as crystalline or amorphous phases were always obtained. This clearly demonstrates that the instant synthesis crystallisation is an effective method to prepare the 1D $M_{12}L_8$ poly- $[n]$ -catenane in a selective manner, as it does not allow the error-checking process (Section 1.3). The error-checking mechanism is possible due to the labile nature of the coordination bond. During the slow crystallisation, the

formation of alternative structures such as the above-mentioned coordination polymers or other potential structures can take place because the coordination bond can be broken and re-formed until the most thermodynamically stable structure is self-assembled (*i.e.* error checking). It is important to note that structures **1** and **2** are completely different because the self-assembling process follows a different reaction coordinate (Figure 3.9). Kinetic products tend to form structures with large voids, as in **1**, while thermodynamic products form denser structures with smaller channels/pores, such as in **2**. This can also be seen by the different densities 1.690 g/cm³ and 1.904 g/cm³ in **1** and **2**, respectively and the difference in void space (36% vs. 30%). Another important aspect is that kinetic products tend to be dynamic and hence can undergo guest exchange reactions, but also can undergo further transformations towards more stable structures upon external stimuli (*i.e.* heating) following crystal-to-amorphous-to-crystal transformations. Thus, the crystallisation process has a direct effect on the final structure formed and is therefore very important to gain product control. The ability to direct at will the product formed in a chemical reaction has a crucial role both in chemical synthesis and material sciences.

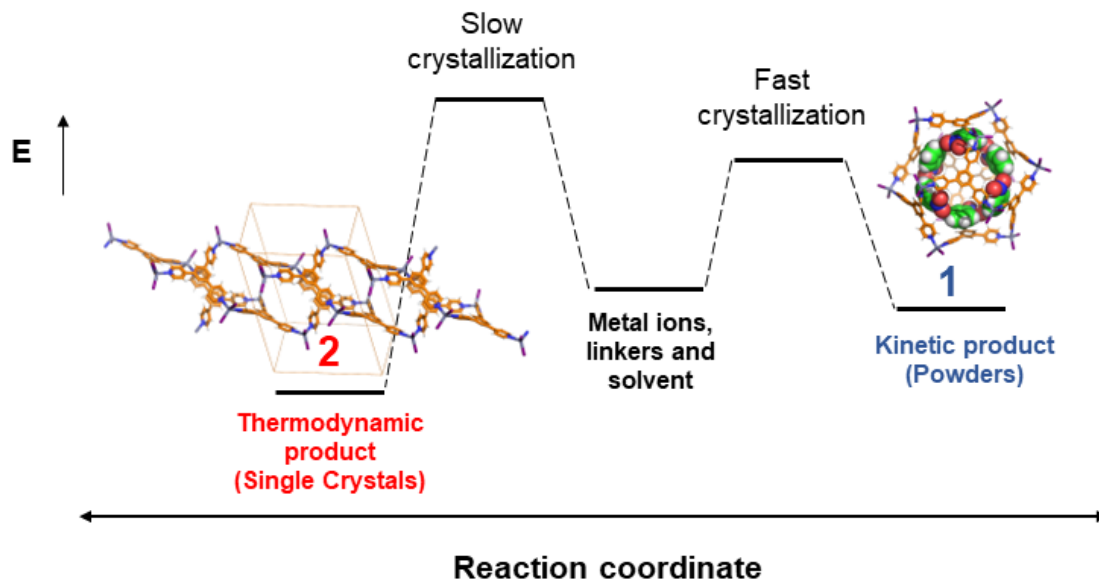


Figure 3.9 — Kinetic control for the synthesis of **1** using instant synthesis. Slow crystallisation leads to the formation of thermodynamic structures like coordination polymer **2**.^[125]

3.1.4 Solid-state synthesis of $M_{12}L_8$ poly-[n]-catenane and xylene uptake

The synthesis of poly-[n]-catenanes in the solid-state is not common, and even less in systems like the $M_{12}L_8$ interlocked cages. While it has been demonstrated that it is possible to obtain the TPB- $ZnBr_2$ poly-[n]-catenane as an amorphous material^[126] both the TPB- ZnI_2 and TPB- $ZnCl_2$ structures have not yet been reported in the solid-state following a solvent-free approach at the time of the experiments.

TPB and ZnI_2 were mixed in a 1:1.5 molar ratio (TPB 30 mg : ZnI_2 47 mg) and ground using a mortar and pestle for 15 minutes. During the grinding process, the reagents and products mixture was always solid. The product, hereafter named **a2** (74 mg), was washed with a mixture of methanol (4 ml) and chloroform (4 ml) and left to equilibrate for 1 day. The weight after the washing process was 60 mg.

The yellowish solid **a2** (Figure 3.10) was analysed by P-XRD, which showed two broad bumps characteristic of only short-range ordering as in **a1** (Appendix 13.6). To corroborate that the $M_{12}L_8$ poly-[n]-catenane was formed, **a2** was immersed in a MeOH/toluene mixture and stirred for 4 hours. Then the solid was filtered and immediately checked again by P-XRD. The similarity between the experimental P-XRD of the new crystalline phase (Appendix 13.6a) and the simulated from SC-XRD of **1**, indicates that the $M_{12}L_8$ poly-[n]-catenane is obtained (Appendix 13.6b). The same synthetic approach has been carried out for the solid-state synthesis of the TPB- $ZnCl_2$ amorphous $M_{12}L_8$ poly-[n]-catenane.

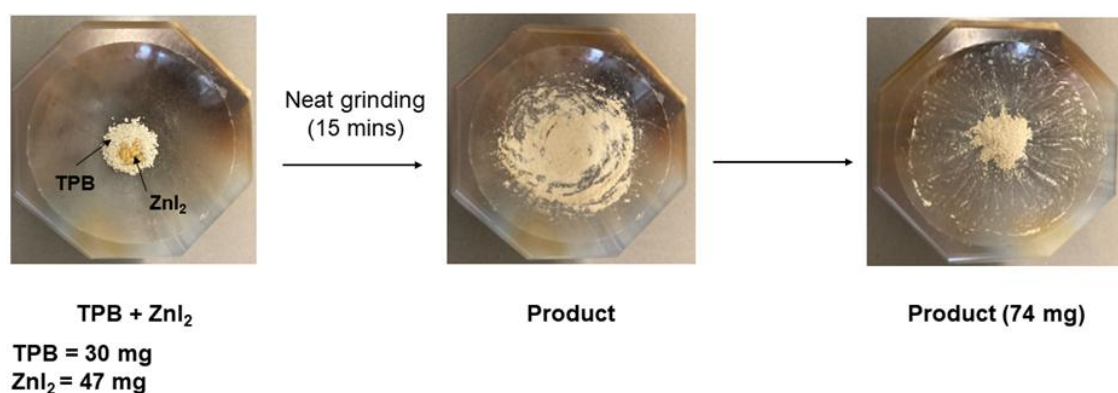


Figure 3.10 — Images of the mortar taken during the neat grinding experiment.^[125]

Inclusion of xylene isomers by amorphous TPB-ZnI₂ M₁₂L₈ poly-[n]-catenane

Because toluene can be included in the interlocked M₁₂L₈ cages of the amorphous phase, the next step was studying the inclusion of toluene derivatives, such as xylenes, by the uptake of **a2** using heterogeneous solid-liquid reactions. The separation of xylenes is an interesting topic in material sciences, as from an industrial point of view, it is relevant. Some reports have been focusing on the use of MOFs and discrete complexes (0D) for such separation.^[130–132] The inclusion of xylenes in poly-[n]-catenanes, and in particular in M₁₂L₈ poly-[n]-catenanes, has not yet been reported. Thus, an amorphous M₁₂L₈ polycatenane synthesised by neat grinding was used to adsorb *o*-xylene (*o*-xy), *m*-xylene (*m*-xy) and *p*-xylene (*p*-xy) molecules using solid-liquid reactions at ambient conditions.

In a typical experiment, 30 mg of **a2** were immersed in 4 ml of *o*-xy and 1 ml of methanol. The suspension was stirred overnight, filtered, and analysed by P-XRD analysis. As observed in the diffractograms, **a2** transformed from an amorphous to a crystalline phase whose diffractogram corresponds to that of the M₁₂L₈ poly-[n]-catenanes (Figure 3.11a). The same behaviour is observed when *m*-xy and *p*-xy are used instead of *o*-xy in the presence of the amorphous M₁₂L₈ poly-[n]-catenane (Figure 3.11b and 3.11c). The amorphous-to-crystalline transformation is a valid tool to differentiate whether guest inclusion occurs. Thus, the **a2** phase can uptake the three isomers, *para*-, *ortho*-, and *meta*- xylenes that are included in the large M₁₂L₈ nanocages.

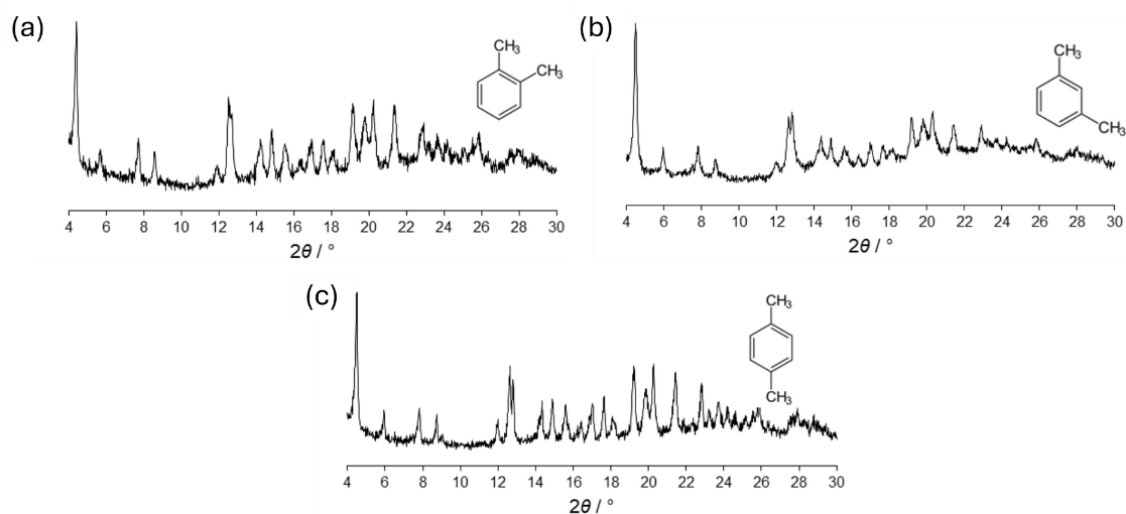


Figure 3.11 — P-XRD pattern of M₁₂L₈ catenane including: a) *o*-xy; b) *m*-xy; c) *p*-xy.^[125]

The instant synthesis was also attempted using *o*-xy, *m*-xy and *p*-xy as templating guests. However, because of the poor solubility of TPB in xylenes, chloroform and methanol had to be used to obtain a homogeneous solution of TPB for the instant synthesis. The instant synthesis produced a low quantity of crystalline materials (≈ 10 mg). Thus, the use of xylenes as templating solvents for the instant synthesis is not convenient. The inclusion of xylenes in the $M_{12}L_8$ nanocages is much more efficient using the amorphous phases **a1** or **a2**, and from an industrial point of view, the amorphous poly- $[n]$ -catenane obtained in the solid-state is preferred.

3.1.5 Solid-state DFT calculations of interaction energies

The availability of the structure of **1** at room temperature, including nitrobenzene, allows DFT calculations to be carried out, giving insights about structural stability and intrinsic local dynamic behaviour of the TPB-ZnI₂ $M_{12}L_8$ poly- $[n]$ -catenanes. Therefore, in collaboration with Prof. Famulari at Politecnico di Milano, DFT calculations specific to solid crystalline states have been carried out considering the energy interactions among $M_{12}L_8$ cages, among the 1D chains, and host-guest energy interactions. DFT calculations were carried out at the PBE/DNP level (where PBE is the functional of Perdew, Burke and Ernzerhof, DNP states for a standard numerical basis set inserted into the Dmol³ package, roughly comparable to the 6-31G** gaussian set). The strategy adopted here has been shown to be good in several recent studies of crystalline systems such as molecules, polymers, and hybrid metal-organic materials.^[133–139] Explicit van der Waals contribution, according to the approach proposed by Grimme, was determined.^[140,141]

Here, it is important to define the model system to be adopted in the DFT calculations. First, the “interaction energies” (E) among non-interlocked and interlocked $M_{12}L_8$ nanocages, which can give a view on the stabilities of the 1D ribbons and of individual (*i.e.* isolated) $M_{12}L_8$ cages, are considered. The second aspect is the “lattice energy” (E^*) that considers the energy of one single $M_{12}L_8$ cage or a 1D chain of interlocked cages immersed within the crystalline lattice (**1**). The last point considers the interaction energy among the $M_{12}L_8$ host and the guest and guest-guest interactions, referred hereafter as $E_{\text{host-guest}}$ and $E_{\text{guest-guest}}$, respectively. The following paragraphs will concern the calculation of each of these interaction energies.

The interaction energies E can be analysed considering E of two close interacting dimers: two interlocked $M_{12}L_8$ cages or two first neighbour cages that are not mechanically interlocked, but that are both stable. The interaction energy into **1**, considering the interlocked $M_{12}L_8$ cages, is *ca.* 89 kcal/mol, which is almost 178 kcal/mol per two cages, and this interaction appears to be strongly affected by the aromatic ring interactions ($d = 3.868 \text{ \AA}$) from the central TPB ring. The E among the non-interlocked $M_{12}L_8$ cages interacting via van der Waals interactions correspond to 47 kcal/mol, or 23.5 kcal/mol per cage.

The lattice energies E^* are calculated considering the extraction of a single 1D chain out of the crystal lattice. The average energy required to extract a single $M_{12}L_8$ cage immersed in the crystalline structure is very high: about 505 kcal/mol. In a similar way, considering the interlocked $M_{12}L_8$ chain along the c -axis and calculating the energy required to remove a single infinite chain of $M_{12}L_8$ interlocked nanocages from the crystalline structure, the calculated E^* is 398 kcal/mol. This indicates that the model of an infinite 1D chain “immersed” in the structure is a good model explaining the high stability of the poly- $[n]$ -catenane architecture.

Because it has been seen that nitrobenzene has an important role in templating the poly- $[n]$ -catenane structure, the same sort of calculation was carried out, but with the $M_{12}L_8$ cages including the six nitrobenzene guest molecules. In this way, it is possible to compare the previously calculated energies against the empty model, not including guest molecules. The interaction of the $M_{12}L_8$ cages with the solvent molecules, the $E_{\text{host-guest}}$, is also important in this case. The $E_{\text{host-guest}}$ is about 46 kcal/mol for each solvent molecule, which is comparable to the energies observed among the non-interlocked cages interacting via electrostatic and van der Waals interactions (*i.e.* the interactions among neighbouring 1D chains). The $E_{\text{guest-guest}}$ interactions (Figure 3.6b) are, as expected, much lower, 4.3 kcal/mol, but not negligible. Thus, the $E_{\text{host-guest}}$ and $E_{\text{guest-guest}}$ interaction energies of aromatic guests are important for the stabilisation of the whole poly- $[n]$ -catenane architecture. While the lattice energy (E^*) values for a single cage and a single chain are higher, and the interaction energies (E) for interlocked cages are also higher, the interaction energy of non-interlocked cages shows a lower interaction energy, from 47 kcal/mol without guests to 27 kcal/mol including guests.

Among catenanes self-assembled of molecular rings, 1D catenanes are interesting because of the dynamic behaviour due to their high conformational degrees of freedom through rotations, translations and rocking motions of the

molecular rings. However, when the chains are formed of interlocked MOCs like the $M_{12}L_8$ large nanocages, translation, rotations and rocking motions are somehow limited by the free window space left after the mechanical bond formation. In the $M_{12}L_8$ poly- $[n]$ -catenanes, the free window space is not large, and therefore the 1D rods are quite stable. Thermodynamically, the interlocking process is favoured from the enthalpic but not from the entropic point of view. Importantly, the 1D chains of interlocked $M_{12}L_8$ nanocages are not completely rigid, as it has been reported that guest molecules can be exchanged,^[128] and stability studies have shown that included guest molecules come out from the cages under vacuum conditions.^[49]

From the DFT calculations, it has been seen that almost all the interactions increase in the presence of guest molecules. This confirms that when the solvent is present in the $M_{12}L_8$ cages, the structure gains stability within the 1D chains. In particular, the energy interactions increase in single cages, the interlocked cages, and the chain of interlocked cages, gaining stability, but the interactions among non-interlocked $M_{12}L_8$ cages, that is, among neighbouring chains, become weaker. The enhancement in structural stability brought by the six included and ordered guest interactions per $M_{12}L_8$ cage influences the electrostatic interactions (lowering) among chains for structure **1**, as observed by DFT. This influences the guest exchange/inclusion properties and the dynamic behaviour of the 1D chains of $M_{12}L_8$ interlocked cages, which might help to explain the guest inclusion/exchange observed in these systems formed of large, mechanically interlocked cages.

The relative displacement among 1D chains of interlocked $M_{12}L_8$ cages, considering two main directions, one perpendicular to the chain propagation (c -axis) and the second parallel to the chain extension (*i.e.* sliding chains), has a low energy cost. While 1 Å displacement in the direction orthogonal to the 1D rod has an energy penalty of 10 kcal/mol, in the sliding direction, the energy penalty is 0.2 kcal/mol per 2 Å translation. These calculations were carried out considering a TPB-ZnBr₂ model system of two $M_{12}L_8$ cages belonging to different chains (*i.e.* non-interpenetrated).^[128]

3.2 Molecular recognition of aromatics in spherical nanocages

The work presented so far highlights the potential for the $M_{12}L_8$ poly- $[n]$ -catenane in host-guest chemistry. The high stability of the material directed toward the exploration of the molecular trapping, guest inclusion and guest exchange processes. This chapter will display the work done to demonstrate the molecular recognition ability of the nanocage by single-crystal-to-single-crystal (SCSC) guest exchange experiments. Combining SC-XRD, DFT and solid-state ^{13}C NMR techniques allowed the description of the high stability (thanks to the mechanical bonds) and at the same time, dynamic behaviour of the pyridines that help the guest inclusion processes.

3.2.1 Synthesis of $M_{12}L_8$ nanocages with two aromatic binding sites

As explained in the previous chapter, using the slow crystallisation method with TPB and ZnI_2 in the presence of an aromatic templating agent leads to the formation of **1** (along with the coordination polymer **2**). To investigate the SCSC guest exchange processes, some crystals were prepared in the same manner.

A TPB- ZnI_2 $M_{12}L_8$ poly- $[n]$ -catenane crystal suitable for SC-XRD analysis was grown by the layering diffusion method using *p*-xy as templating guest. The unit cell was indexed in the trigonal system in the $R\text{-}3$ space group with the lattice parameters (173 K): $a = 38.8631(6)$ Å, $b = 38.8631(6)$ Å; $c = 16.2355(3)$ Å; $\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$; $V = 21235.9(8)$ Å³ (Appendix Table 13.1). Crystallographic analysis resulted in the formula $[(\text{ZnI}_2)_{12}(\text{TPB})_8] \cdot 12(p\text{-xy})$ (**1**), with two ZnI_2 , one TPB, one third of a second TPB ligand and two independent (A and B) *p*-xy guest molecules in the asymmetric unit (Figure 3.12). Therefore, **1** is isostructural to the $M_{12}L_8$ cages presented in the previous chapter. However, the main difference is that each cage is fully occupied with 12 guests, in contrast to the nitrobenzene case, which presented just six ordered guests per cage. The cages are big, so the guests at the centre of the cage are in a disordered state, like a nanodroplet of solvent, influencing the quality of the structure solution process. We note that in some crystals, the R_{wp} values (see crystallographic tables in the Appendix) can be relatively high because the refinement quality is limited by several factors. The guest molecules disordered at the centre of the cage cannot be detected by SC-XRD

and thus affect the quality, increasing the R_{wp} value. Some crystals, affected by disordered guests, can give weak diffraction at high angles, which increases the R -factors. However, for those cases with high R_{wp} values, we note that the $M_{12}L_8$ framework structure is well refined and has good thermal parameters.

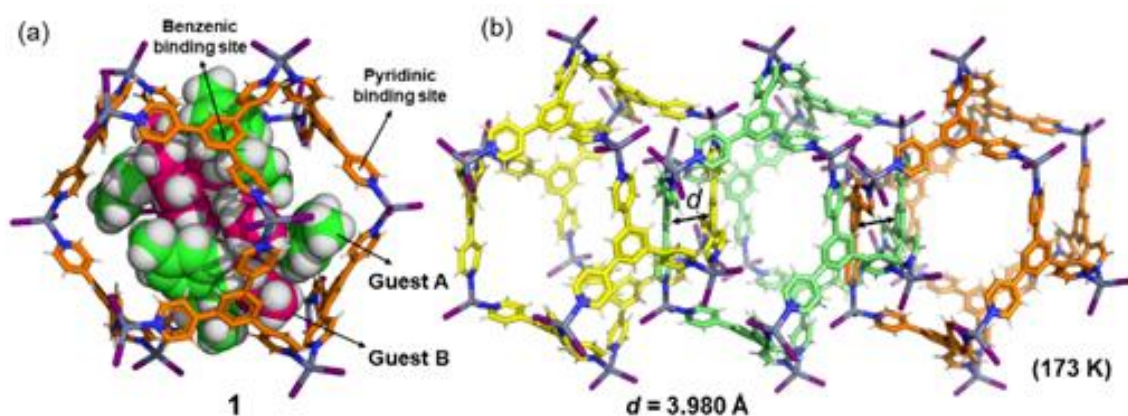


Figure 3.12 — SC-XRD model structure at 173 K of **1**: a) isolated $M_{12}L_8$ nanocage displaying the two binding sites; b) three interlocked nanocages via mechanical bonds.^[142]

The distance among the closest benzene rings belonging to TPB is $3.980 \text{ \AA}$ and is thus an efficient π - π interaction (Figure 3.12b). As in the previous case, a single chain of interlocked cages contains large windows, but once packed in the crystalline state, the structure does not give a bulk channel structure. Importantly, the surface of the crystals is open, thus having a certain porosity where molecules can enter/exit.

In **1**, the guest p -xy A near the walls interacts with TPB via aromatic-aromatic interactions (*i.e.* van der Waals) even if the orientation of the p -xy is not perfectly parallel and the distance between the aromatic rings is $4.233 \text{ \AA}$. The second p -xy, B, fills the more internal part of the $M_{12}L_8$ cages (Figure 3.12b). There are aromatic C-H $\cdots\pi$: $2.865 \text{ \AA}$, and methyl C-H $\cdots$ I: $3.165 \text{ \AA}$ guest-guest interactions, which contribute to the stabilisation of the guest's content and the whole host-guest structure. This was the first X-ray structure of a poly- $[n]$ -catenane constituted of mechanically interlocked $M_{12}L_8$ cages with all the space available in the $M_{12}L_8$ nanocages occupied by ordered aromatic guests.

3.2.2 Molecular recognition of *o*-DCB and NB in gas-solid SCSC reaction

Because of their topology, the mechanical properties of catenanes built of mechanically interlocked cages are still poorly explored despite their potential functional abilities. While most of the solid-state guest uptake/exchange in porous materials takes place because they contain continuous channels, this is less common in materials lacking connected cavities. To see if **1** can uptake new guests, and hence to directly monitor the molecular recognition to external stimuli, the same single crystal of **1** used for the SC-XRD was exposed to vapours of *o*-DCB for 4 days in a closed chamber at room temperature (Figure 3.13).

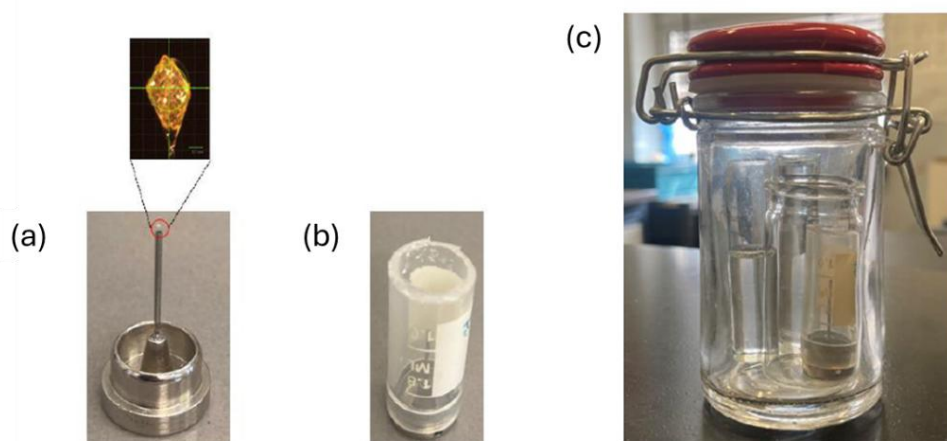


Figure 3.13 — a) Pin with single crystal; b) pin with open cap; c) pin and vial with volatile solvent inside the sealed chamber.^[142]

Thus, the guest exchange reaction was carried out in a gas-solid manner. In this way, there is a lower risk for any potential crystal decay induced by a faster and more aggressive liquid–solid guest exchange, but also, **1** cannot be solubilised and recrystallised as it could happen by immersing **1** in the new guest. The SC-XRD analysis allows the host MOC to be refined well, but not the guest. Thus, **1** was exposed further for another two days to *o*-DCB. After the exposure of **1** to *o*-DCB vapours (hereafter named **1'·o-DCB**) for six days, the crystal did not break and still diffracted well. The unit cell of **1'·o-DCB** was (173 K): $a=38.3737(6)$ Å, $b=38.3737(6)$; $c=15.5927(3)$; $\alpha=\beta=90^\circ$, $\gamma=120^\circ$; $V=19884.7(7)$ Å³ (Appendix Table 12.2). Clearly, the main lattice change is along the *c*-axis ($\Delta = 0.6428$ Å), the direction of the mechanical bond propagation, but interestingly, the aromatic-aromatic interlocking π - π distance remained almost constant (3.974 Å in **1'·o-DCB** and 3.980 in **1**). The interlocked M₁₂L₈

height after the guest exchange decreased to 11.619 Å (before guest exchange 12.322 Å). The unit cell volume decreased by 1351 Å³, clearly indicating the guest uptake. The guest exchange reaction induces a M₁₂L₈ “compression” along the *c*-axis. Since there are several SCSC reactions, the first one is referred to as SCSC-1 (Figure 3.14).

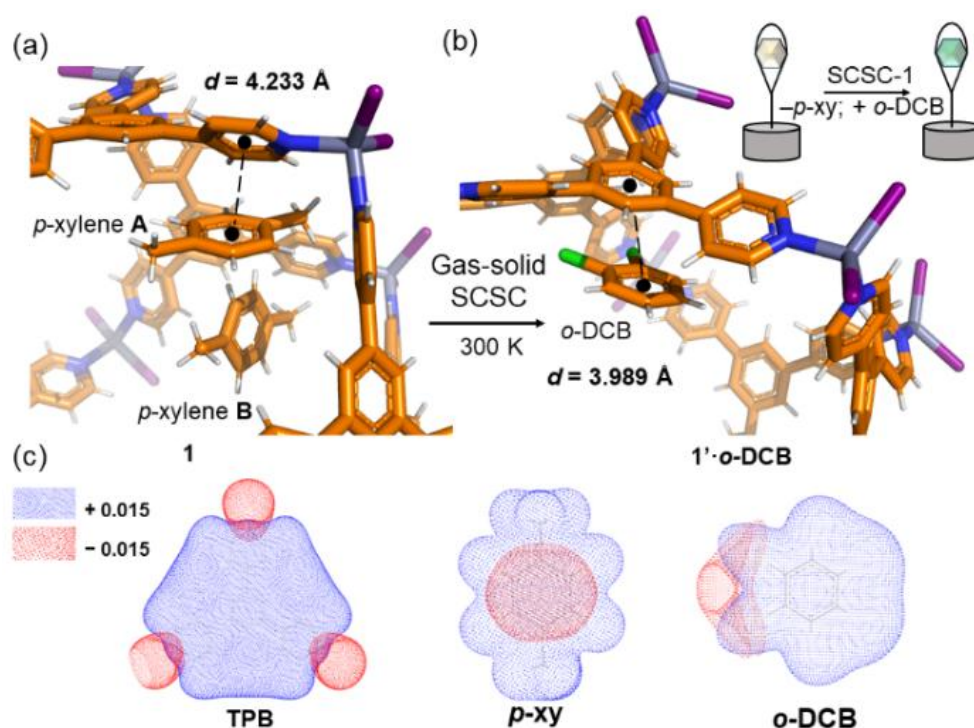


Figure 3.14 — a) SC-XRD model of the pristine crystal (**1**); b) SC-XRD model after guest exchange (**1'·o-DCB**); c) DFT MEPs of TPB, *p*-xy and *o*-DCB molecules. ^[142]

Unambiguously, the **1'·o-DCB** SC-XRD data show that there is one ordered *o*-DCB in the asymmetric unit and not two *p*-xy as in **1** (Figure 3.14). The *o*-DCB in the M₁₂L₈ nanocage is in a different binding site compared to the original *p*-xy A (Figure 3.14), which evidences that the guest content in the M₁₂L₈ nanocages has changed upon exposition to new guests. After guest exchange, the *o*-DCB is under the benzenic binding site of the TPB host and not below the pyridinic binding site as in the *p*-xy (Figure 3.14b). The aromatic-aromatic distance between TPB and *o*-DCB is 3.989 Å, which is shorter with respect to the original guest and TPB (*i.e.* 4.233 Å). The orientation of the polar *o*-DCB showed to be strongly influenced by the molecular electrostatic potentials (MEPs) of TPB and aromatic guest molecules, with the negative end of *o*-DCB MEP pointing towards the positive area of TPB MEP (Figure 3.14c). Since *p*-xy is apolar, it can adjust within the cage below the aromatic rings without any

preferential orientation, favouring, at the same time, a denser packing with two *p*-xy in the asymmetric unit, as is observed in polycatenane **1**. Therefore, not only the distance but also the location of the guest molecule is different after the **SCSC-1** guest replacement (Figure 3.14). The molecular exchange is also evidenced by geometrical changes in the icosahedral $M_{12}L_8$ nanocage, particularly the benzene-pyridine torsion angles that in **1'**·*o*-DCB are higher than in **1** (Figure 3.15), but also on the Zn coordination angles N-Zn-N which decreased after the guest uptake (101.7° and 102.3° in **1** and to 98° and 98.8° in **1'**·*o*-DCB).

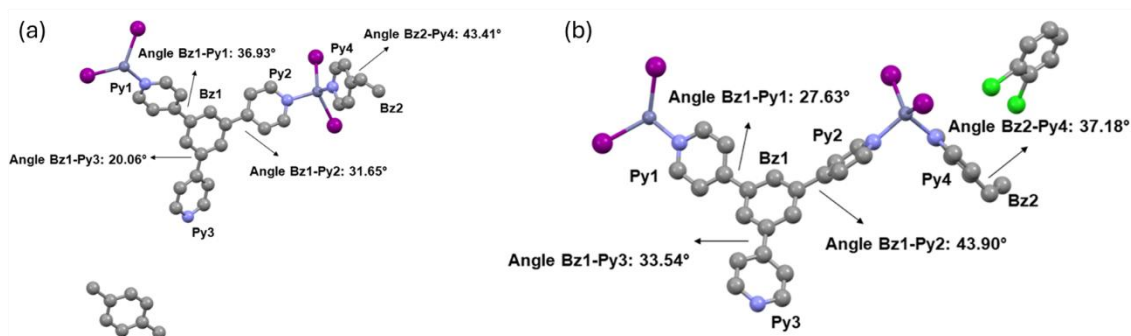


Figure 3.15 — Dihedral angles between pyridine and benzene rings in: a) **1**; b) **1'**·*o*-DCB.^[142]

These structural differences show that the host $M_{12}L_8$ icosahedron adapts to the new guest molecules, showing an important structural responsiveness upon external stimuli. The interlocking $\pi - \pi$ distance is 3.926 Å, which is very close to the $\pi - \pi$ distance observed in **1**. The structural changes of the interlocked $M_{12}L_8$ nanocage framework are important but not enough for inducing a change in the trigonal *R*-3 symmetry. To evaluate the molecular recognition capabilities of the $M_{12}L_8$ nanocages in **1**, it is necessary to have other examples of guest uptake in a gas-solid process. This helps extract any information regarding preferential molecular recognition processes by crystals of **1**, but also thermodynamic aspects of the guest inclusion. Thus, in a closed chamber, a single crystal of **1** was exposed to NB vapours at room temperature for two days and analysed by SC-XRD (173 K). In this case, NB can be refined and resolved at 173 K without applying guest restraints, confirming, unambiguously, the guest exchange via the **SCSC-2** process to give **1''**·NB (Appendix Table 13.3) in a gas-solid reaction (Figure 3.16).

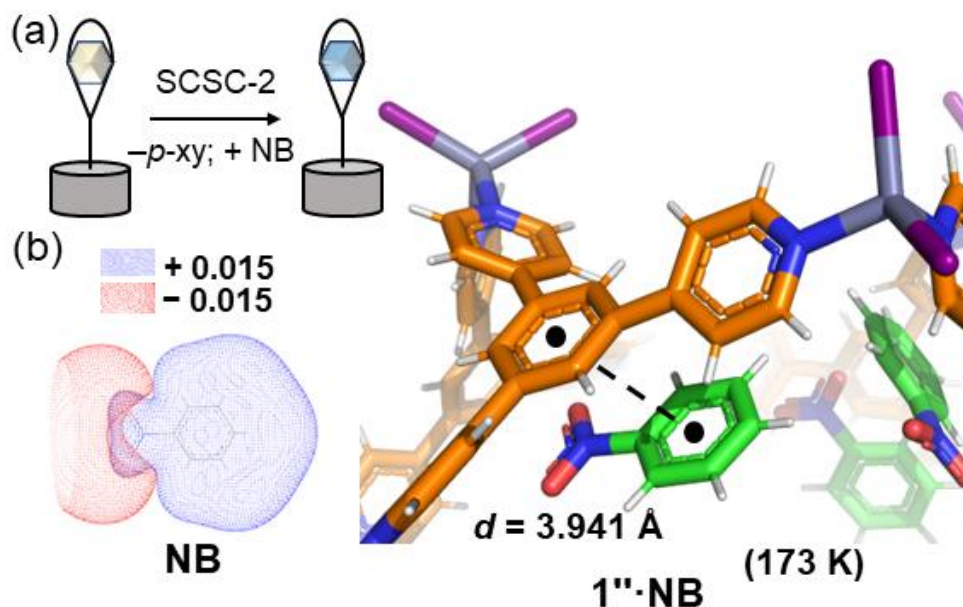


Figure 3.16 — a) SCSC-2 process and SC-XRD model of $1''\cdot\text{NB}$; b) DFT molecular electrostatic potential of NB.^[142]

SCSC processes are fundamental to understand the guest uptake, reactivity and molecular recognition events of a given solid. SCSC-2 (Figure 3.16) confirms the SCSC-1 (Figure 3.15) result, with the significant difference that NB was adsorbed faster (2d) than o -DCB (6d). Also, in this case, the new guest orients to optimise the interactions between the MEPs, with the more electronegative regions of the guest pointing towards the more positive regions of the TPB ligand. Crucially, the molecular recognition event placed NB under the benzenic binding site at $3.941 \text{ \AA}$. Conversely, the pyridinic binding site is less effective in the molecular recognition as NB is poorly oriented and is further away ($4.636 \text{ \AA}$). The lattice parameters of the exchanged guest measured at 173 K are all lower than those measured in **1** with two p -xy guests, showing that the M_{12}L_8 nanocages adapted to accommodate NB guest (Figure 3.16). In both SCSC-1 (Figure 3.15) and SCSC-2 (Figure 3.16) experiments, the unit cell volume contracts upon guest absorption. From an enthalpic point of view, the SCSC-2 (Figure 3.16) is a favoured process.

3.2.3 DFT calculations of energy host–guest interactions

The presence of more than one binding site, where guest molecules can be recognised by the host MOC, opens up preferential molecular recognition experiments. But which guest is absorbed by the $M_{12}L_8$ nanocage if NB and *o*-DCB (both guests have similar size and a strong aromaticity and polarity) are present in the gas phase at the same time with the same volumes? To gain additional information regarding the host–guest affinity in terms of energetic interactions, as done in the previous chapter, molecular modelling analysis has been performed. The calculations (performed by Prof. Famulari) were carried out following the same approach described in section 3.1.5 to determine the $E_{\text{host-guest}}$ energy considering NB, *o*-DCB, *p*-xy, *m*-xy, *o*-xy interacting with the TPB moiety at the internal walls of the $M_{12}L_8$ nanocages. The geometry of the host/guest complexes has been optimised. DFT results showed that NB is the molecule with stronger host–guest interactions (44 kcal/mol), while the $E_{\text{host-guest}}$ interaction energy of *p*-xy, *m*-xy and *o*-xy are quite similar (ca. 35 kcal/mol). However, the $E_{\text{host-guest}}$ of *o*-DCB is lower (25 kcal/mol). So, the $E_{\text{host-guest}}$ interaction energy follows the order $\text{NB} \gg p\text{-xy} \gg o\text{-DCB}$. The calculated $E_{\text{host-guest}}$ interaction energies are important, highlighting the fact that the templating effect of the guest is crucial for the self-assembly from solution and for the reconstruction of the amorphous $M_{12}L_8$ cages obtained in the solid-state. Remarkably, the strongest host–guest interaction energy difference ($\Delta E_{\text{host-guest}}$) is among NB and *o*-DCB with a $\Delta E_{\text{host-guest}}$ of 20 kcal/mol, followed by the $\Delta E_{\text{host-guest}}$ among *p*-xy and *o*-DCB, which is 10 kcal/mol. The $\Delta E_{\text{host-guest}}$ among xylenes is negligible. Thus, exposing mixtures of NB/*o*-DCB and *p*-xy/*o*-DCB to single crystals of **1** in a gas-solid environment will give significant information about the guest that will be absorbed by the $M_{12}L_8$ nanocages. Hence, molecular recognition events can be monitored directly via SCSC reactions using **1**.

3.2.4 Preferential uptake of aromatics in multiple SCSC gas–solid reactions

To evaluate not only the preference for a given guest, but the strength of **1** as a sensor of aromatic molecules, **1** was exposed to various guests in repetitive gas-solid SCSC experiments. First, this will prove the molecular recognition ability of **1**, but also it will show that the 1D chains of interlocked $M_{12}L_8$ cages in the poly- $[n]$ -catenanes

are robust yet dynamically responsive to the presence of certain aromatic guest molecules. A new single crystal of **1**, including *p*-xy, was exposed only to vapours of NB for 18 h. SC-XRD unambiguously showed that the nitroaromatic guest was absorbed by the $M_{12}L_8$ cages ($SCSC_1-3$) below the benzenic binding site at 4.029 Å and oriented according to the MEP analysis (Figure 3.17b), giving $1''' \cdot NB$ (Appendix Table 13.4).

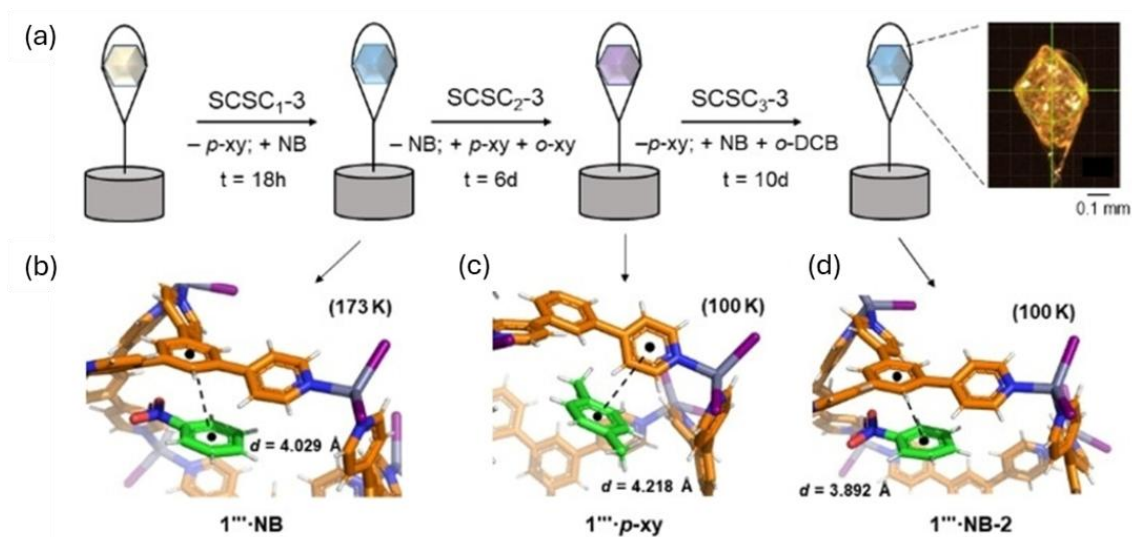


Figure 3.17 — a) multiple SCSC guest exchange on the same crystal; b) SC-XRD model of $1''' \cdot NB$; c) SC-XRD model of $1''' \cdot p\text{-xy}$; d) SC-XRD model of $1''' \cdot NB-2$.^[142]

Later, the same crystal was further exposed to a 3 mL : 3 mL mixture of *p*-xy and *o*-xy for 6 days. The SC-XRD crystallographic analysis (Appendix Table 13.5) shows that NB has been replaced by *p*-xy, which is below the pyridine binding site of the TPB ligand (Figure 3.17c), forming $1''' \cdot p\text{-xy}$ in the $SCSC_2-3$ reaction. The position of the *p*-xy guest is now different from the NB and is oriented as in **1** obtained from the layering method (bottom-up self-assembling; Figure 3.12a). The π - π distance (pyridine TPB/*p*-xy) is 4.218 Å, almost the same as in **1**. Thus, the adsorbed *p*-xy corresponds to *p*-xy A (Figure 3.12a and 3.14a), while the second ordered guest, *p*-xy B, cannot be observed. Because the crystal still maintained good quality, following the same protocol of $SCSC_2-3$, it was further exposed to vapours of NB and *o*-DCB (3 mL:3 mL) for 10 days in another molecular recognition process ($SCSC_3-3$). Surprisingly, the single crystal was not damaged (Figure 3.17a) and still diffracted well after about 17 days of exposure to the aromatic vapours at room temperature (Appendix 13.8). The SC-X-ray structure solution shows that NB is absorbed by the

interlocked $M_{12}L_8$ cages and stabilised by the benzenic binding site at 3.892 Å (Figure 3.17d), giving $1''' \cdot \text{NB-2}$ (Appendix Table 13.6). The shorter distance with respect to the previous guest, *p*-xy, indicates a different $E_{\text{host-guest}}$ strength in the molecular recognition process that contributed to the stabilisation of NB instead of *o*-DCB by the benzenic binding site. The results agree with the DFT data showing that NB is the “preferred” guest from the competitive NB versus *o*-DCB experiment. The guest uptake observed in the xylenes shows that *p*-xy is adsorbed with some preference over *o*-xy, however, it is difficult to reach a clear conclusion based on the similar host–guest affinities. Molecular shape, hindrance, and the MEP might have a strong effect in this case. In fact, slow crystallisation of single crystals grown with *o*-xy and *m*-xy tends to form coordination polymers (**2**) with 1D channels where the solvent occupies 38% of the lattice volume. This suggests that the templating effect of *p*-xy is better for the formation of interlocked $M_{12}L_8$ cages. Since they have both practically the same $\Delta E_{\text{host-guest}}$, the absorption observed could be ascribed to molecular geometry effects.

Next, for the *p*-xy/*o*-DCB competitive experiment, a single crystal grown in chloroform/methanol/paracetamol as templating guests was exposed to vapours of *p*-xy and *o*-DCB (**SCSC-4**). The original crystal did not contain ordered guests at 173 K, but after 1d of *p*-xy/*o*-DCB gas solid reaction, *p*-xy could be located under the benzenic binding site in the $M_{12}L_8$ cages at 3.727 Å. Considering the MEP, the negative part of the guest interacts with the most positive area of coordinated ligand TPB. The other guest, *o*-DCB, is not observed. The preferred molecular recognition is in accordance with the calculated DFT values, where *p*-xy shows stronger $E_{\text{host-guest}}$ interaction energy. The *p*-xy absorption takes only 1d, which shows the good affinity of the xylene towards the interlocked $M_{12}L_8$ cages. The internal $M_{12}L_8$ surface is covered with aromatic binding sites due to the presence of benzene and pyridine rings, which have an important influence on the molecular recognition. The $M_{12}L_8$ guest uptake shown in Figure 3.17 is quite remarkable because **1** can discriminate which molecules among mixtures of NB/*o*-DCB and *p*-xy/*o*-DCB will be stabilised in an ordered manner below a certain aromatic ring of TPB. Because in the crystalline state the internal voids of the $M_{12}L_8$ nanocages are not connected (*i.e.* there are no channels), the guest diffusion from the first $M_{12}L_8$ cages at the surface of **1** towards the centre of the crystals must follow a cooperative effect induced by external stimuli.

3.2.5 Rotor-like behaviour of M₁₂L₈ pyridine rings

The X-ray Crystallographic analyses on the SCSC guest exchange reactions show the structural responsiveness of **1** that adapts its framework to uptake *o*-DCB, NB and *p*-xy guests. Combining SC-XRD, DFT calculations and solid-state NMR, the dynamic behaviour was further investigated. TPB is a rigid triangular panel with a static central benzene ring and peripheral aromatic pyridines coordinated to a Zn metal. Solid-state NMR analysis of a microcrystalline M₁₂L₈ poly-[*n*]-catenane sample using *o*-DCB as templating solvent was carried out to study the dynamic behaviour of the aromatic rings and the guest molecule. The ¹³C high-power decoupling (HPDEC) MAS NMR spectrum (Appendix 13.9) shows sharp peaks assigned to the mobile guest *o*-DCB and broad lines attributed to the M₁₂L₈ host framework. Importantly, the very weak signal belonging to the quaternary atoms of the benzene ring (136–129 ppm) compared to the quaternary atoms of pyridines (150–147 ppm) shows the static behaviour of the benzene ring, therefore, serving as a good anchoring point for defining the molecular rotor axis (Figure 3.18a). In fact, the TPB pyridine's rotation has been observed experimentally by SC-XRD at 300 K with an angle $\alpha = 35.7^\circ$ between the pyridine rings in the two positions (Figure 3.18b). DFT calculations showed that the pyridine rotation along that axis has a maximum energy penalty of about 3 kcal/mol $\tau = 90^\circ$ (where τ is the dihedral angle between the benzene and pyridine rings), with the minimum value at $\tau \approx 35^\circ$ (Figure 3.18c). These interaction energies are one order of magnitude lower than the host–guest energy interactions (≈ 44 kcal/mol in the case of NB) and two orders of magnitude lower than the mechanical bond interactions (≈ 145 kcal/mol). These energetic considerations, combined with the rigidity of **1**, due to the mechanical bonds, and dynamic pyridine nanorotor behaviour of TPB, allow the guests to diffuse in and out of the M₁₂L₈ nanocages whilst maintaining good single crystallinity after 17d of guest-exchange experiments (Appendix 13.8). Therefore, the pyridine rings in **1** can be considered as nanorotors and, due to their dynamic behaviour, allow the guest absorption/exchange in the solid-state. The presence of large M₁₂L₈ cages with a large internal volume and the lack of channels connecting them, makes the uptake of guests a particular host–guest system.

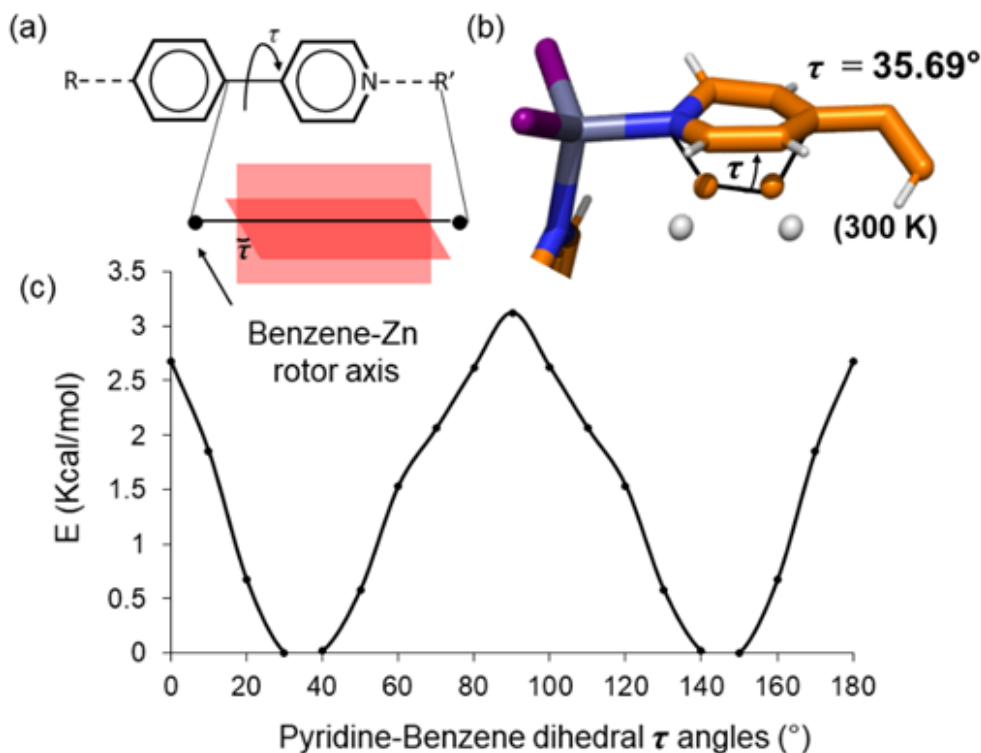


Figure 3.18 — a) Rotor-like behaviour of the pyridine along the benzene-Zn axis; b) SC-XRD model of the disordered pyridine; c) plot of potential energy barrier for the pyridine-benzene dihedral torsion angle.^[142]

3.3 Small molecules guest uptake and breathing-like effect

The work presented so far is about the molecular recognition of aromatic guest molecules. This section will instead focus on the trapping of small non-aromatic molecules. The first part will be an explanation of the lattice variation experimented in the two cases (aromatic templating agent vs small non-aromatic molecules) under *in-situ* variable temperature SC-XRD (VT-SCXRD). The second part will describe the investigation carried out on the guest exchange between an aromatic molecule (*i.e.* benzaldehyde) and a small nitro compound (*i.e.* nitromethane).

3.3.1 *In-situ* X-ray study of breathing-like effect

Starting from room temperature, SC-XRD data collection of an $M_{12}L_8$ poly-[n]-catenane single crystal, the evolution of the lattice parameters is studied by *in-situ* variable temperature SC-XRD experiments to understand the $M_{12}L_8$ host dynamic behaviour upon heating. This mechanism is different depending on the type of guests. When the temperature in the diffractometer is increased, the aromatic templatic agent (*i.e.* p -xy) induces a swelling-like behaviour while small non-aromatic molecules (*i.e.* methanol) induce a breathing-like behaviour.

Variable temperature SC-XRD (VT-SCXRD) experiments were carried out using two single crystals self-assembled from interlocked icosahedral $M_{12}L_8$ nanocages. The first experiment was performed on a poly-[n]-catenane with $M_{12}L_8$ nanocages filled with p -xy guests (**1**), while the second crystal contains methanol (**1·MeOH**) partially filling the $M_{12}L_8$ cages. In the *in-situ* VT-SCXRD experiments, the temperature was gradually increased by 50 K from 100 K to 300 K. Single crystals of **1** and **1·MeOH** were grown using a triple-layering approach as in the previous cases. Single crystals **1** and **1·MeOH** were taken from the crystallisation tube, immersed in mineral oil and, within 30 seconds, mounted on a loop and placed under a liquid N_2 flow. For the *in-situ* VT-SCXRD experiments on **1** and **1·MeOH**, five data sets were measured from 100 K to 300 K at intervals of 50 K, the lattice parameters monitored and their structures solved (Figure 3.19).

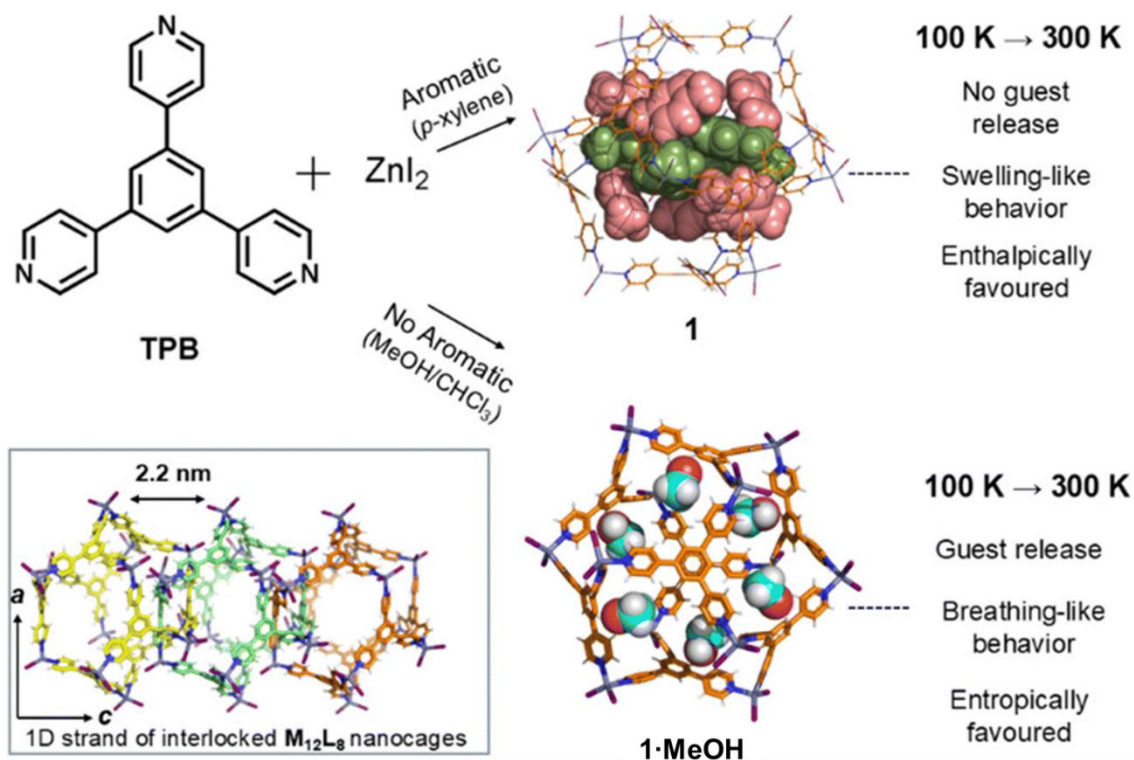


Figure 3.19 — Synthesis of **1** and **1·MeOH** with the inset showing the interlocking of the nanocages.^[143]

3.3.1.1 Structural evolution as a function of temperature of **1**

The templating effect on the dynamic behaviour of the M₁₂L₈ nanocages in **1** and **1·MeOH** is evidenced by their different lattice parameter evolution (Figure 3.20). In **1**, the *a/b* lattice parameters increase from 100 K to 300 K, and the *c*-axis increases from 100 K to 250 K but experiences a small decrease at 300 K. The unit cell volume (*V_c*) variation in **1** in the 250–300 K interval is a decrease of ~50 Å³ (Figure 3.20). The small compression is not because of solvent loss, as the SC-XRD data show that both A and B *p*-xy molecules are in the asymmetric unit. The interpretation of this lattice evolution is that the M₁₂L₈ cages did not suffer a significant change. This behaviour is explained by the templating *p*-xy guests not allowing much compression of the M₁₂L₈ nanocages due to the good interactions with the M₁₂L₈ host structure (*i.e.* π - π contacts in a tight environment). The X-ray structures at 100 K will be named **1@100 K** and at 300 K will be named **1@300 K**. SC-XRD analysis of **1@100 K** resulted in the formula [(ZnI₂)₁₂(TPB)₈]₁₂(*p*-xy), with two ZnI₂, one TPB ligand, one-third of a second TPB in the host sub-structure and two independent (A and B) *p*-xy guest molecules in the guest sub-structure per asymmetric unit. Viewed along the *a*-axis direction, guest A

occupies the upper and lower poles of the $M_{12}L_8$ nanocages, while guest B is in the central area of the cage. In **1**@300 K, guests A and B remain in the cages with minor structural variations with respect to **1**@100 K. The guests A and B occupy slightly different positions. Guest B is a little more flattened or “squeezed” along the c -axis. However, the main information is that the structure is stable, and the guest’s templating effect is very important to fill the $M_{12}L_8$ voids.

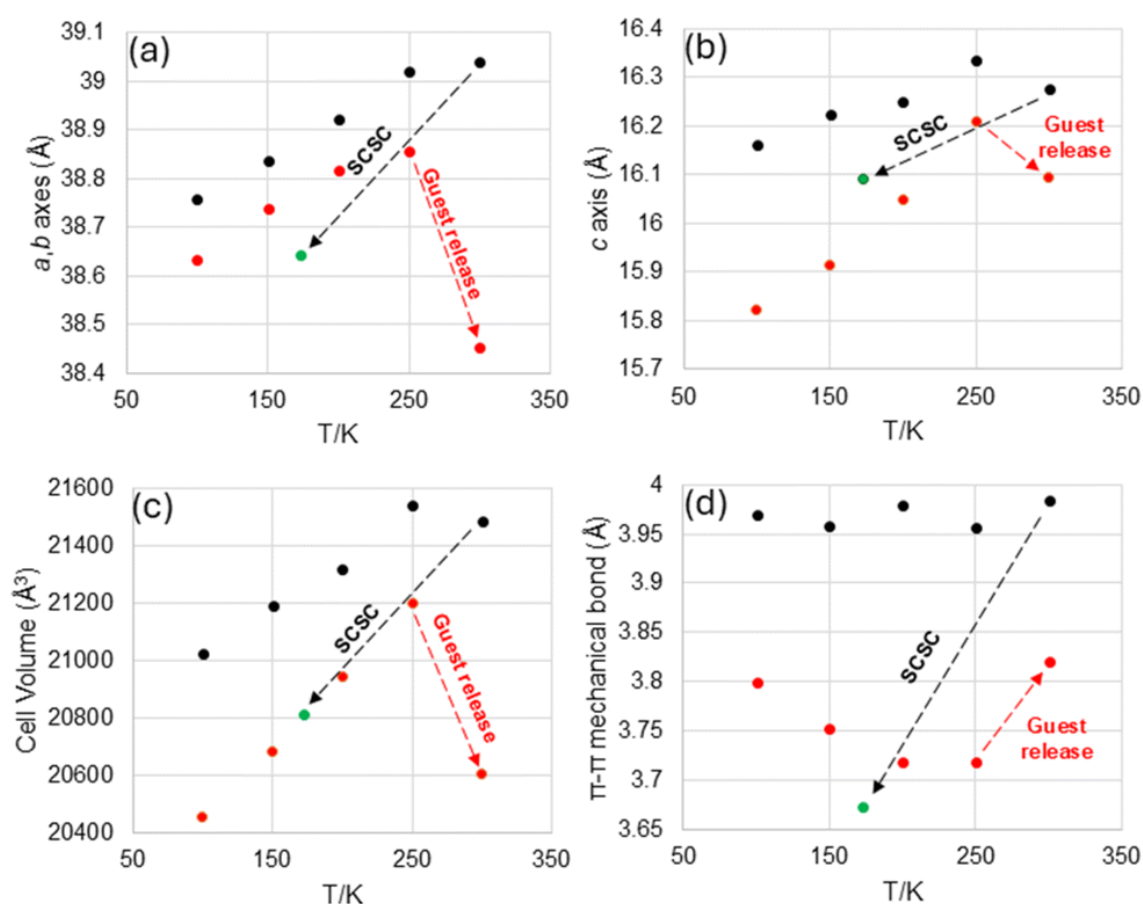


Figure 3.20 — Lattice parameter evolution from 100 K to 300 K, **1** black dots, **1·MeOH** red dots: a) a - and b - axes; b) c -axis; c) unit cell volume (V_c); d) TPB benzene-benzene distances.^[143]

3.3.1.2 Structural evolution as a function of temperature of **1·MeOH**

It is important to notice that large single crystals of $M_{12}L_8$ poly- $[n]$ -catenanes were grown for the first time using a mixture of small guest molecules, like chloroform and methanol, that are not efficient as templating agents, because there are no host–guest aromatic–aromatic interactions. Hence, in this case, there must be an important entropic/enthalpic contribution of the guest sub-structure in the self-assembly of

1·MeOH to form such large single crystals. SC-XRD analysis of **1·MeOH@100 K** resulted in the formula $[(\text{ZnI}_2)_{12}(\text{TPB})_8] \cdot 6(\text{MeOH})$, with two ZnI_2 , one TPB ligand, and one-third of a second TPB as host sub-structure in the asymmetric unit. Only one methanol guest per asymmetric unit (six per M_{12}L_8 cage) could be determined by SC-XRD in the 100–250 K range, whereas at 300 K, methanol was not localised. In **1·MeOH**, the void space considering the methanol guest is 29% of the total unit cell volume. In **1·MeOH**, while from 100 K to 250 K, the behaviour is similar to that of **1**, with an increase in the $a/b/c$ lattice parameters, there is a significant decrease in the lattice vectors a and b (*i.e.* 0.4 Å) from 250 K to 300 K. In this thermal range, the c -axis behaves as it does in the crystal containing p -xy (**1**) with a slight decrease. Compared to **1**, in **1·MeOH**, V_c undergoes a significant variation, decreasing by 600 Å³. In a SCSC guest exchange reaction starting with the same type of M_{12}L_8 PCs-MOCs, V_c was reduced by ~1350 Å³ when p -xy was replaced by *o*-dichlorobenzene (*o*-DCB). In such cases, the main lattice change is in the c -axis, which is decreased by ~0.64 Å, but maintaining the π – π distance of 3.926 Å in the mechanical bonds.

3.3.1.3 Structural analysis of M_{12}L_8 unit cell void volume variation upon temperature increase

An understanding of the dynamic behaviour of the M_{12}L_8 nanocages was obtained by monitoring the variation in the unit cell void volume. The calculated void volume corresponds to the M_{12}L_8 internal space occupied by the guests, and it is important to describe their templating effect. In **1**, the efficient templating of the p -xy guest sub-structure means that it can maintain the increasing trend of the cage's void. It is worth pointing out that with heating **1**, the solvent does not leave the cages. As shown in Figure 3.21a, in general, the V_c variation increases until 300 K. This M_{12}L_8 V_c change is like a *swelling process*. Thermodynamically, in this case, the voids evolution is favoured from an enthalpic point of view as no guest release takes place and the electrostatic interactions are still good (in **1@300 K**, py-centroid to p -xy-centroid is 4.152 Å). In this regard, DFT calculations also revealed that the host–guest interactions for molecules such as NB and p -xy are important with values from 44 to 25 kcal/mol, thus explaining the observed stability. Conversely, **1·MeOH**, upon heating, shows a different trend in the cage volume. It starts with a sharp increase in the void volume, as the guests increase their dynamic behaviour, but at *ca.* 250 K, the void volume shows an abrupt decrease and returns to a similar volume to that at 100 K. After **1·MeOH** is frozen (100 K), and the included guests interact with each other more, the

disorder is reduced. However, upon heating, the solvents move more, increasing the $M_{12}L_8$ cage volume (*i.e.* the fraction of the cell volume occupied by the solvent is higher). Upon reaching 250 K, there is an increase in the guest disorder, and the cages swell to a maximum, and then the solvent leaves the $M_{12}L_8$ cages, inducing a decrease in the cages void volume at 300 K (Figure 3.21b). This void decrease is mainly due to the a/b contraction. This process is like a *breathing effect* and is entropically favoured, which is also corroborated by SC-XRD data, as the crystallographic analysis does not resolve the methanol in the $M_{12}L_8$ nanocages, as methanol has escaped the cages (Figure 3.21b).

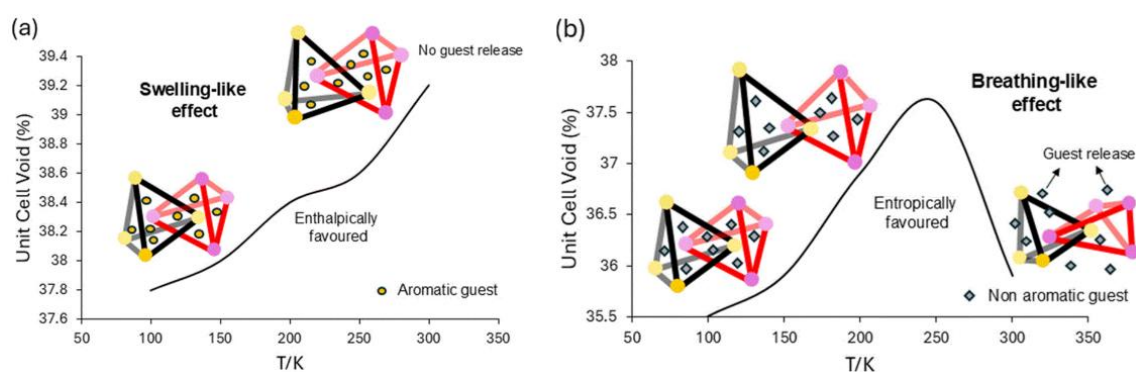


Figure 3.21 — Evolution of the unit cell voids as a function of temperature of: a) **1** with swelling-like effect; b) **1**·MeOH with breathing-like effect.^[143]

In both crystals (**1** and **1**·MeOH), the mechanical bonds remain stable during the external stimuli. Moreover, even if thermal treatments affect the V_c , the high stability is preserved due to the structural topology of the materials.

3.3.2 Nitromethane gas absorption

The synthesis of $M_{12}L_8$ poly- $[n]$ -catenane using small non-aromatic molecules was already presented in the previous chapter using chloroform/methanol. To further understand the molecular trapping of small molecules, single crystals of **1** were grown using benzaldehyde (BA, hereafter **1**·BA) as a guest and then subjected to SCSC guest exchange with nitromethane (NM, hereafter **1**·NM).^[144]

3.3.2.1 Single crystal growth and crystal structure description of **1·BA**

A single crystal of **1·BA** was grown using the standard slow crystallisation experiment using benzaldehyde as a templating agent. SC-XRD at low temperature (100K) (Figure 3.22). X-ray crystallography shows that the material crystallises in the high symmetry trigonal $R\bar{3}$ space group with the following lattice parameters: $a = b = 38.3500(8)$ Å, $c = 15.8061(4)$ Å, $V = 20,132.0(10)$ Å³. The structure corresponds to the poly-[n]-catenane $M_{12}L_8$ interlocked structure, which contains six ordered benzaldehyde molecules per cage (Figure 3.22). In the asymmetric unit, there is one TPB ligand and one third of a second TPB ligand, two ZnI_2 and one benzaldehyde guest molecule. From the X-ray data, the new **1·BA** polycatenane is formulated as $[(TPB)_8(ZnI_2)_{12}] \cdot 6(\text{benzaldehyde})$, considering the ordered part. The structure of **1·BA** is formed of 1D chains in which one single $M_{12}L_8$ cage is interlocked by two neighbouring MOCs. The interlocked cages are formed via mechanical bonds where the distance among the centroids of the benzene rings is $d = 3.755$ Å. The BA guest molecule interacts with the walls of the $M_{12}L_8$ nanocage via aromatic-aromatic interactions. The efficient π - π interactions among both the host (TPB) and guest benzene rings, with a centroid-centroid distance of 3.947 Å (Figure 3.22), stabilise the aromatic guest near the walls of the $M_{12}L_8$ cage. The centre part of the cages is not empty but occupied by disordered guest molecules. The unit cell void space not occupied by ordered BA corresponds to 18.3% of the total unit cell, which is 3686 Å³ (*i.e.* 1229 Å³ per $M_{12}L_8$).

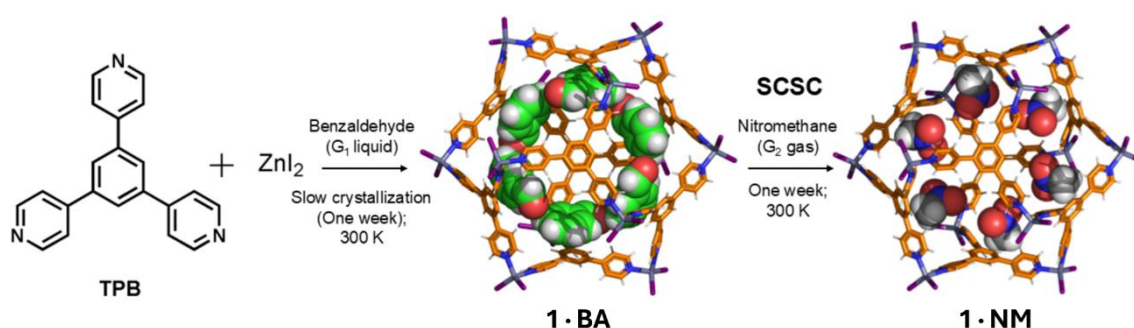


Figure 3.22 — Synthetic scheme of $M_{12}L_8$ poly-[n]-catenane including benzaldehyde (**1·BA**) and the SCSC guest inclusion of nitromethane (**1·NM**) from the gas phase.^[144]

3.3.2.2 Gas-solid guest inclusion of nitromethane via SCSC using **1·BA**

So far, the SCSC guest exchange presented previously involved large aromatic guest molecules because the good host-guest electrostatic interactions help the guest stabilisation in the $M_{12}L_8$ cages. Here, the investigation was carried out to check if nitromethane could be adsorbed by poly- $[n]$ -catenane **1·BA**. A **1·BA** single crystal was mounted in the pin used for SC-XRD analysis and introduced into a sealed chamber containing liquid NM and left for one week at room temperature. After the gas-solid exposure, the crystal was analysed by low-temperature SC-XRD crystallography. The crystal did not show crystal decay, indicating that it was not damaged by the exposure to NM vapours. The crystallographic system and space group were maintained (trigonal, $R\bar{3}$), and the lattice parameters of the crystal measured at 100 K are as follows: $a = b = 38.4738(7)$ Å, $c = 15.7177(3)$ Å, $V = 20,148.8(8)$ Å³. The lattice parameters are very similar to the starting phase **1·BA**. The crystallographic analysis clearly shows that the ordered guest molecule included in the $M_{12}L_8$ interlocked cages is not the aromatic BA but instead is NM (Figures 3.22 and 3.23). This unambiguously evidences that NM was adsorbed by the $M_{12}L_8$ cages of **1·BA** to give **1·NM**. There is one NM molecule per asymmetric unit, which implies that there are six per single $M_{12}L_8$ nanocage. One oxygen from the NO₂ group in **NM** interacts with the pyridine rings of the host $M_{12}L_8$ cage via two C_{py}—H···O weak electrostatic interactions ($d = 2.444$ Å and $d = 2.566$ Å). The NM molecule interacts at the interface of the mechanical bond. The NM inclusion is relevant, as so far, all the guests studied via gas-solid reactions using $M_{12}L_8$ poly- $[n]$ -catenanes have been “large” flat aromatic molecules. It is important to note that the high symmetry of the cages also induces a high symmetry of the guest molecules that are found severely disordered within the cages. Because in some cases two independent guest molecules can be found in the asymmetric unit, one of the guests (*i.e.* the one in the centre of the cage) tends to be disordered. After the guest inclusion, the unit cell void space not occupied by ordered **NM** corresponds to 28.2% of the total unit cell, which is 5676.7 Å³ (*i.e.* 1892.2 per $M_{12}L_8$).

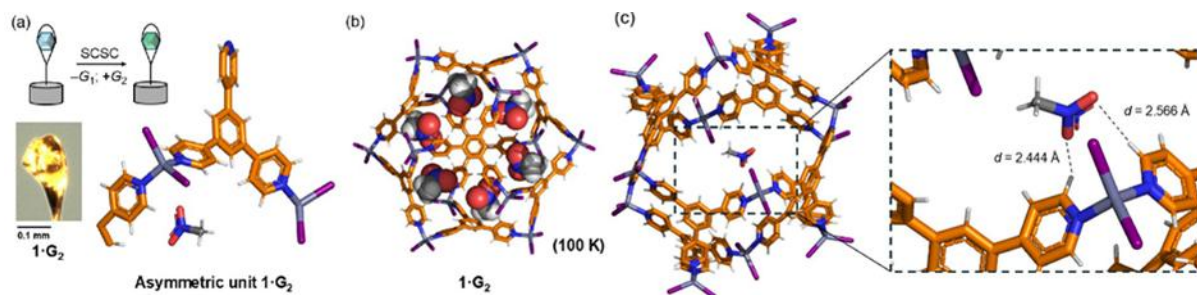


Figure 3.23 — Crystal structure of **1·NM**. a) SCSC guest exchange, picture of the crystal used in the experiment, asymmetric unit; b) isolated $M_{12}L_8$ nanocage filled with six nitromethane molecules; c) one nitromethane molecule in one $M_{12}L_8$ cage in **1·NM**.^[144]

3.4 Conclusions and outlook

It has been demonstrated that by coordinating the TPB ligand with the ZnI_2 , it was possible to obtain a large supramolecular system of interlocked icosahedral MOCs. This kinetic product is trapped using the instant synthesis method, allowing the control of the formation of the assembly of TPB and ZnI_2 . The product obtained in a one-pot reaction was characterised by P-XRD, TGA and ^1H NMR, revealing an amorphous phase (**a1**) that was transformed into a crystalline phase (**1**) when exposed to a nitrobenzene environment. Using a slow-crystallisation approach, it was possible to obtain a mixture of single crystals, $M_{12}L_8$ poly- $[n]$ -catenane (**1**) and a coordination polymer (**2**). In the absence of solvent, using the neat grinding approach, a new amorphous phase (**a1'**) is obtained just after 15 minutes of grinding. This powder can uptake aromatic molecules like the xylenes isomers and transform into the crystalline phase (**1**). Merging SC-XRD and solid-state DFT calculations allowed the definition of the interaction energies of the system (including the host-guest and guest-guest interactions). This study, performed mainly in the powder state, opens up a wide range of applications, such as the use of these cages for the selective trapping of aromatic isomers, which will be explored in the future for a possible industrial application.

The trapping of aromatic molecules and description of the guest exchange were further explored in the second section. The presence of a cooperative effect that allows the entrance and exit of guest molecules inside the cages in the solid-state is described through a series of gas-solid SCSC guest exchange reactions. Using SC-XRD and DFT

calculations, the binding sites of the large $M_{12}L_8$ icosahedral cages are highlighted. These cages present anchoring sites for aromatic molecules such as nitrobenzene, *p*-xylene or *o*-dichlorobenzene. Experimental evidence supported by theoretical calculations defined a preferential inclusion order of the studied guests, with NB being the favourite over *p*-xy over *o*-DCB. Multiple gas-solid SCSC guest exchanges proved the robustness and stability of the frameworks in the solid state, even after weeks exposed to the guest environment. The description of the guest inclusion and exchange mechanism was proposed using a combination of SC-XRD, DFT calculations and solid-state NMR. The results showed that the pyridine ring of the TPB rotates around the static benzene ring. This rotor-like behaviour has a low energy barrier that allows the guest entrance into the cages, stabilising the overall structure when fixed in the binding site. Due to the robustness of the framework, dynamic behaviour and presence of binding sites, this material is a good candidate for molecular recognition of aromatics and can be used in sensing applications.

The response of the cages to variable temperatures and the trapping of non-aromatic molecules was investigated in the third part of this first chapter. The mechanical bonds in the $M_{12}L_8$ poly- $[n]$ -catenane ensure stability even after exposure to external stimuli. Thermal treatments induce a change in the lattice parameters, but maintain the structural topology without modifying the symmetry of the system. Upon heating, the lattice evolution is different depending on the included guests. In the presence of included *p*-xy, the $M_{12}L_8$ shows a swelling-like effect, but if the included guests are non-aromatics (methanol/chloroform), a breathing-like effect with guest release is observed. Also, through a gas-solid process, nitromethane can be trapped in the cages and help stabilise the structure. This is particularly interesting and further studies aimed at the inclusion of toxic gases such as SO_2 , NO_x compounds or for carbon capture applications, as the important theme of CH_4 and CO_2 trapping has never been more relevant than it is today.

4 Paracetamol inclusion in mechanically interlocked nanocages

Having a clear understanding of the role of aromatic molecules as templating agents in the self-assembly of TPB and ZnI_2 into M_{12}L_8 poly- $[n]$ -catenanes is important. In this regard, an interesting advance in this research field was the inclusion of larger molecules with respect to the previously used NB, *o*-DCB or Tol. For this reason, experiments focusing on the inclusion of a drug, like paracetamol (PC), in the poly- $[n]$ -catenane and its 3D structural elucidation, combining XRD data and DFT calculations, were carried out.^[145] After many attempts to grow single crystals of the M_{12}L_8 poly- $[n]$ -catenane using paracetamol as a templating agent (using the standard slow crystallisation technique applied before), no successful result was obtained. Although single crystals were formed, the guest content could not be determined. Therefore, in the absence of single crystals containing paracetamol, the idea was to perform guest inclusion of the PC molecules into the amorphous M_{12}L_8 poly- $[n]$ -catenane (**a1**), which was previously demonstrated to lead to a crystalline phase (**1**) upon guest inclusion. Due to the microcrystalline nature of the material, the 3D structure solution was carried out using P-XRD structure solution in combination with SC-XRD data and DFT calculations.

Developing greener strategies for minimising time and solvents in the synthesis of supramolecular structures is important from a Green Chemistry point of view. The synthesis of interlocked M_{12}L_8 cages, the poly- $[n]$ -catenane, was done by neat grinding of TPB and ZnI_2 for 15 min at room temperature. The product of the solid-state reaction was the amorphous product **a1**. The guest inclusion was carried out by post-synthetically stirring a suspension of **a1** for 12 h at room temperature in a concentrated methanol solution of paracetamol (*ca.* 1 g/15 ml). Then, the suspension was filtered and analysed by P-XRD. The X-ray analysis showed that the diffractogram turned crystalline with Bragg reflections characteristic of the poly- $[n]$ -catenanes of

interlocked $M_{12}L_8$ cages but with an important background component and severe peak overlap (Figure 4.1a). The transformation corresponds to an amorphous-to-crystalline **a1** $\rightarrow$ **1·PC** process.

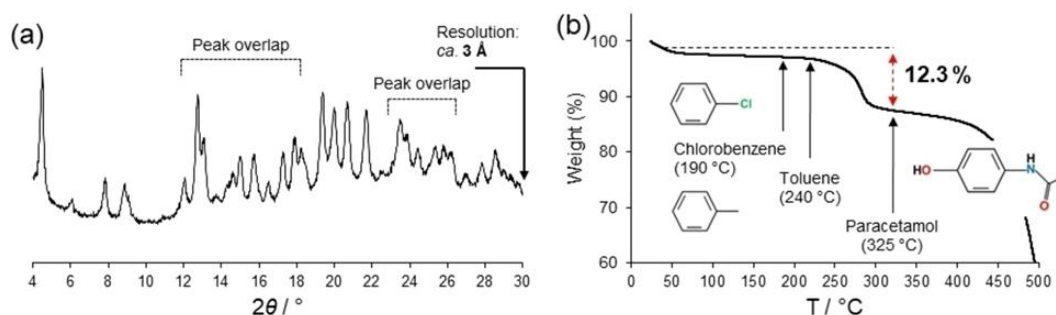


Figure 4.1 — a) P-XRD pattern of **1·PC** showing severe peak overlap and low resolution; b) TG plot of **1·PC** with the release of paracetamol and comparison with the release temperature of chlorobenzene and toluene.^[145]

TG analysis was carried out to determine the amount of paracetamol included in **1·PC**. The weight loss corresponds to 12.3%, as shown in Figure 4.1b, which corresponds to *ca.* 6 PC molecules (Materials and methods, Figure 9.4). The mass loss fits with that of paracetamol calculated from ^1H NMR (Materials and methods, 9.2.1.2), confirming that the drug was included in the amorphous phase **a1** following a transformation from the amorphous to the crystalline state. The temperature at which PC is released is higher than the temperature observed in aromatic guests, according to the different boiling points, but also suggests that paracetamol is kept in the solid structure in an efficient way. For instance, in a microcrystalline sample of TPB- ZnI_2 poly- $[n]$ -catenane, the encapsulated guests, chlorobenzene and toluene, are completely released at 190 °C and 240 °C, respectively, while in **1·PC**, complete guest release occurs at ~ 325 °C, as shown in Figure 4.1b.

Crucially, **a1** can also be synthesised using ZnX_2 salts (where $\text{X} = \text{Br}$ and Cl), resulting in amorphous phases **a2** and **a3**, respectively, which can be used to uptake various aromatic and nonaromatic guest molecules. Thus, the amorphous-to-crystalline transformation upon paracetamol inclusion was also monitored for the chloride and bromide counterparts of the amorphous catenanes in the liquid-solid phase. In all the experiments, short-range to long-range order transformations were observed (Appendix 13.10 and 13.11). **1·PC** did not become amorphous when left in contact with the atmosphere for more than a month. This confirms that the guest is

not volatile, thus keeping the poly- $[n]$ -catenane in the crystalline state after filtration. The paracetamol inclusion experiments were repeated four times, and in all the cases an amorphous-to-crystalline transformation (**a1** $\rightarrow$ **1-PC**) was observed. In all the experiments, the samples showed different degrees of crystallinity, probably due to different guest loadings. The P-XRD pattern corresponding to that of the $M_{12}L_8$ poly- $[n]$ -catenane with reflections corresponding to Miller indices (2-10) and (101) is clearly observed, fitting the simulated P-XRD patterns from single crystals of $M_{12}L_8$ poly- $[n]$ -catenanes containing aromatic guests.

Poly- $[n]$ -catenane **1** is unstable in aqueous media because the Zn-N coordination bond breaks to yield TPB and zinc halides, releasing the guest molecules from the $M_{12}L_8$ nanocages, which can be quantified by NMR (Materials and methods 9.2.1.2). From the solution ^1H NMR data, the included paracetamol in **a1-a3** ranged from 2 to 6 molecules per $M_{12}L_8$ cage. Values higher than those, which the $M_{12}L_8$ cages can theoretically include (*i.e.* according to the cage volume and the guest volume), have not been observed. This excludes the scenario that the released paracetamol measured by NMR corresponds to guests attached to the surface of **a1-a3**. Regarding the variability of the included paracetamol in all the experiments, it might be related to the structure of the amorphous poly- $[n]$ -catenanes formed in the solid state, as in each reaction, the product structure of the amorphous phase can be different. For instance, it is not known whether the 1D chains of the interlocked $M_{12}L_8$ cages are interwoven structures, which might cause problems in filling and packing the 1D chains after the amorphous-to-crystalline transformation and thus filling the $M_{12}L_8$ empty cages, resulting in this statistical variation. Additionally, if the $M_{12}L_8$ cages are squeezed in such a way that the opened windows are completely closed, guest inclusion might yield different values.

4.1 Synergistic approach for determining the crystal structure of a challenging sample using P-XRD data and solid-state DFT

The most powerful technique for the 3D structure elucidation of a crystalline solid is SC-XRD. However, in this case, because single crystals did not include

paracetamol, full structure determination of **1** was attempted from P-XRD data using the product from the **a1** $\rightarrow$ **1**·PC reaction. It is important to note that determining the structure of **1**·PC from P-XRD data is challenging due to the following aspects: i) Despite the inclusion of paracetamol, the sample has a significant background, which is often a problem in the indexing and profile fitting process; ii) because the sample was synthesised by solid-state grinding, the particle sizes are intrinsically small and Bragg reflections overlap significantly (Figure 4.1a); and iii) the P-XRD data have been recorded up to 30 degrees in 2θ to create a low resolution dataset (2.99 Å), as it is known that many materials obtained after solid state reactivity show poor crystallinity, so this case is also challenging from a resolution point of view. Thus, the indexing step and space group determination, one of the most critical points in the structure solution process, could not be carried out using P-XRD data. Despite the low quality of **1**·PC, from a crystallinity and resolution point of view, structure solution can still be carried out if experimental and theoretical DFT techniques are combined. According to the SC-XRD data, in all the SCSC guest exchange reactions carried out in crystals of M₁₂L₈ poly-[*n*]-catenanes were affected by small lattice variations, and the trigonal space group was maintained. Therefore, indexing and space group determination of **1**·PC were carried out using the symmetry of a known crystal structure of M₁₂L₈ poly-[*n*]-catenane containing NB determined at room temperature.

Thus, the starting unit cell was: $a = b = 38.6805$ Å; $c = 16.0202$ Å; $\alpha = \beta = 90^\circ$ and $\gamma = 120^\circ$; $V = 20,758$ Å³. The space group was (*R*-3). With these lattice parameters and space group, a Pawley refinement was carried out using the DASH^[146] program. The refined cell was: $a = b = 38.4795$ Å; $c = 15.8455$ Å; $\alpha = \beta = 90^\circ$ and $\gamma = 120^\circ$; $V = 20,319$ Å³ with an acceptable fit of $\chi^2 = 4.77$. This unit cell was used to perform the structure solution from P-XRD using laboratory data. **1**·PC was solved in the direct-space using the simulated annealing (SA) method implemented in the DASH^[146] program. For the structure solution, a first structural fragment (**SF1**), comprising two ZnI₂, 1.3 TPB molecules, and a second structural fragment (**SF2**), consisting of one PC molecule, were used as a starting structural model (Figure 4.2a).

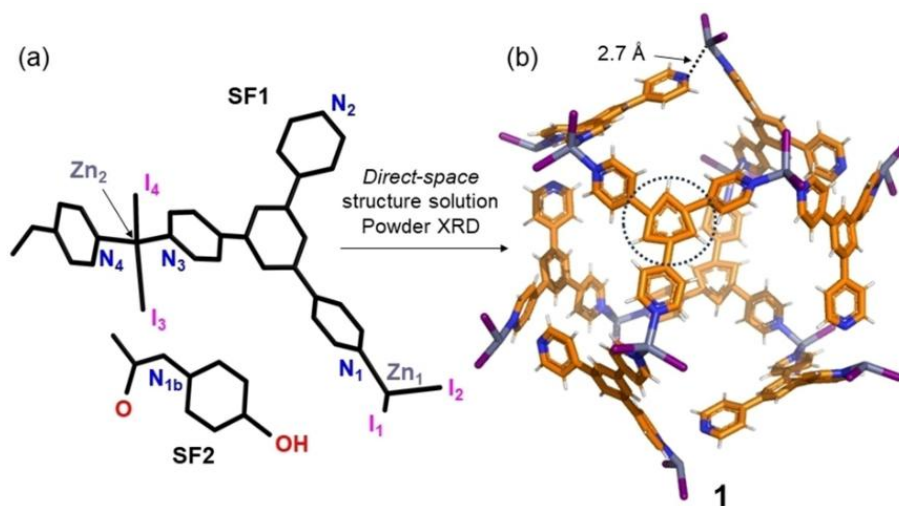


Figure 4.2 — a) Structural fragments **SF1** and **SF2** used in the direct-space calculations; b) crystal structure obtained by using *DASH*^[146] program.^[145]

One PC molecule was considered because of the experimental ¹H NMR and TG data, which indicated that 6 guest molecules are included per M₁₂L₈ cage (*i.e.* *R*-3 has 6 symmetry operators). The structural model was not treated as a rigid body, and only the torsion angles (τ) of the M₁₂L₈ host were allowed to rotate during the structure solution process. Seven torsion angles ($\tau_1, \tau_2, \dots, \tau_7$) in the structural model were defined considering **SF1** and **SF2**. In total, 13 structural variables (Γ), including the three positional variables $\{x, y, z\}$, the three orientational variables $\{\theta, \Phi, \Psi\}$ and the seven torsion angle variables $\{\tau_1-\tau_7\}$, define the structural model. In the P-XRD structure solution, it is important to note that the process of finding the global minima (*i.e.* the structure with the lowest R-factor) is like exploring an *N*-dimensional hypersurface where *N* is the number of structural variables (Γ). In a structure refinement, it is assumed (generally) that an initial model has been obtained from a similar structure in a database (**SF2**) or from a Patterson or Direct methods (**SF1**) structure solution. Additionally, for a successful refinement, the initial model must be sufficiently close to the true crystal structure for an acceptable Rietveld refinement.

From all DASH-solved structures, the structure with the lowest χ^2 was selected for complete structural analysis (Figure 4.2b). The crystal structure solution showed the incomplete formation of the M₁₂L₈ nanocage with a distorted six-member ring (*i.e.* the six-member ring could be recognised) generated after the symmetry operators. The other structural aspect that does not yield a chemically reasonable structure involves the pyridine (py) rings generated by the symmetry operators, which are too far to be considered a reasonable py-Zn coordination bond (*ca.* 2.697 Å), as shown in

Figure 4.2b. This could be due to the low-resolution P-XRD data used in the structure solution. Moreover, the paracetamol guests are too close to each other, leading to a molecular arrangement without chemical meaning (Appendix 13.12). The fact that **1•PC** was not completely solved using P-XRD could be because the obtained structure was trapped in a local minimum in the Γ -dimensional hypersurface. Thus, we decided to use DFT calculations to explore if the structure could be further improved (by using the total energy of the model system as an additional parameter to be minimised) and converge into a structure with reasonable geometries that could be, if necessary, used in a new Rietveld refinement step. Thus, DFT structure optimisation helps to eliminate inaccuracies due to the low resolution and peak overlap of the P-XRD dataset, possibly resulting in a more reliable structure from a chemical point of view.

The best structure obtained from direct-space, **1•PC**, was used in the DFT optimisation procedure. DFT calculations were performed in collaboration with Prof. Famulari, under periodic conditions and with symmetry constraints. It is important to note that QM optimisation methods are capable, with a reasonable starting guess geometry, of reaching the closest minima of the potential electrostatic surface (PES) while, in general, maintaining the overall symmetry of the analysed structure. Thus, even if many independent degrees of freedom were used, the DFT calculations converged with reasonable computational costs. The outcomes yield good $M_{12}L_8$ cage structures and guest geometries, in which the distorted rings in the initial nonoptimized structure (**1•PC**) became flat benzene rings generated by the symmetry operators. Likewise, all py-Zn coordination bonds were coherent with the previously observed SC-XRD structures with distances ranging from 2.09 Å to 2.12 Å (Figure 4.3).

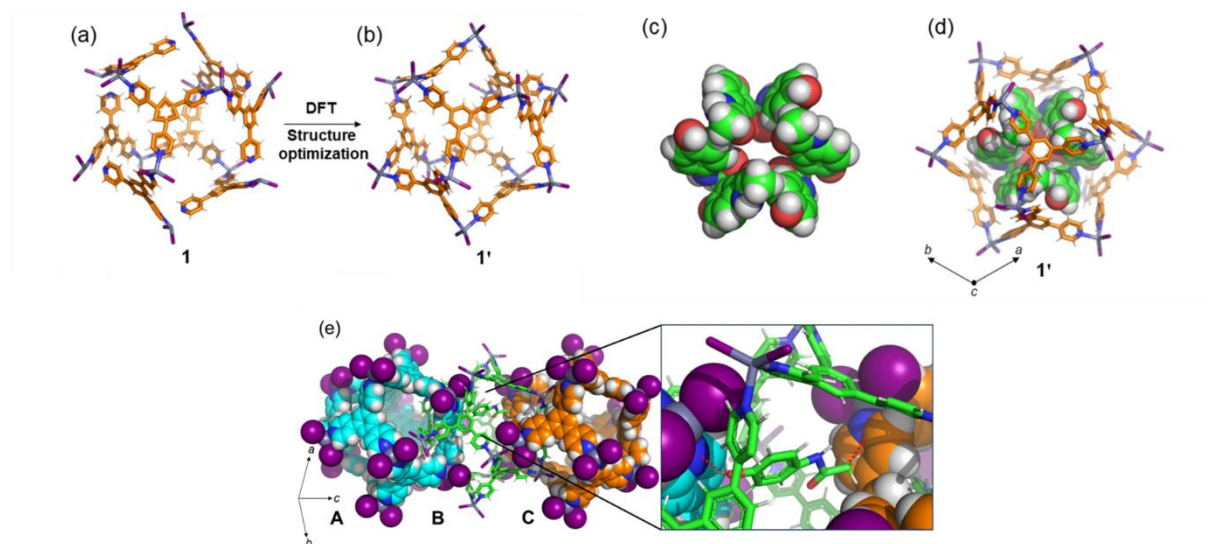


Figure 4.3 — Crystal structural model of: a) **1**; b) DFT optimised **1'**; c) isolated cluster of six paracetamol guest molecules; d) cluster included in the cage; e) expanded view of the included paracetamol interacting with the two adjacent cages.^[145]

In the DFT calculations, the unit cell used for the structure solution was maintained, which is essential in the DFT geometry optimisation step to match the experimental P-XRD data. The DFT-optimised structure shows good PC geometry, and guest-guest contacts are reasonable (Figure 4.3b). In fact, we can observe good alignment of the MEPs of the PC molecules. The DFT-optimised structure is hereafter named **1'·PC**.

The lattice parameters and space group used for the structure determination were subjected to a further LeBail (structureless) refinement using GSAS (General Structure Analysis System) software^[147]. The LeBail refinement led to a good profile fitting with $R_{wp} = 2.98\%$, indicating a correct indexing and space group determination (Appendix 13.13). Then, using the unit cell from the LeBail refinement, **1'·PC** was introduced to GSAS, and the Rietveld refinement was started. The structural model was “fixed” using angles and bond distances obtained in the DFT-optimised structure (*i.e.* **1'·PC**). Standard restraints were applied to bond angles and bond lengths, and planar restraints were applied to the benzene and phenyl rings. Common isotropic displacement parameters were fixed for all non-hydrogen atoms, and the isotropic displacement parameters of H atoms were set at 1.2 times this value. The final Rietveld refinement was $R_{wp} = 4.67\%$ for a structure with the formula $[(TPB)_8(ZnI_2)_{12}] \cdot 6(PC)$ (Appendix 13.13).

1'·PC shows that the poly- $[n]$ -catenane formed from interlocked $M_{12}L_8$ nanocages via π - π interactions (3.347 Å), responsible for the mechanical bond formation and the generation of the 1D chains, includes PC. **1'·PC** contains six PC molecules per $M_{12}L_8$ nanocage, corroborating the ^1H NMR and TG analysis results. Interestingly, PC guests are oriented differently from the other $M_{12}L_8$ poly- $[n]$ -catenane structures, including other aromatic guests (nitrobenzene, *o*-dichlorobenzene, *p*-xylene, etc.), described thus far, in which guests are situated just below the aromatic TPB rings and stabilised through aromatic-aromatic interactions ranging from 44 to 25 kcal/mol, as determined by DFT.

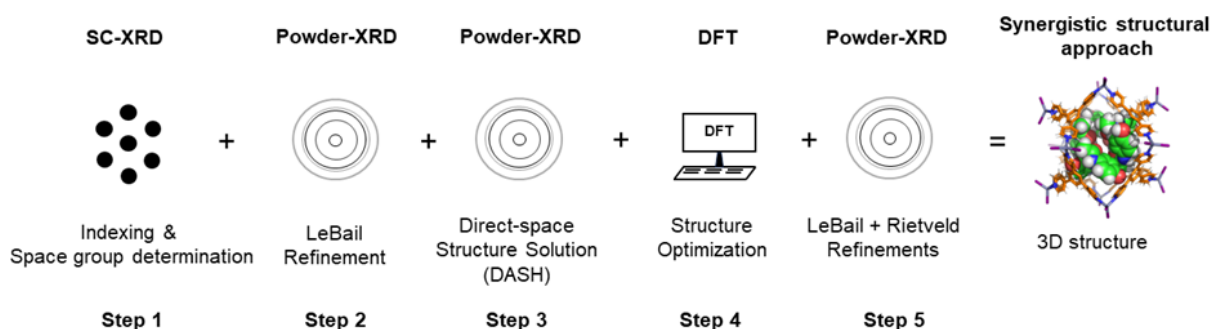


Figure 4.4 — Multi-step approach using X-ray diffraction data and DFT calculations for solving a challenging structure from powder XRD data.^[145]

4.2 The crystal structure of **1'·PC**

In **1'·PC**, PC is in a position like in the room temperature SC-XRD structure containing two *p*-xy guests in the asymmetric unit. The PC guest is in the type B position following the structural description reported in the previous chapter. Because PC is longer (8 Å) than *p*-xy (5.9 Å), six PC molecules cannot fit in the type A position via efficient aromatic-aromatic interactions; hence, PC sits in the central part of the $M_{12}L_8$ cage (type B), optimising the electrostatic interactions in a different way (*i.e.* not via host-guest π - π interactions). In fact, the PC included in one cage interacts with two interlocked $M_{12}L_8$ cages, forming the 1D chains of cages propagating along the *c*-axis (Figure 4.3b and 4.3c). The first short contact interaction (2.534 Å) occurs among the –OH group of the PC, which is oriented towards the N atom of the pyridine of TPB from cage A (Figure 4.3c). The oxygen atom in the alcohol group also interacts

with the aromatic C–H group of the pyridine of TPB (2.367 Å). The methyl group of PC interacts via C–H $\cdots\pi$ interactions with the benzene ring of TPB (2.383 Å) from the adjacent cage C (Figure 4.3c).

In each M₁₂L₈ cage (cage B), PC guests mainly interact with two TPB ligands belonging to interlocking cages A and C (Figure 4.3c). Within a given cage, PC also interacts with neighbouring PC molecules, defining a cluster of guests in the central part of the M₁₂L₈ nanocage (Figure 4.3b and 4.3c). Thus, guest-guest interactions are also important for the stabilisation of the M₁₂L₈ cages.

4.3 Packing efficiency of paracetamol in M₁₂L₈ interlocked nanocages

The structural elucidation of **1'·PC** is crucial for determining how many guests can be included in the M₁₂L₈ cages of TPB-ZnI₂ poly-[*n*]-catenanes. Using a probe with a radius of 1.2 Å, **1'·PC** shows that the void left per unit cell is 13.4% (2722 Å³), considering that in one cell there are 3 cages; in one single cage, there are still 907 Å³ that can be filled by additional PC (Appendix 13.14). From **1'·PC**, by manually removing the guests and calculating the remaining void space, using the volume of the empty M₁₂L₈ cage 2269 Å³ (*i.e.* 6807/3), the volume occupied by one PC molecule inside a M₁₂L₈ cage is 2269 Å³ – 907 Å³ = 1316 Å³, which is divided by 6 paracetamol molecules per cage to obtain 227 Å³ per PC molecule. Therefore, another ~4 paracetamol guests (907 Å³ / 227 Å³) can be included in one M₁₂L₈. From these calculations, we expect that a fully loaded M₁₂L₈ nanocage will contain approximately 10 paracetamol molecules per M₁₂L₈ cage. This is realistic because 12 *p*-xy guests can fit in one M₁₂L₈ cage, as seen in the previous chapter. It must be said that *p*-xy is symmetric and smaller, while PC is asymmetric and slightly larger. These two aspects have to be considered in the construction of the unit cell contents by the asymmetric unit and the symmetry operators.

4.4 Solid-state DFT calculations

Studying the strength of the interactions among host and guests in systems involving MOCs is important to enhance our knowledge about their guest inclusion/exchange properties. Therefore, to obtain further insights into the host-guest affinity, molecular modelling analysis was carried out. DFT calculations (carried out as explained in section 3.1.5) have been performed. The calculations were aimed at determining the host-guest energy interactions, considering a PC guest interacting with the TPB moiety at the internal walls of the $M_{12}L_8$ nanocages. The geometry of the host/guest complex has been fully optimised.

The total stabilization energy per guest molecule was determined by calculating the host-guest mean interaction energy ($E_{host-guest}$): the energy difference between the overall crystalline energy (per unit cell immersed in the crystalline structure, *i.e.* periodical conditions) and the sum of the energies of the empty crystalline host structure (per unit cell, immersed in the empty crystalline structure, *i.e.* periodical conditions) and the energy of the isolated PC molecules (18 per unit cell). The outcome value was quite high, 46 kcal/mol per PC molecule, demonstrating the relevance of the guest molecules inside the $M_{12}L_8$ nanocages in the overall stability of the crystalline structure. Clearly, the favourable guest-guest pair interaction contribution of about 2 kcal/mol must be considered, which is intrinsically included in the host-guest total stabilisation energy. Thus, the net stabilisation is about 44 kcal/mol per PC molecule (Figure 4.5), which is comparable to the value observed for the TPB- ZnI_2 poly- $[n]$ -catenane including NB. These $E_{host-guest}$ values highlight the importance of guest inclusion and may be one of the main driving forces of guest absorption by the amorphous phase and in amorphous-to-crystalline transformations. The guest-guest orientation within the cages maximises the interactions among guests by orienting themselves (*i.e.* PC molecules) in an antiparallel manner within the $M_{12}L_8$. This is also corroborated by the MEP analysis, shown in Figures 4.5a-c, where negative and positive areas of the PC guests interact with the corresponding counterpart of the TPB moiety to optimise attractive forces.

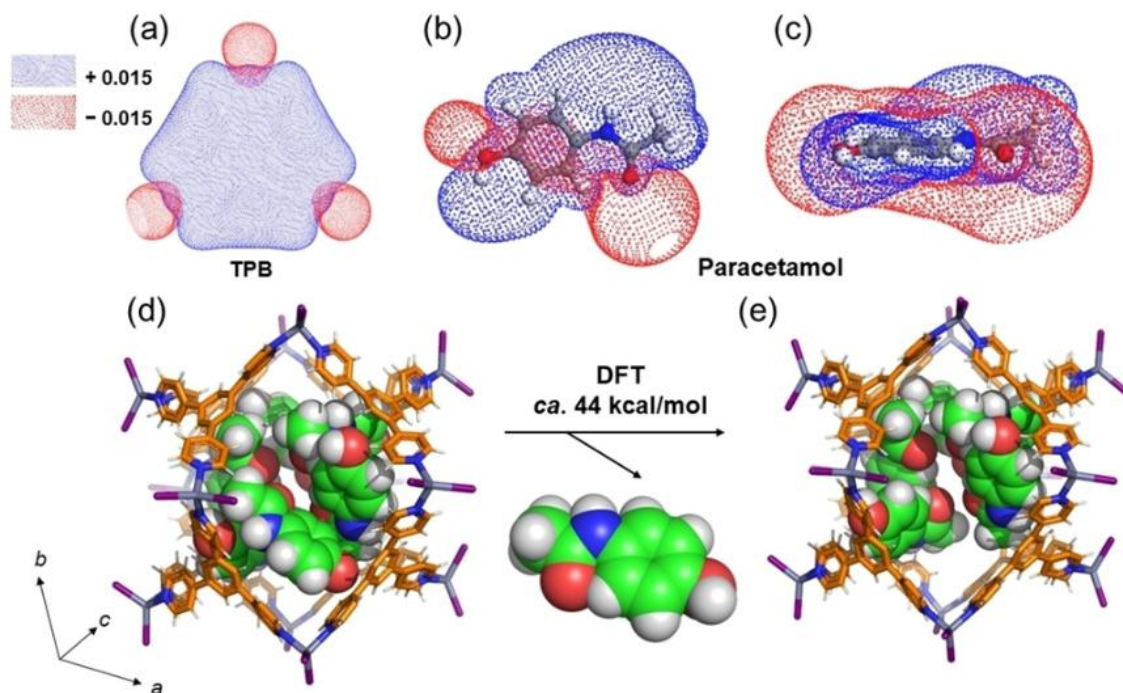


Figure 4.5 — DFT computed MEP for a) TPB; b),c) PC. Scheme for the DFT host-guest energy d) before and e) after removal of one paracetamol.^[145]

4.5 Kinetic trapping of paracetamol within the M₁₂L₈ nanocages via instant synthesis

The mechanochemical reaction yielding **a1** results in the self-assembly of amorphous catenane from mechanically interlocked M₁₂L₈ nanocages, as no other crystalline structures are observed. Such behaviour is like that observed in the solution state when the self-assembly method involves instant synthesis (Chapter 3) in the absence of aromatic guests, which also yields an amorphous phase formed from interlocked M₁₂L₈ cages. Thus, solid-state synthesis by neat grinding selectively yields poly-[*n*]-catenanes made of M₁₂L₈ nanocages. As it is a fast crystallisation process, it is considered a kinetic product. The synthetic path in the solid-state by neat grinding is an entropically favoured self-assembling process due to the severe disorder in **a1**, while PC guest inclusion is enthalpically favoured. Since kinetic products are metastable structures, it is possible to exploit their structural adaptability (dynamic behaviour), for instance, for guest inclusion, as demonstrated by the PC drug uptake. Importantly, M₁₂L₈ poly-[*n*]-catenane is stable and can be reused several times because

the guest can be removed whilst keeping its structural integrity. This is in part due to the mechanical bond that brings dynamic behaviour and structural stability to the $M_{12}L_8$ interlocked cages, which strongly interact with one another via electrostatic interactions. From the guest loading point of view, using the amorphous phases (**a1-a3**), the maximum achieved loading was 6 molecules per cage, which is 60% according to the theoretical limit (~10 guests). To improve the guest loading, a different PC inclusion approach was explored by using the instant synthesis method (*i.e.* under kinetic control). The idea is to exploit the immediate formation of poly- $[n]$ -catenanes using the instant complexation of TPB ligands by Zn(II) in the presence of a concentrated solution of PC. When complexation occurs, the guests are trapped, and if they are stabilised in the $M_{12}L_8$ cages, they can be stored in the solid-state. Thus, a solution of the tridentate ligand was prepared by dissolving TPB (31 mg) in 4.5 ml of chloroform and 3 ml of methanol. To this TPB solution, 186 mg of paracetamol was added. Crucially, PC is very soluble in the TPB solution because it dissolves immediately without the need for stirring, forming a transparent and homogeneous solution. Then, a methanolic solution of ZnI_2 (52 mg) was quickly added to the stirred TPB and PC solution. A white precipitate formed instantaneously (hereafter named **1IS**, where IS stands for instant synthesis), and after filtration, using a low-vacuum water pump, the sample was analysed by P-XRD. The diffractogram showed that the material was crystalline but had a significant background (Appendix 13.15), which is consistent with the P-XRD pattern of **1·PC**. Interestingly, the same sample measured 12 hours later showed better crystallinity, suggesting that the chains of the $M_{12}L_8$ nanocages reorganised, yielding a more packed structure. The sample, analysed by TG analysis, showed that the weight loss was *ca.* 14%, which corresponds to ~7 (6.8) PC guest molecules. Significantly, a second sample synthesised using the same approach gave 6.4 guest molecules included in the $M_{12}L_8$ nanocages with a 13.3% of weight loss. In both cases, the quantity of PC included was less than 10 molecules per cage, as estimated from the **1'·PC** X-ray structure. Compared to guest inclusion by single crystal formation, which usually requires several days, alternative approaches such as solid-state grinding and instant synthesis have led to significant advances in the synthesis of MIMs, such as polycatenanes self-assembled from large $M_{12}L_8$ cages, and in their guest-behaviour.

4.6 Conclusions and outlook

In this chapter, the trapping of paracetamol in the $M_{12}L_8$ nanocages was illustrated. Because the direct formation of single crystals of the interlocked cages containing PC was not possible, the inclusion of PC was carried out using the amorphous phase of the $M_{12}L_8$ polycatenane obtained by mechanochemistry by immersing it in a PC solution. Structural confirmation was carried out by a combination of XRD data and solid-state DFT calculation because the low quality of the P-XRD data did not allow *ab initio* structure determination. Using this combined approach, it was possible to confirm that the structure corresponds to the $M_{12}L_8$ poly-[*n*]-catenane having six PC guest molecules per cage, confirmed by TGA and ^1H NMR. Once the PC is encapsulated, it can be released because the cage in an aqueous environment is not stable and is destroyed. In this case, the TPB ligand, insoluble in water, can be recovered and reused for other preparations. The controlled release is important for future studies in the field of drug release. The material must be subject to toxicological and eco-toxicological testing, but the capability to include drug molecules and the controlled release is a good initial point for future studies in the field of drug release. The capture and controlled release are important not only for drug molecules, but also open the study of other types of molecules. For example, the trapping of two different reactants that can position in a very stereospecific manner could allow the reaction in the cage, followed by the controlled release of the product. The use of $M_{12}L_8$ interlocked cages as potential nanoreactors will be investigated in the future.

5 *Ligand diversification*

One of the main features that supramolecular assemblies like MOFs and MOCs have in common is the extreme diversification that can occur in the final architecture upon a slight change in one of the structural subunits. For this reason, one part of the PhD focused on the functionalization of TPB to obtain very similar ligands but with different moieties, and to use these ligands in coordination with the zinc salts. The aim was to check if the geometric features persisted and the icosahedral interconnected cages still formed, or if the final product was completely different, yielding new supramolecular structures.

The first approach was to append a small ancillary group to the pyridinic moiety, such as a methyl group. So, the first step was to synthesise the 2,4,6-tris(2-methylpyridin-4-yl)benzene (hereafter mTPB) to then coordinate it with zinc halides. The other TPB modification was to elongate the TPB “arm”, adding another phenyl group in between the central benzene and the pyridine to get 2,4,6-tris(phenyl-4-pyridyl)benzene (hereafter extTPB). In this way, we could check if larger ligands would form the same but larger $M_{12}L_8$ cage or if the geometrical constraints would prevent its formation.

The most direct synthetic route to obtain functionalized aromatic compounds is to go through a Suzuki-Miyaura coupling.^[148] It works starting from 1,3,5-tribromobenzene and three equivalents of the desired functionalized boronated pyridine in the presence of a base and a palladium ferrocene catalyst. With a methyl group on the boronated pyridine, the resulting product is the mTPB ligand. With the additional phenyl group, the resulting product is the extTPB ligand. The raw products were purified by column chromatography and characterised by NMR, mass spectroscopy, IR, SC-XRD and P-XRD techniques. The mTPB ligand is later used in coordination with $ZnBr_2$ to test if the additional methyl group will hinder the self-assembly into the interlocked coordination cages. The outcome of the self-assembly is the formation of a new bidimensional (2D) MOF with an interesting trigonal topology and potential for application in areas such as gas adsorption or electron conductivity.

5.1 Synthesis and isolation of mTPB using Suzuki-Miyaura coupling

The simple addition of a methyl group on every pyridinic moiety of the TPB could influence the final result of a self-assembly process due to electronic and steric reasons.

Three methyl-substituted pyridines were bound to the benzene by cross-coupling their boronated derivatives to 1,3,5-tribromobenzene. The quality of the synthesis, after purification by chromatography column, was confirmed by NMR, IR and mass spectrometry techniques (see Materials and methods). The product was recrystallised in chloroform, and by evaporation, single crystals were obtained and analysed by SC-XRD. The single crystal is considered stable at room temperature as there was no evident decay in the crystal morphology when selected, mounted on the loop and then subjected to SC-XRD analysis. The structure of mTPB ($C_{24}H_{21}N_3$), solved at 300 K, is here reported to be in the triclinic space group $P-1$ with the following unit cell parameters: $a = 7.8599(2) \text{ \AA}$, $b = 10.2595(3) \text{ \AA}$, $c = 13.1951(4) \text{ \AA}$, $\alpha = 85.688(3)^\circ$, $\beta = 89.484(3)^\circ$, $\gamma = 75.632(3)^\circ$, $V = 1027.79 \text{ \AA}^3$.

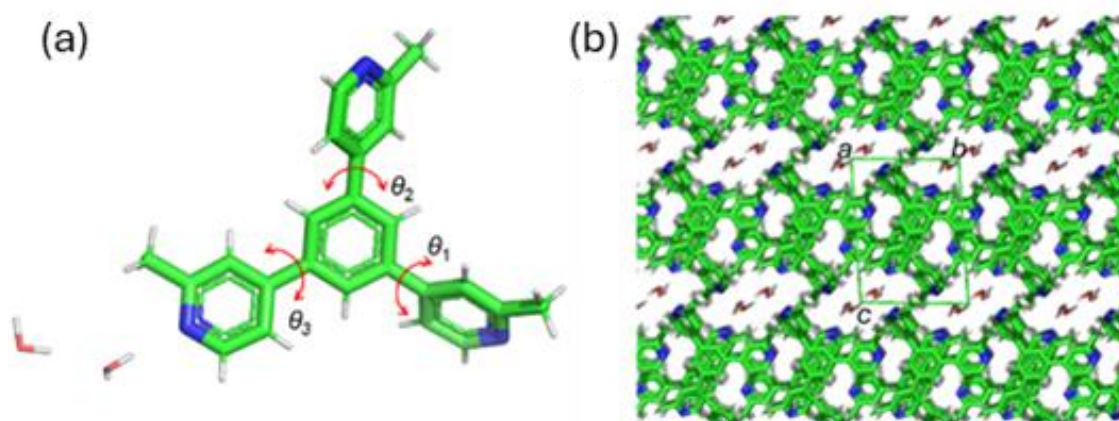


Figure 5.1 – SC-XRD: a) asymmetric unit of mTPB; b) packing state view along the a-axis.^[149]

In the asymmetric unit, there is one mTPB and two water molecules. The presence of water is very likely due to the humidity in the air during the crystallisation process. The distance between the two mTPB molecules in the unit cell is $4.052 \text{ \AA}$ (distance calculated between the benzene rings' centroids). The angles between the planes of the benzene rings and the pyridines are $\theta_1 = 41.95^\circ$, $\theta_2 = 43.20^\circ$, $\theta_3 = 25.82^\circ$.

and this great torsion of the pyridine's moieties is due to the presence of the methyl group. Such torsions are present to achieve the least steric hindrance among the aromatic rings. It should be noted that the presence of various kinds of hydrogen bonds. First, the ones between the electron-rich nitrogen of one pyridine group of the mTPB molecule that interacts with the hydrogen of a water molecule within a distance of 1.986 Å (-N...H-O-H). There are hydrogen bonds between the molecules of water themselves (H-O...H-O-H, $d = 1.971$ Å). There is also the presence of short contacts between the pyridine nitrogen and the hydrogen of the benzene ring of a neighbour mTPB molecule (-N...H-Benz, $d = 2.645$ Å) or with the hydrogen of the pyridine ring of a neighbour mTPB molecule (-N...H-Py, $d = 2.719$ Å). Moreover, there are some kinds of electrostatic interactions established between the benzenic carbon atom of a mTPB molecule and a hydrogen atom of a pyridine group of another molecule (Benz-C...H-Py, $d = 2.710$ Å) or another pyridinic carbon atom (Benz-C...C-Py, $d = 3.249$ Å). One hydrogen atom of the methyl group branching off from the pyridine takes part in electrostatic interactions with a carbon atom of a pyridinic moiety with an approximate distance of 2.826 Å (Met-H...C-Py). The P-XRD pattern of the obtained powder has well-defined peaks that trace the positions of the simulated peaks from SC-XRD, indicating that the mTPB single crystal is representative of the bulk powder (Materials and methods, Figure 7.8).

5.2 Synthesis of a thermally stable 2D MOF using mTPB

Having synthesised and characterised the ligand, the next step was to investigate the coordination of the ligand with zinc metal salts. The aim was to understand the coordination chemistry of the ligand, and having information on the TPB that forms $M_{12}L_8$ poly-[n]-catenane, it is possible to study the influence of the methyl group in the formation of the catenane.

5.2.1 Solid-state reactivity of mTPB and ZnBr₂ by mechanochemistry followed by heating

The solid-state chemistry of mTPB has been explored for the first time, self-assembling with ZnBr₂ by carrying out first a mechanochemical reaction by NG, followed by annealing. The NG experiment resulted in an amorphous phase without starting mTPB, suggesting that it reacted with ZnBr₂ (Figure 5.2a). The P-XRD diffractogram of the NG product resembles that observed in the solid-state synthesis of poly-[*n*]-catenanes self-assembled of mechanically interlocked M₁₂L₈ MOCs. The diffractogram shows two large bumps at $2\theta/^\circ \approx 14$ and 26, indicating that in the product there is some short-range ordering (Figure 5.2a). To keep the solid-state process, in the absence of solvents, heat was used to further proceed with the reaction.

Thus, the amorphous phase (hereafter **a2**) obtained in the NG process was further annealed to 300 °C for one hour and allowed to cool down to ambient temperature for *ca.* 4 h. The P-XRD diffractogram of **a2** shows that the sample became crystalline with several Bragg reflections (Figure 5.2b). The crystal size of the annealed **a2** was microcrystalline but of low resolution to attempt the structure solution from P-XRD.

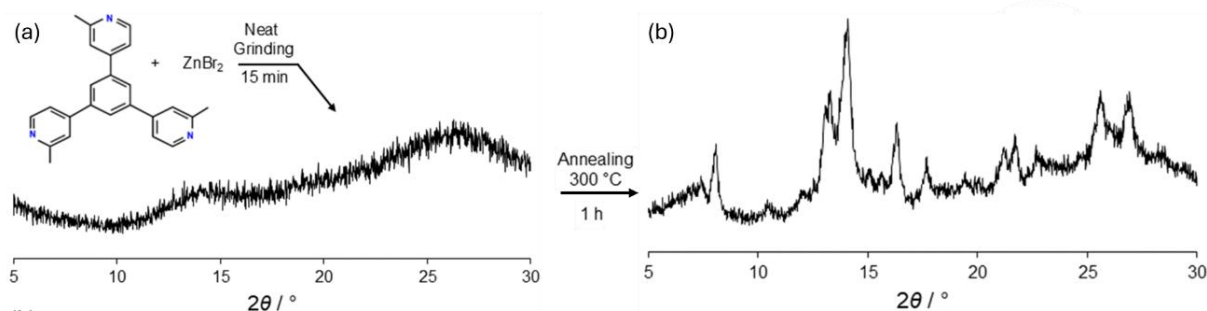


Figure 5.2 – P-XRD pattern: a) after neat grinding of mTPB and ZnBr₂; b) after thermal annealing of the sample.^[149]

To understand the crystalline structure obtained by NG and annealing of **a2**, slow crystallisation was tried to grow a single crystal by mixing mTPB and ZnBr₂ in the presence of *o*-dichlorobenzene. After three days, large crystals (hereafter **3**) were obtained. One single crystal, stable at room temperature, was taken and measured by SC-XRD. SC-XRD shows that **1** is a MOF including disordered methanol crystallising in the trigonal space group *R*-3 with the crystallographic formula (C₁₆H₁₄Br₂N₂Zn)·(MeOH). The asymmetric unit is composed of a ZnBr₂ coordinated

to one third of mTPB (Zn...N) twice and contains one disordered methanol molecule. The unit cell parameters are (302 K) $a = 21.4323(2)$ Å, $b = 21.4323(2)$ Å, $c = 19.3803(2)$ Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 120^\circ$, $V = 7709.54(13)$ Å³. Interestingly, the trigonal space group is the same as the M₁₂L₈ poly-[*n*]-catenanes.

The 2D layers are porous layers containing large window openings. The minimum circuit formed of mTPB ligand and ZnBr₂ contains six ligands and six metal centres. In the coordinated mTPB, the two angles between the planes containing the benzene rings and pyridines are $\theta_1 = 38.71^\circ$ and $\theta_2 = 35.18^\circ$. The 2D layers stack the *c*-axis. The stacking of layers does not yield a channel structure due to the translation of adjacent layers. The open space in a single layer has an internal opening of 8.4 Å (Br-Br), 17.3 Å (Br-CH₃) (Figure 5.3c). In the stacking layers, there are three different distances among centres of the rings (i.e., 4.023 Å, 4.047 Å and 7.264) as shown in Figure 5.3d. While the first two contacts can be considered π - π interactions, the longest one cannot be considered as such due to the presence of guest molecules. Therefore, these aromatic interactions do not expand continuously along the *c*-axis, which would be important to study electron conductivity. About the short contacts established in **3**, the bromide atoms form weak electrostatic interactions with the pyridine hydrogens (Py-H...Br-Zn, 2.959 Å). These interactions are responsible for keeping the 2D planes stacked together. Importantly, there is no interaction involving methyl groups with adjacent layers or guests.

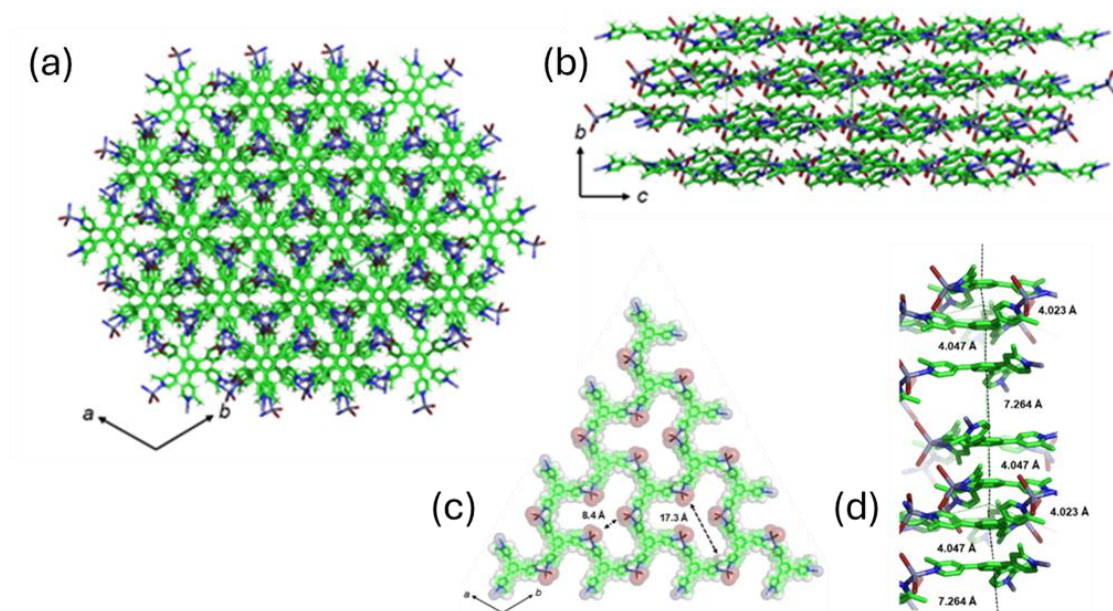


Figure 5.3 – SC-XRD model structure of **3**: a) view along the stacking direction, *c* axis; b) view along the *a* axis; c) view along the *c* axis, just one layer; d) view of the aromatic-aromatic distances.^[149]

The space occupied by the solvent corresponds to 7% ($531 \text{ \AA}^3$) of the total unit cell volume in **3** (spherical probe with a $1.2 \text{ \AA}$ radius). The voids in **3** are below the central benzene rings of the mTPB ligand, and there are three per unit cell, which are not connected (Appendix 13.14).

After one month, a microcrystalline powder was deposited at the bottom of the crystallisation tube. The P-XRD of the solid matched that of the simulation from **3**, demonstrating that the selected single crystal **3** is representative of the bulk powder (Figure 5.4a). Thus, no other crystalline phases are formed with **3** after long crystallisation experiments using the stratification method. An important aspect of the reported 2D is that the weak inter-layer interactions observed in **3** opens for exfoliation studies. In this way, it should be possible to create 2D nanosheets with potential applications in various research areas due to the presence of large voids in the 2D structure.

5.2.2 Thermal stability of **3**

An important aspect of a given 2D MOF is its stability. Thus, the thermal stability of the 2D MOF was also monitored by annealing **3** up to $300 \text{ }^\circ\text{C}$ for 1h in an oven and then measured by *ex-situ* P-XRD. The diffractogram shows that **3** is still

highly crystalline, and the diffraction pattern did not change upon heating, indicating that the structure is maintained (Figure 5.4). This good thermal stability is important for the potential applications of this type of layered MOF material.

The annealing effect promoted the self-assembling of mTPB and ZnBr_2 to give the 2D layered arrangement. This solid-state reactivity is significant as it shows that the templating effect in the self-assembling process is not crucial, as the structure forms regardless of the solvent. This was corroborated by heating experiments showing the stability of the structure in the absence of solvent. Also, the solid-state reactivity allows the synthesis of a 2D MOF in a completely solvent-free process, which is important from a green chemistry point of view.

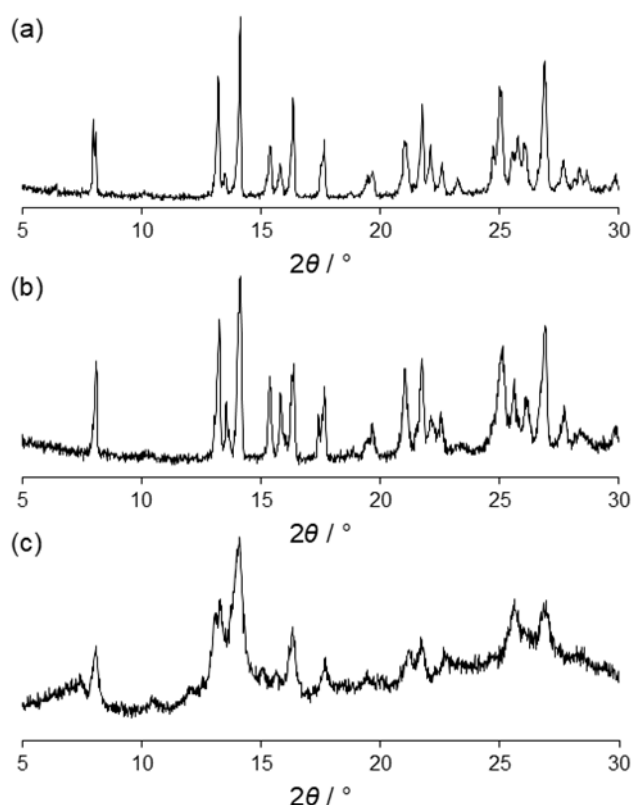


Figure 5.4 – P-XRD pattern of **3**: a) microcrystalline powder after filtering; b) after heating to 300 °C for 1 h; c) the product from neat grinding and annealing.^[149]

5.2.3 Polycatenanes made of MOCs vs 2D MOFs using mTPB and ZnBr₂

In self-assembling systems driven by coordination bonds, “small” changes in one of the building blocks, either the organic ligands or the metal ions, can have a strong influence on the final product. In the present case, introducing a methyl group into the 2-position of the 4'-pyridyl rings in the triangular panel-like TPB ligand does not promote the formation of the interlocked icosahedral M₁₂L₈ nanocages in the solid-state.

It is important to note that the presence of the CH₃ group does not change the coordination vector direction, as the lone pairs of the N atoms are not altered. Also, the rotation of the interring C–C bonds does not influence the directionality of the N lone pairs. In fact, the Zn–N coordination bonds in **3** are formed with a significant rotation of the methylated pyridine rings to avoid repulsion among the halogen atoms and the CH₃ groups. Importantly, similar values in the pyridine's rotation θ angles ($\theta = 36^\circ$) have been observed in M₁₂L₈ mechanically interlocked nanocages, which are also crucial to allow guest exchange mechanisms via SCSC reactions (as presented in chapter 3.2). Thus, the presence of the CH₃ group should not impede the formation of non-interlocked M₁₂L₈ nanocages. Moreover, the benzene-benzene aromatic interactions, which play an important role in the mechanical bonds and in the formation of the interlocked M₁₂L₈ nanocages, can also be formed in **3**, as shown in Figure 5.3d.

While the interlocking of M₁₂L₈ nanocages might be feasible due to the large openings of the nanocages (window dimensions 13 Å x 22 Å), the constrained environment due to the methyl groups within the mechanical bonds most likely destabilises a potential polycatenated M₁₂L₈ structure. Thus, the presence of CH₃ groups switches the formation to other structures like 2D MOFs (**3**) instead of PC-MOCs, which could be seen as a steric effect. Nevertheless, it is important to note that due to the above-described structural aspects, the lattice packing of **3** and the M₁₂L₈ catenane shows many similarities. Figure 5.5 depicts the structure of the PC-MOCs and the 2D MOF **3** viewed along the *c*-axis. In both structures, the same trigonal symmetry is observed, reflecting the C₃ high symmetry of both TPB and mTPB triangular panel-like ligands.

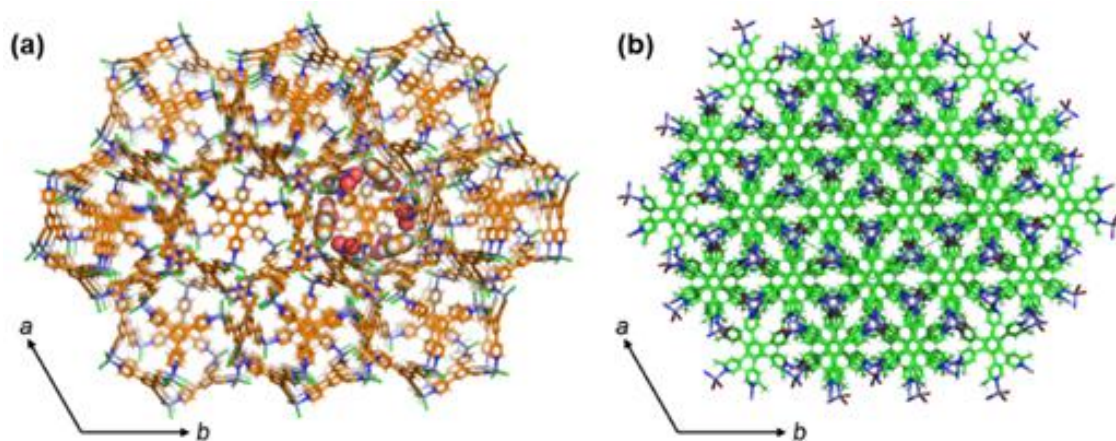


Figure 5.5 – Crystal structure model view along stacking direction c -axis of: a) $M_{12}L_8$ poly-[n]-catenane; b) 2D MOF 3.^[149]

5.3 Synthesis and isolation of extTPB using Suzuki-Miyaura coupling

For the synthesis of the extTPB ligand, the starting point was the 1,3,5-trisbromobenzene reacted via Suzuki coupling with three equivalents of a phenyl pyridine boronic ester (Materials and methods). The product was purified and characterised by NMR and XRD techniques. Single crystals were grown by evaporation and studied by SC-XRD crystallographic analysis. The colourless solid extTPB crystallised in the monoclinic system with the space group $P2_1/c$. The unit cell parameters are $a = 11.8072(3) \text{ \AA}$, $b = 25.5600(4) \text{ \AA}$, $c = 10.3908(3) \text{ \AA}$, $\beta = 116.010(3)^\circ$, $V = 2818.25 \text{ \AA}^3$. There is no extTPB structure reported in the CSD. Therefore, the X-ray structure has been deposited in the CSD.

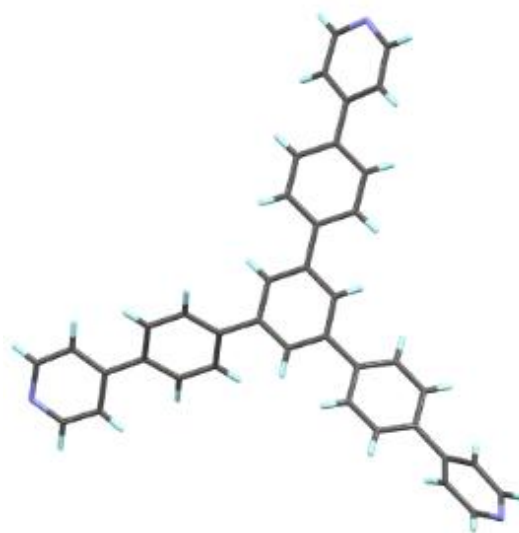


Figure 5.6 – SC-XRD structure of the crystallised extTPB.

The asymmetric unit is composed of one entire extTPB molecule. In the solid-state, there are interactions involving the various hydrogens of the benzenes and pyridines. The strongest interactions occur between the H of the pyridines and the N atoms on the extremities of the molecule ($d = 2.6 \text{ \AA}$). There are also interactions between the N and the H atoms of the intermediate phenyl groups ($d = 2.851 \text{ \AA}$). Also, the H of the central benzene is involved in interactions with an N from the pyridines ($d = 2.507 \text{ \AA}$). As for the original TPB, the molecule is not planar. The presence of H atoms along the skeleton of the tridentate molecule, with their steric hindrance, imposes torsions in the aromatic rings to optimise the attractive and repulsive forces taking place in the solid state. The angles between the planes of each pyridine with respect to the central benzene and between the planes of each intermediate phenyl group with respect to the central benzene are all different. This could influence the self-assembly and crystallisation with metal units, making it harder to obtain good-quality single crystals suitable for SC-XRD. Also, the torsion of the pyridines and phenyl groups could behave like in the TPB, making these groups dynamic with respect to the static central benzene and act as rotors on their bond axes. This could have a strong impact on the dynamic behaviour of the final coordination assembly.

After the synthesis of the pure extTPB ligand, it was used in coordination with Zn salts, but no results were yet obtained as the crystals were too small to be analysed by SC-XRD. Further development will follow.

5.4 Conclusions and outlook

This chapter reports the study of TPB ligand diversification and its self-assembly with ZnBr_2 using similar crystallisation conditions employed in the synthesis of M_{12}L_8 polycatenanes. Two new rigid panel-like triangular ligands were synthesised using the Suzuki-Miyaura Coupling reaction. Starting from the TPB, one ligand adds a methyl group on the pyridine group, obtaining the mTPB ligand. Neat grinding and annealing of mTPB and ZnBr_2 form a new 2D MOF with porous layers. This means that the presence of the additional methyl group prevents the formation of the M_{12}L_8 interlocked nanocages, probably due to steric or electrostatic reasons. The other conceptualised new ligand was obtained by extending the “arm” of the TPB by adding another phenyl group, forming the extTPB. There are no results yet on the coordination of this ligand with zinc salts, as no single crystals suitable for SC-XRD were obtained. Future studies will include the self-assembly of mTPB with ZnCl_2 and ZnI_2 to see if the results are similar to the mTPB- ZnBr_2 layered material, and the synthesis of new TPB-related triangular ligands and their coordination with zinc halides and other metal salts. The 2D MOF structure needs to be explored in the topology and its potential in application studies, for example, guest inclusion, electron conductivity or exfoliation experiments. It will be important to investigate the coordination of the extTPB with Zn-based salts, which could lead to MOCs larger than the M_{12}L_8 icosahedral ones and maybe maintain the mechanical bond.

6 *Solid-state synthesis, X-ray structure, and guest inclusion in octahedral M_6L_4 cages self-assembled by TPB*

Depending on the shape and dimensions of the organic ligand (L) and the coordination geometry of metal ions (M) in the self-assembling blocks, the MOCs structures can display different volumes and geometries, and display different degrees of symmetry, which are crucial aspects that influence their host-guest chemistry. Following Fujita's^[22] first report (Section 1.2.1.1), the chemistry of octahedral M_6L_4 MOCs with triangular tris-pyridine-based ligands has been largely studied, being applied as nanoreactors, guest trapping media and in photophysical processes.

The synthesis of new M_6L_4 derivatives varying only in the central aromaticity of the tridentate ligand by analysing their solid-state structures and host-guest chemistry is crucial for their further development. In the synthesis of M_6L_4 -type structures, replacement of TPT with a ligand with the same geometry and denticity (the same coordination direction) but differing only in the aromaticity of the central ring, such as TPB, is worth studying. In fact, the non-planarity due to the dihedral angle θ among the benzene and the 4-pyridyl groups, and the electronic distribution of TPB could affect the host-guest chemistry of the self-assembled MOCs. The use of TPB as an independent building block in M_6L_4 octahedral cages is rare, and the X-ray solid-state evidence of the $Pd_6(TPB)_4$ has never been reported. Although the structure of the $Pd_6(TPB)_4$ should be homologous to the $Pd_6(TPT)_4$ cage, its internal voids and external surface will be different from a chemical point of view (electron-rich TPB vs. electron-deficient TPT). Therefore, the host-guest chemistry of TPB M_6L_4 , in the solid state and in solution, may be different from that observed in $Pd_6(TPT)_4$ cages. In this regard, host-guest chemistry, such as molecular guest inclusion, recognition, and reactivity using $Pd_6(TPB)_4$ cages, has not been studied.

For this reason, in this chapter, the work on the self-assembly of TPB with Pd²⁺ ethylenediamine (en)*cis* protecting group by mechanochemical and solution state synthesis, with templating guests to help in the formation of single crystals, is reported. Combining XRD, DFT and NMR techniques, it was possible to fully characterise the self-assembled products for the first time in the solid-state.^[150]

6.1 Synthesis of Pd₆(TPB)₄ in the solid-state by neat grinding

At the date of this work, there were no reports of the mechanochemical solid-state synthesis of M₆L₄ cages using TPB and Pd²⁺ ions. Therefore, the synthesis of the Pd₆(TPB)₄ octahedral complex was explored by NG. The solid-state reaction was performed using a mortar and a pestle by grinding (en)-Pd(NO₃)₂ with TPB in a 3:2 molar ratio (Figure 6.1). The solid-state reaction has been monitored by solution state ¹H NMR and P-XRD at different times (Appendix 13.17, 13.18, 13.19). It is important to mention that TPB is not soluble in D₂O, and it is not observed by ¹H NMR even at 322 K. After 15 minutes of NG, the formation of some intermediate TPB complexes (side products) is observed together with the M₆L₄ cages in the solution state (Figure 6.1a). After 25 minutes of NG, the presence of the M₆L₄ complex is clear, along with some side products (Figure 6.1b). The ¹H NMR shows that the reaction has been practically completed after 40 minutes (Figure 6.1c). Further grinding for up to 50 minutes did not show a significant difference in the formation of the product (Figure 6.1d). The NG experiment was reproduced and monitored after 10 minutes of reaction, and, in that case, the formation of the M₆L₄ cages is not yet observed (Appendix 13.18). This is important as it shows that the M₆L₄ formation is not immediate. The evolution of the M₆L₄ formation in the second experiment follows a similar behaviour to that shown in Figure 6.1. The P-XRD at 30 minutes shows that the Pd₆(TPB)₄ product is amorphous (Appendix 13.19).

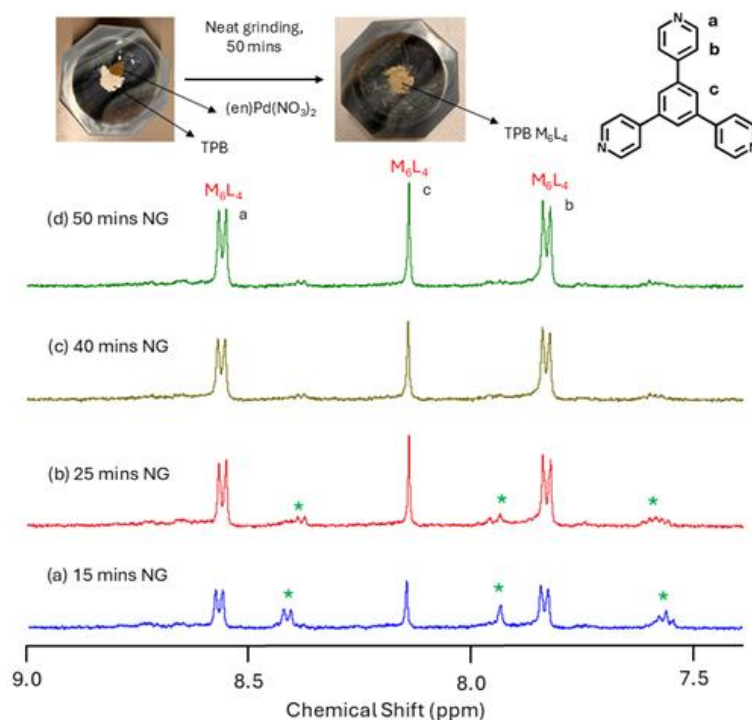


Figure 6.1 – Images of the mortar during the NG process; ^1H NMR spectrum (303 K, 400 MHz, D_2O) 9–7.5 ppm region of NG reaction after a) 15 mins; b) 25 mins; c) 40 mins; d) 50 mins.^[150]

The ^1H NMR analysis evidences the following features. Because the M_6L_4 is highly symmetric (T_d symmetry), all twelve pyridine rings in the M_6L_4 are equivalent, and the spectrum of $Pd_6(TPB)_4$ cage shows only one set of pyridine protons. The two doublet-like signals appearing at chemical shift (δ) 8.59 and 7.72 ppm are assigned to the PyH_{α} and PyH_{β} , respectively, of the pyridine rings of the M_6L_4 nanocage of TPB ligand (Figure 6.1). The singlet at δ 8.05 ppm corresponds to the H in the central benzene ring of TPB that is not present in the TPT ligand. A singlet signal at δ 2.94 ppm is assigned to the CH_2CH_2 protons of M_6L_4 . The CH_2CH_2 protons of the unreacted Pd end-capping group appear at *ca.* 2.6 ppm (Appendix 13.17). Downfield shift indicates coordination of 4-pyridyl groups in TPB to a Pd^{2+} centre. The single proton signal of the uncoordinated Pd disappeared at 30 minutes, and ligand TPB reacted, thus indicating the presence of $Pd_6(TPB)_4$ cages as the main product with some unknown side products (Appendix 13.17).

The self-assembly of $Pd_6(TPB)_4$ nanocages in the solution state is carried out at *ca.* 80 °C, and at such temperatures, due to the lability of the Pd–N coordination bond, the error-checking mechanisms (Section 1.3) take place. Thus, if intermediate structures are formed, they can be transformed into M_6L_4 cages. In the solid-state, the reaction occurs at room temperature and relatively fast (*i.e.* within 25 minutes), the

M₆L₄ cages are produced (Figure 6.1). Probably, for this reason, the side products observed in the ¹H NMR data are because the self-repairing processes have not been able to completely transform the intermediate products into the M₆L₄ cages. However, after 40 minutes of NG, the M₆L₄ cages are the main product. Therefore, the mechanical force in NG must help convert side products into M₆L₄ cages. Thus, the reaction temperature in the solution state (~80 °C), in the solid state, is substituted by the mechanical force to allow eventual self-repairing processes and hence the formation of the Pd₆(TPB)₄ cages as the principal product. Importantly, in the second NG experiment, after shorter reaction times (10 minutes), the M₆L₄ cages are not yet observed because the intermediates are formed first, as demonstrated by the ¹H NMR results. However, after further grinding for 20 minutes, the Pd₆(TPB)₄ cages are already formed.

6.2 Synthesis and SC-XRD of Pd₆(TPB)₄ in the solution-state

The formation of Pd₆(TPB)₄ cage was also corroborated in the solution state. From the ¹H NMR spectrum, the protons in the pyridine and benzene rings can be easily determined (Appendix 13.20). The thermodynamic stability of the cages in water and in an acidic solution (containing citric acid) at room temperature was monitored for several weeks by ¹H NMR analysis. The NMR data show that the M₆L₄ cages are stable in water and acidic medium for one month (Appendix 13.21, 13.22). The stability of Pd₆(TPB)₄ in solution is important for potential applications in molecular recognition and separation purposes in aqueous media.

Evaporation of the Pd₆(TPB)₄ aqueous solution yielded small octahedral crystals unsuitable for SC-XRD due to weak diffraction. It is known that templating by guest molecules is very important in the self-assembly of octahedral M₆L₄ cages in the solid-state in stable form at room temperature.^[22] Thus, crystallisation of Pd₆(TPB)₄ was carried out in the presence of guests that could fit in an M₆L₄ cage in aqueous solution. The templating guests were 3-phenylpropionic acid (G1) and adamantane carboxylic acid (G2). The synthesis of the M₆L₄ with the templating guest was done with the addition of G1 and G2 to the M₆L₄ solution (see Materials and methods). Large, colourless single crystals at the bottom of the vials were observed by optical

microscopy. While single crystals were obtained with both guests, only G1 gave a “good” single crystal because the unit cell was maintained throughout the SC-XRD experiment. Obtaining a reliable unit cell was challenging, as in many cases, doubled or triplicated unit cell axes were measured at different orientations of the single crystal, complicating the structure determination of the $\text{Pd}_6(\text{TPB})_4$ cages in the crystalline state.

A single crystal grown in the presence of G1 was mounted for SC-XRD analysis at low temperature. X-ray crystallography showed that $\text{Pd}_6(\text{TPB})_4$, self-assembled as large octahedral crystals (Figure 6.2a), diffracts up to a *ca.* 0.83 Å resolution. $\text{Pd}_6(\text{TPB})_4$ crystallizes in the tetragonal system in the $I4_1/amd$ space group with the following unit cell parameters: $a = b = 27.2127(12)$ Å, $c = 27.6881(8)$ Å, $V = 20503.9(19)$ Å³, $Z = 4$ and $Z' = 0.125$ (100 K). This is a close unit cell to that of the original $\text{Pd}_6(\text{TPT})_4$ cage, including 1-adamantane carboxylic acid (G2) reported by Fujita: $a = b = 26.913(3)$ Å, $c = 27.383(6)$ Å, $V = 19842(2)$ Å³, (173K) with the same space group. In $\text{Pd}_6(\text{TPB})_4$, the asymmetric unit contains two 1/2 *cis*- en-Pd end-capping groups and 2/3 of the TPB ligand. Like in many $\text{Pd}_6(\text{TPT})_4$ structures, the NO_3^- anions cannot be located due to severe disorder. The M_6L_4 cage is a cationic $[\text{Pd}_6\text{L}_4]^{12+}$ structure. Several Q peaks that form a ring are also observed in the asymmetric unit, but the refinement is quite challenging due to disorder, making it difficult to locate the guest molecules, unless many constraints are applied. Thus, the solvent mask (SQUEEZE) protocol^[151] was used to refine the structure. From the high-resolution SC-XRD data, the host M_6L_4 framework was unambiguously determined with reasonable R factors (R-factor = 14.7%; without SQUEEZE, the R-factor ~26%) for this structure.

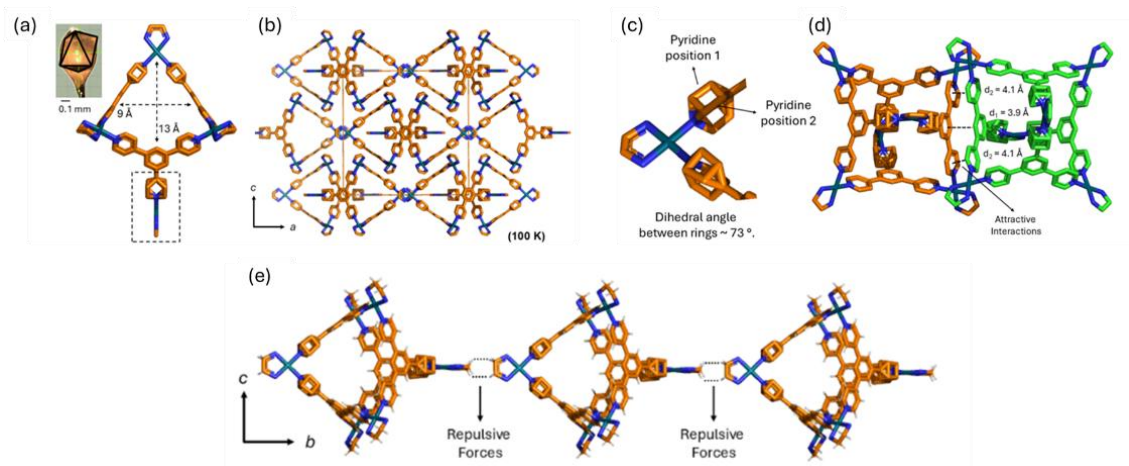


Figure 6.2 – SC-XRD: a) single crystal and M_6L_4 cage; b) view along the b -axis; c) view of the disordered pyridines; d) aromatic interactions between two adjacent M_6L_4 cages; e) repulsive forces between neighbour M_6L_4 cages.^[150]

In $Pd_6(TPB)_4$, the four TPB ligands occupy only half of the triangular faces in alternate positions in the upper and lower parts of the octahedral cage. Thus, the structure is an open octahedron with window sizes of *ca.* 9 Å × 13 Å (Figure 6.2) and hence the guest molecules can be inside the cages, but also, they can protrude from them through the windows. The Pd···Pd distances are 19.0 Å and 18.5 Å, which represent the height and width of the cage and the N(pyridine)-Pd-N(pyridine) angles are 83.2° - 88.4°. Compared to the analogous $Pd_6(TPT)_4$,^[22] one of the three pyridine rings is disordered (Figure 6.2c), denoting the dynamic behaviour of some of the aromatic components in the cage. The dihedral angle between the two disordered pyridine rings is ~73°, which can be considered as a local dynamic host framework component. This 4-pyridyl group rotation movement in TPB is the same as that observed in the $M_{12}L_8$ nanocages (Chapter 3). DFT calculations have determined that such rotation has a low energy cost of ~3 kcal/mol with its minimum at $\theta = 36^\circ$.

The packing of M_6L_4 nanocages in the solid state is in part controlled by the aromatic-aromatic interactions from the external surfaces of the octahedrons, involving the TPB central benzenes and peripheral pyridines. Measured from the centroid of each ring, the aromatic interactions are 3.918 Å (benzene-benzene) and 4.072 Å (pyridine-pyridine) as shown in Figure 6.2d. Such face-to-face aromatic interactions are fundamental for keeping the MOCs in a crystalline state (100 K). Importantly, the M_6L_4 packing leaves one pyridine ring that does not interact via aromatic interactions and, for this reason, is disordered. In fact, the disordered pyridine might have an effect on guest order. The end capping groups are interacting

frontally with adjacent methylene groups as repulsive forces (C–H··H distance is 2.409 Å) due to the H atoms (Figure 6.2e). The internal volume of the M_6L_4 is ~ 450 Å³ and has a strong hydrophobic character as it is surrounded by four electron-donating benzene rings.

When crystals of $Pd_6(TPB)_4$ are left in contact with air for one month, they do not become powders, as SC-XRD spots are still observed. Diffraction can only be detected at very low-resolution (*ca.* 2.7 Å), not allowing for structure solution. Nevertheless, indexing was possible, giving a unit cell that is slightly smaller in unit cell volume even if it was measured at 300 K: $a = b = 26.53(2)$ Å; $c = 27.68(4)$ Å, $V = 19482(30)$ Å³. This shows that the M_6L_4 nanocages are still maintained in the solid-state despite having an important part of the lattice content disordered.

6.3 Solid-state DFT calculations

QM calculations can be very useful for a quantitative comparison of isostructural MOCs through the estimation of the corresponding stabilisation energies. DFT calculations were carried out as explained in section 3.1.5. In the DFT calculations, the X-ray determined geometries of the M_6L_4 into $Pd_6(TPB)_4$ and $Pd_6(TPT)_4$ have been adopted, and anions ($12 \cdot NO_3^-$) and cations ($[Pd_6L_4]^{12+}$) per M_6L_4 were considered. Only X–H distances have been properly adjusted in the calculations. To compare the intrinsic stability of covalently bonded structures, it is convenient to consider the binding energy (E_b) of the system. That is the energy required to separate the individual atoms constituting the structure.

Even if this quantity cannot be directly related to a real, specific experimental value, it represents a useful parameter (by mimicking an ideal atomization process) for comparing the stability of different atomic structures. The estimated E_b of $Pd_6(TPB)_4$ and the $Pd_6(TPT)_4$ significantly differ by about 6000 kcal/mol (Figure 6.3a), the latter being more stable. Despite being isostructural materials, the internal M_6L_4 cavities in $Pd_6(TPB)_4$ and the $Pd_6(TPT)_4$ cages have different electrostatic surfaces and hence chemical environments. In this regard, DFT calculations show that TPB has an electron-rich surface while TPT is electron-deficient due to the triazine core, as shown by the maps of electrostatic potential (MEPs) (Figure 6.3b).

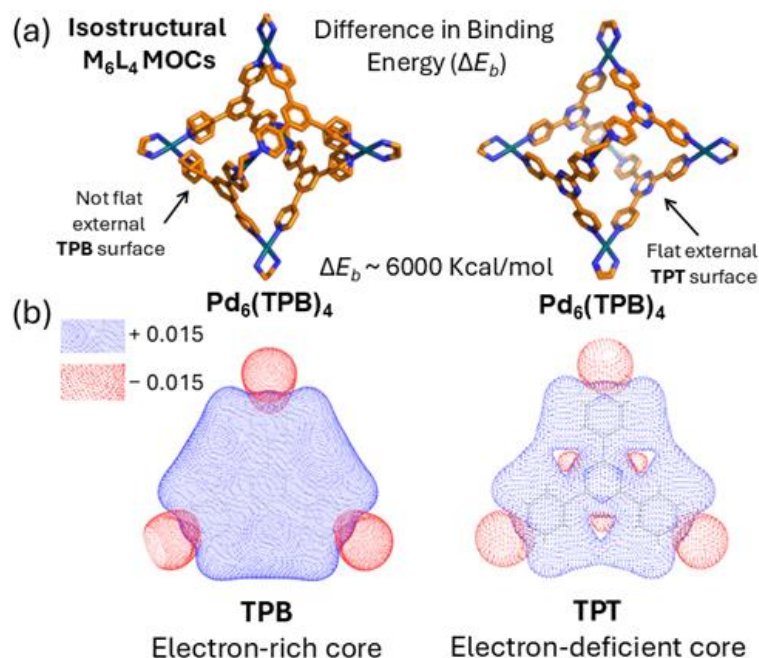


Figure 6.3 – a) DFT binding energy difference between the two isostructural M_6L_4 ; b) MEPs of TPB and TPT ligands.^[150]

Interestingly, the different internal M_6L_4 walls' surfaces can influence molecular recognition events in the solution state. TPT ligand has electron-deficient regions that can electrostatically interact via the external flat surface of the TPT M_6L_4 cages with other MOCs. In fact, considering the aromatic centroids in $Pd_6(TPT)_4$ cages, the pyridine-pyridine (3.993 Å) and triazine-triazine distances (3.825 Å) are shorter than in $Pd_6(TPB)_4$, even if the X-ray data is at 173 K. Also, the cation-anion interactions and the higher degree of planarity of the aromatic moieties in TPT are important, which is reflected in a higher $Pd_6(TPT)_4$ density compared to $Pd_6(TPB)_4$ (1.22 kg/m³ vs 1.05 kg/m³). All these considerations justify that $Pd_6(TPB)_4$ is less stable than the $Pd_6(TPT)_4$ cage, suggesting the importance of entropic contributions for the stability of the primer.

6.4 Solution-state guest inclusion studies in $\text{Pd}_6(\text{TPB})_4$

The host-guest chemistry of $\text{Pd}_6(\text{TPB})_4$ cages, including guests such as bulky adamantane and adamantane derivatives, has been thoroughly studied by Fujita.^[22,23,25] Therefore, the following step was to explore the guest behaviour of $\text{Pd}_6(\text{TPB})_4$ by studying the inclusion of G1 in M_6L_4 synthesised in the solid-state by neat grinding. Guest inclusion experiments were performed using a 1:8 molar ratio. The ^1H NMR data show that G1 guests are included in the $\text{Pd}_6(\text{TPB})_4$ cage as indicated by the chemical shift (Appendix 13.23, 13.24, 13.25). However, 8 guests cannot be physically included in the M_6L_4 cage at the same time. Therefore, we believe that on an NMR timescale, eight guests are involved in the encapsulation process, but only 4 can be physically included at any one time, as suggested by the X-ray results. The ^1H NMR data show that a single set of signals is present when the cage is present, indicating that the host-guest exchanges occur in the fast exchange regime.

The ^1H NMR plots show that the guest signals were shifted upfield due to shielding by the panel ligands of the TPB M_6L_4 , suggesting guest binding with the cage. This can be compared to guest G1 alone in D_2O (Figure 6.4a). In the guest aromatic area, the observed peak shift is due to inclusion in the M_6L_4 cages. The difference in the peak shift is indicative of the orientation of the guest molecule in the M_6L_4 nanocage. Since the aromatic peaks are shifted more (0.41-0.43 ppm for aliphatic vs 0.82-1.06 ppm for the aromatic), their interaction (shielding) with TPB is more pronounced. The aromatic part of G1 points to the interior of the cage, while the polar carboxylic group protrudes from the cavity. The ^1H NMR spectrum also demonstrates that the peaks corresponding to the pyridine protons (PyH_α) belonging to the M_6L_4 shifted to higher ppm due to the presence of the guest molecules in the cages (Appendix 13.26) as observed in other open octahedron M_6L_4 hosts.^[22]

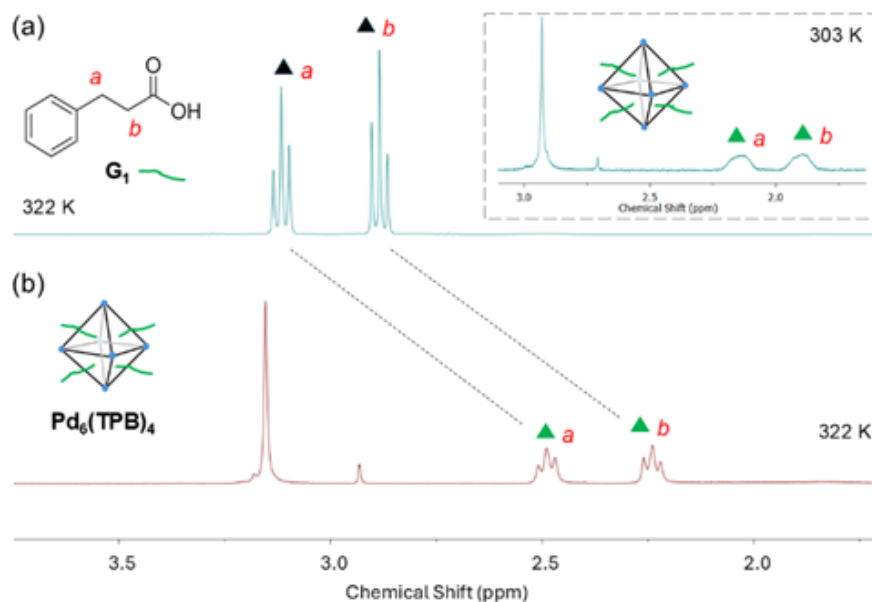


Figure 6.4 – ^1H NMR spectrum showing the aliphatic region with the two peaks corresponding to a) G1 and (b) belonging to $\text{Pd}_6(\text{TPB})_4$, including G1.^[150]

6.4.1 Titration experiments

To better understand the guest inclusion in $\text{Pd}_6(\text{TPB})_4$, in the solution state, titration experiments were carried out (Materials and methods). In the ^1H NMR spectrum, the evolution of the chemical shift for the H corresponding to PyH_α is observed in Figure 6.5. In the ^1H NMR plot, the protons within the cavity of $\text{Pd}_6(\text{TPB})_4$ shift continuously upon the addition of guest G1, indicating that the shielding/deshielding effect of the guests on the $\text{Pd}_6(\text{TPB})_4$ cage increases gradually with the progressive addition of G1. The most significant shift in the PyH_α is from the 1:1 to 4:1 guest/host ratio, while the signals of $\text{Pd}_6(\text{TPB})_4$ remain basically unchanged upon the addition of further equivalents of 3-phenylpropionic acid (Figure 6.5). The ^1H NMR stoichiometry plot of the titration of $\text{Pd}_6(\text{TPB})_4$ with G1 is shown in Appendix 13.27. The plot refers to the chemical shift of PyH_α of $\text{Pd}_6(\text{TPB})_4$. A series of 2.4 mM solutions of $\text{Pd}_6(\text{TPB})_4$ containing varying amounts of G1, ranging from 2.4 to 28.8 mM, was prepared. The solutions were allowed to equilibrate before they were examined by ^1H NMR spectroscopy. The stoichiometry was found to be *ca.* 4 guest molecules per one host molecule using the mole ratio method (Appendix 13.28).^[152]

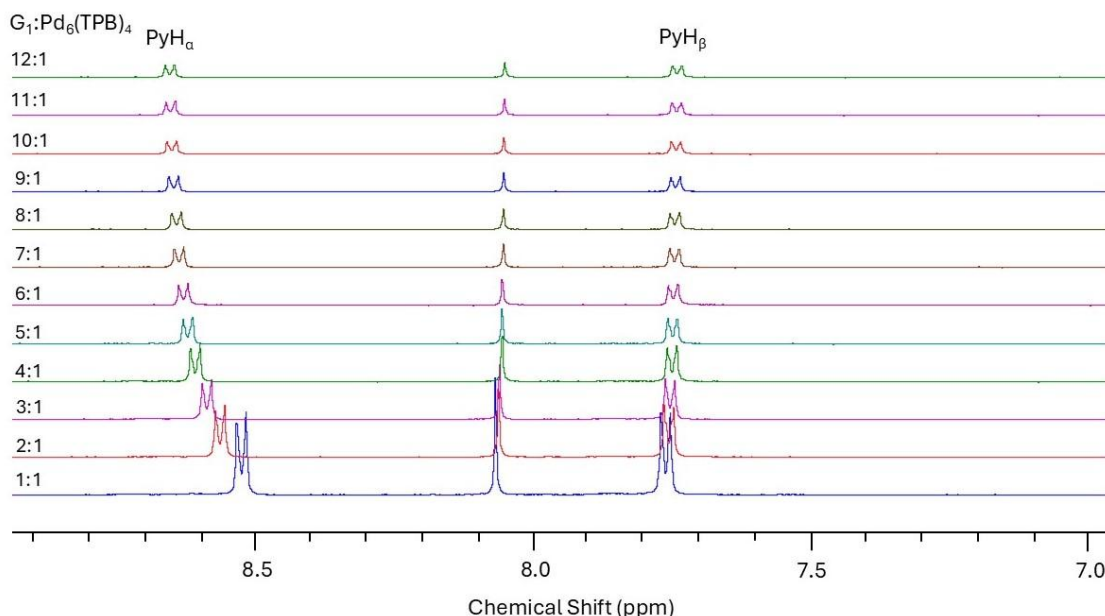


Figure 6.5 – 9–7 ppm range of ^1H NMR spectra of the titration experiment.^[150]

6.5 Solid-state guest inclusion analysis in $\text{Pd}_6(\text{TPB})_4$ and in $\text{Pd}_6(\text{TPT})_4$

The high dynamic content in $\text{Pd}_6(\text{TPB})_4$, such as counter anions and guest molecules, could be facilitated by the large internal space of the M_6L_4 nanocages. In $\text{Pd}_6(\text{TPB})_4$, the void space corresponds to 63.5% of the total volume of the unit cell. This is a very large fraction of the open space where ions and/or guest molecules can be hosted. In $\text{Pd}_6(\text{TPB})_4$, the voids are connected, forming a 3D network of channels (Figure 6.6a) where the part of the guest protruding from the M_6L_4 (determined from ^1H NMR data) can be located. The $\text{Pd}_6(\text{TPT})_4$ cage contains four G2 guest molecules per cage, with the guest at the entrance of the cages (Figure 6.6b), and the host-guest ratio is corroborated in the solid and solution states.

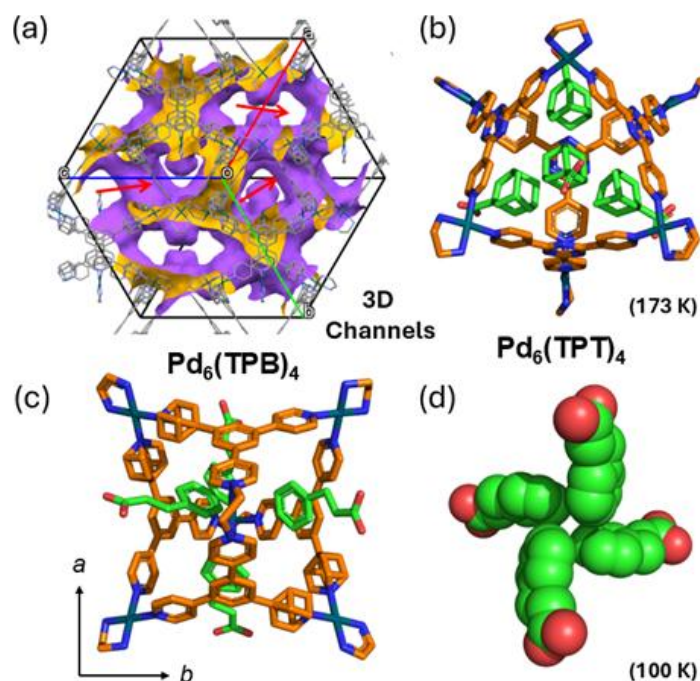


Figure 6.6 – a) View of $\text{Pd}_6(\text{TPB})_4$ along the [111] direction showing the 3D channel structure; b) X-ray structure of the $\text{Pd}_6(\text{TPT})_4$ includes **G2**; c) one TPB M_6L_4 cage including **G1**; d) space-filling model of the four **G1**.^[150]

To further understand the number of G1 molecules that can be included in the $\text{Pd}_6(\text{TPB})_4$ cages in the solid state at 100 K, a model consisting of one G1 molecule per asymmetric unit has been obtained from SC-XRD data (Appendix 13.29). This 100 K model explains that a single M_6L_4 cage $\text{Pd}_6(\text{TPB})_4$ can accommodate four G1 molecules, taking into account positional disorder during the time- and space-averaged SC-XRD data experiments. From the SC-XRD data, in the asymmetric unit, several Q peaks can be modelled as an aromatic ring corresponding to guest G1. Then it was decided to refine the structure by building a constrained guest G1 model. This allowed us to determine that in the asymmetric unit, there is one G1 molecule with an occupancy factor of 0.5, with one of the oxygen atoms (O1) in a special position (*i.e.* mirror plane). The high symmetry of the M_6L_4 (*Td* symmetry) imposes the spatial position of the guest molecules at a particular spot within the cage. Considering the volume of **G1** and the internal void of the M_6L_4 , the proposed model at 100 K consists of a disordered guest sub-structure where the guests can be located at eight different positions within the cage, but not at the same time. That is, because SC-XRD is scattering data averaged in space and time that was recorded for ~41 minutes, and the crystal is built up of millions of unit cells with many M_6L_4 , including guests. The proposed solid-state host-guest model is shown in Figures 6.6c and 6.6d.

In $\text{Pd}_6(\text{TPB})_4$, guest molecules can tumble within a single cage, and throughout the data collection, the four guests can be in the M_6L_4 as shown in Figure 6.6c. Figure 6.6d shows four green G1 molecules (occupancy factor 0.5, representing two molecules per M_6L_4) that are symmetrically related. The other guest positions with four other molecules with 0.5 occupancy factor are placed in the remaining space left in the same M_6L_4 cage (Appendix 13.29). Therefore, each M_6L_4 is occupied by four guest G1 molecules in the solid state, which, considering the low temperature model (100 K), is the maximum number of G1 guests that can be allocated in a $\text{Pd}_6(\text{TPB})_4$ cage at this temperature. More than four molecules of G1 per $\text{Pd}_6(\text{TPB})_4$ at 100 K in the solid-state might not be included.

Interestingly, the pyridine dynamic behaviour, found in two positions at 100 K, each with an occupancy factor of 0.5 (Figure 6.6c), might influence guest disorder. In fact, this local rotor-like behaviour of the pyridine ring can be associated with the guests dynamic behaviour (positional disorder). Within the $\text{Pd}_6(\text{TPB})_4$ cages, the G1 are oriented with the aromatic part (hydrophobic) pointing towards the centre of the M_6L_4 cavity, which is corroborated by the ^1H NMR data. This is reasonable as the cavity is strongly aromatic due to the presence of the benzene core of TPB. The non-aromatic and polar (hydrophilic) part of G1 with the carboxylic group protrudes from the cages (Figure 6.6c).

6.6 Conclusions and outlook

Mechanochemistry (neat grinding) has been used for the solid-state synthesis of TPB M_6L_4 type cages as demonstrated by ^1H NMR. The octahedral M_6L_4 nanocages are formed at room temperature and within 30 min, reducing the time and temperature required to form the MOCs in the solution state. The crystal structure of $\text{Pd}_6(\text{TPB})_4$ has been elucidated for the first time by SC-XRD data (100 K), confirming that (en)- $\text{Pd}(\text{NO}_3)_2$ is a suitable ancillary ligand for the self-assembly of $\text{Pd}_6(\text{TPB})_4$ in the solid state.

The TPB- M_6L_4 is isostructural to the $\text{Pd}_6(\text{TPT})_4$ reported by Fujita^[22]. Comparing the two isostructural cages, it was possible to further understand the structural features and stabilities that lead to the formation of the stable thermodynamic products. Solid-state DFT calculations demonstrated that the

$\text{Pd}_6(\text{TPT})_4$ cage is more stable than the TPB counterpart by calculation of the binding energies. The material was obtained in a short time, at room temperature and in the absence of solvents, in contrast to the procedure in the solution state. The M_6L_4 cages can include and exchange guest molecules in the fast regime, as proven by ^1H NMR. The cages are stable in water, and this allows for trapping hydrophobic guest molecules and bringing them into this environment. Exploring the solution- and solid-state synthesis allows a better design of the potential applications in the fields of molecular recognition and hydrophobic molecule transfer in aqueous media. Based on this, future studies will include the investigation of new molecules as guests to be trapped and brought into the water environment. It is interesting to study the coordination of the new ligands proposed in Chapter 5 with the enPd group. This could lead to new supramolecular assemblies with potential properties that open new investigation routes in that direction.

7 Further work

This chapter will present some preliminary experiments carried out during the PhD programme that are still under study. The CLASSIC NMR and synchrotron High-resolution P-XRD experiments allowed a further investigation of the dynamic behaviour of the M₁₂L₈ poly-[*n*]-catenane.

7.1 Synchrotron study

The study carried out at the Diamond Light Source (Didcot, UK) was divided into two sections: CO₂ inclusion and thermal treatment of M₁₂L₈ poly-[*n*]-catenane.

Amorphous to crystalline transformation upon CO₂ inclusion

Initial investigations of CO₂ inclusion in M₁₂L₈ poly-[*n*]-catenanes were carried out by BET adsorption experiments and indicated that the adsorption capacity is 10 CO₂ molecules per cage, a modest amount for this type of material. As explained in the previous chapters, when the amorphous polycatenane is exposed to aromatic templating agents, there is an amorphous-to-crystalline transformation (**a1** → **1**). For this reason, it was interesting to study whether the inclusion of CO₂ induced the same type of transition.

Thus, the first part of the synchrotron proposal was based on the *in-situ* investigation of the phase evolution upon CO₂ inclusion to demonstrate if small gas molecules can induce the amorphous-to-crystalline transformation. The amorphous sample in the capillary was mounted on the gas cell and, after the line was checked for leaks with an He flux, the capillary was evacuated to prepare to blow the CO₂. During the evacuation, the diffractometer was collecting the data to check any eventual phase transition, but the phase remained amorphous without any change. Having evacuated the capillary, the CO₂ was fluxed in, first reaching atmospheric pressure and keeping these conditions for about 8 hours. Then, since no change was observed, the pressure was gradually increased up to 48 bar. The resulting PXRD

patterns did not give drastic changes, but just a slight intensity alteration in the amorphous phase can be identified between the first (0.03 bar) and the last (48 bar) scan collected, as can be seen in Figure 7.1. The expected transition from amorphous to crystalline upon CO₂ inclusion did not occur, but there is definitely a structural change, as can be seen by the outline. Eventual amorphous structural changes and CO₂ trapping will be further investigated, given the current importance of CO₂ trapping technologies.

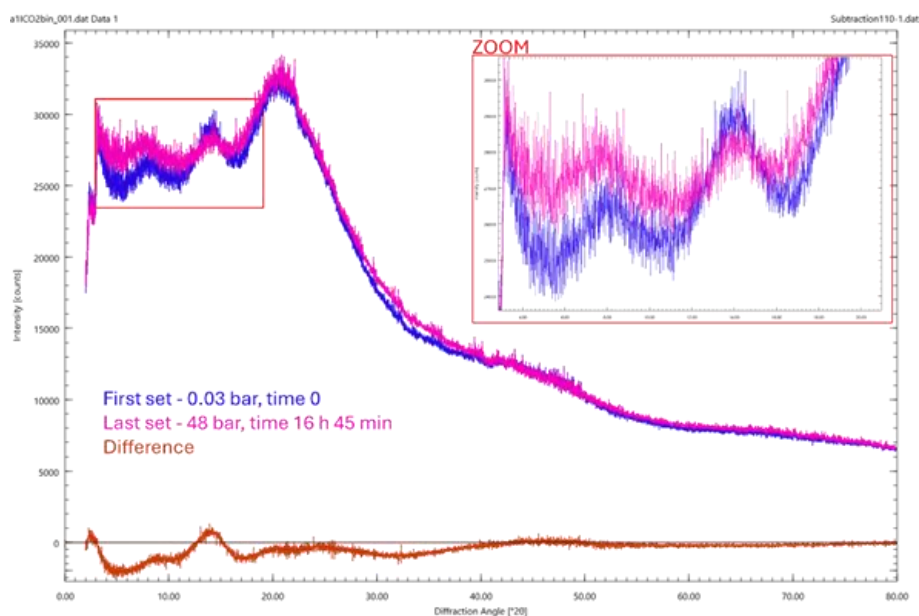


Figure 7.1 – Evolution of the amorphous phase upon CO₂ inclusion.

Temperature and pressure effects on the phase transition

The amorphous-to-crystalline transformation is based on a templating effect governed by the presence of a solvent in the cages. Now, if it is possible to induce the transition into the crystalline state and maintain it, by exposing the material to an aromatic molecule, maybe by removing this agent, it would be possible to return to the initial state and further demonstrate the existence of the catenane in the amorphous phase. Two possible ways were explored to do this. The first approach was to act on the temperature, increasing it to induce the guests into the gas phase and leave the material. The second approach was focused on the pressure and applying a vacuum that would strip the guest.

The temperature approach was first explored *ex-situ* in a laboratory. A crystalline powder sample **1**, prepared with TPB, ZnCl₂ and *o*-dichlorobenzene, is

exposed at 150 °C in an oven for about 4 hours, then the powder is cooled down near room temperature and subjected to P-XRD analysis. The result is an amorphous pattern, matching the **a1** phase, to demonstrate the idea that removing the guest by volatility takes the catenane back to its collapsed state. But what if we keep increasing the temperature? The procedure was repeated, in the exact same way, in steps of 20 °C up to 270 °C. Interestingly, having reached 200 °C, there is the formation of a new crystalline phase (**T2**), probably formed thanks to the given thermal energy that is enough to induce a phase transition. This new phase is not solved yet, and it is still under study. The same study was done on the samples prepared with ZnBr₂ and ZnI₂. For ZnBr₂, the behaviour is the same, but the transition temperature into phase **T2** is 230 °C. Instead, with this *ex-situ* experiment, it was not possible to detect the formation of a new crystalline phase, probably because it occurs at a higher temperature. The different temperatures at which this transition occurs can be ascribed to the different electrostatic interactions that are established based on the counterion size and polarizability.

The results are summed up in Table 7.1.

Table 7.1 – Thermal stability trend (*Am*: amorphous; *Cr*: crystalline)

	TPB+ZnBr ₂	TPB+ZnCl ₂	TPB+ZnI ₂
150 °C	<i>Am</i>	<i>Am</i>	<i>Am</i>
170 °C	<i>Am</i>	<i>Am</i>	<i>Am</i>
190 °C	<i>Am</i>	<i>Am</i>	<i>Am</i>
200 °C	<i>Am</i>	<i>Cr</i>	<i>Am</i>
210 °C	<i>Am</i>	<i>Cr</i>	<i>Am</i>
220 °C	<i>Am</i>	<i>Cr</i>	<i>Am</i>
230 °C	<i>Cr</i>	<i>Cr</i>	<i>Am</i>
240 °C	<i>Cr</i>	<i>Cr</i>	<i>Am</i>
250 °C	<i>Cr</i>	<i>Cr</i>	<i>Am</i>
260 °C	<i>Cr</i>	<i>Cr</i>	<i>Am</i>
270 °C	<i>Cr</i>	<i>Cr</i>	<i>Am</i>

The *ex-situ* study is practical and can give good starting information on the behaviour of the material. But, for a more detailed description, an *in-situ* study is essential, as anything can happen during the temperature variation.

For this purpose, the second part of the synchrotron proposal was based on these premises. The experiment carried out enabled us to continuously collect high-resolution P-XRD data while increasing the temperature of the capillary with a hot air blower. A set of experiments, each with the corresponding zinc halides (*i.e.* ZnCl_2 , ZnBr_2 , ZnI_2), was carried out with a given temperature ramp.

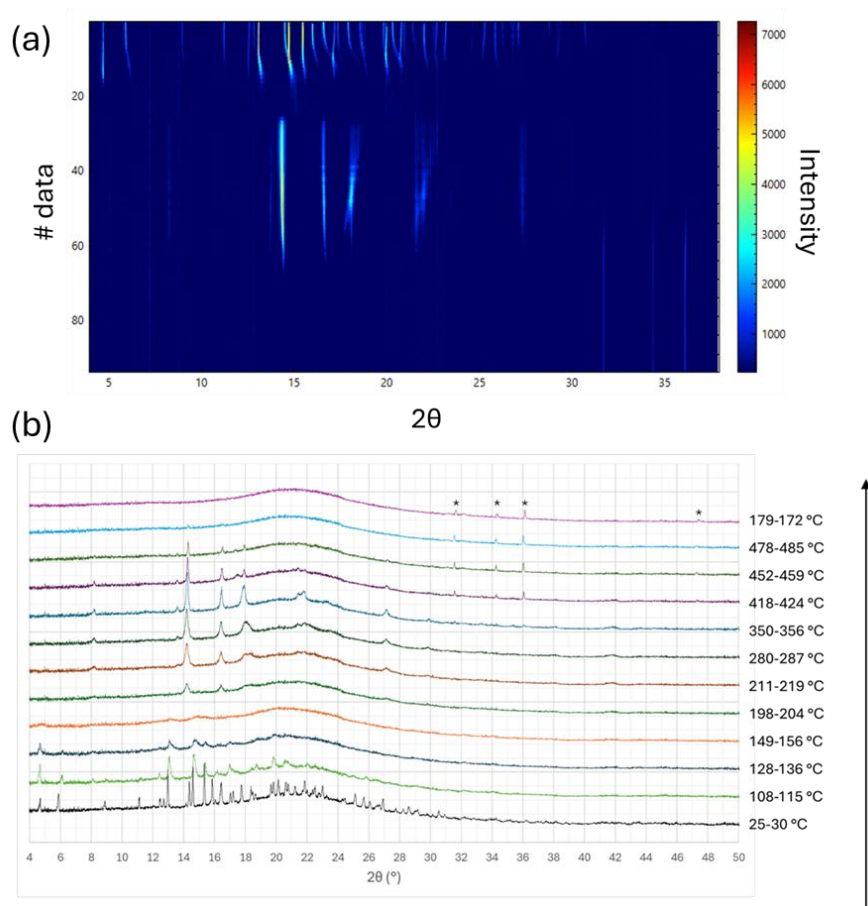


Figure 7.2 – a) Collection of all the P-XRD data into a 2D plot showing the evolution of the peaks;
b) P-XRD stacked data of the thermal annealing experiment.

The crystalline ZnCl_2 sample was exposed to a thermal ramp from room temperature to 500 °C at a rate of 12 °C/min, then cooled down to room temperature at the same rate. As expected, the material transition from crystalline (**1**) to amorphous (**a1**) occurs around 150-160°C. Then, when the temperature is about 200 °C there is the start for the transition to the **T2** phase starts, up to about 350 °C, where it reaches the highest degree of crystallinity. Increasing again and reaching 420 °C, the crystallinity of **T2** starts decreasing while new peaks start appearing in the range 30-50 °C, peaks assigned to ZnO . At this high temperature, the **T2** phase starts

decomposing, with the Zn metal part rearranging in the stable ZnO form. Looking at the evolution plot (Figure 7.2), just before the first transition to amorphous, you can notice a slight shift of the peaks toward high angles, meaning a gradual decrease of the unit cell parameters as expected from the squeezed cages and superimposed chains when no templating agent is present. The sample with ZnBr₂ chosen was not crystalline but amorphous, and the transition to the second crystalline phase starts occurring at 240 °C. The amorphous sample prepared with ZnI₂, for which a transition was not detected in the *ex-situ* experiment, here shows the amorphous to crystalline transformation, and this happens at around 250 °C. The transition temperatures for each halide match the values found in the *ex-situ* experiments.

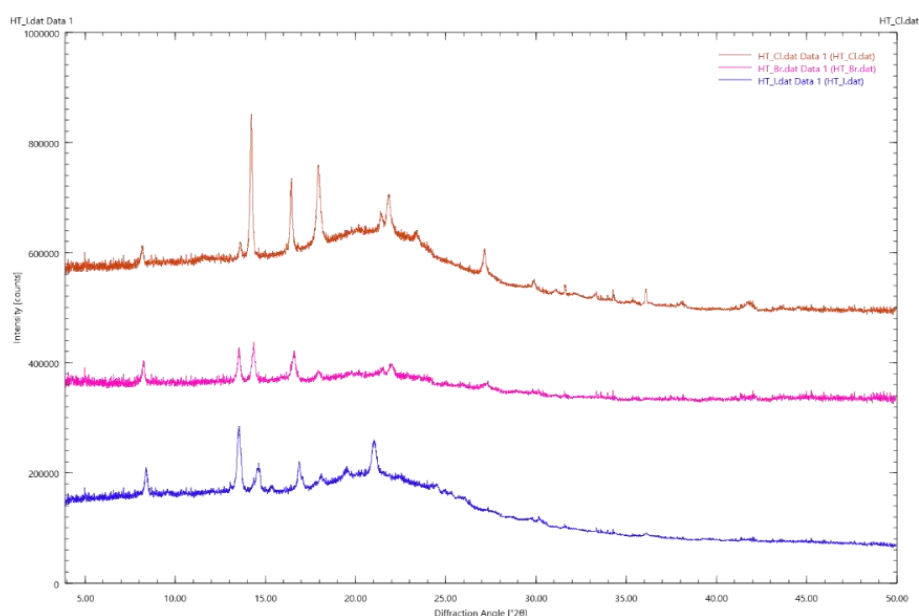


Figure 7.3 - Comparison of the phases obtained at high temperature for the three halides (Cl, Br, I).

Comparing the new crystalline phases obtained from different zinc halides, the three phases present some differences that can be characteristic of the counterion of the zinc metal salt used in the coordination compound (Figure 7.3). Such results need to be studied to understand the differences, whether it is only preferential orientation or if the metal unit plays a fundamental role in the structural rearrangement.

The second approach, based on the pressure, was developed at the synchrotron facility too. In this case, the crystalline sample prepared with ZnCl₂ was loaded on a quartz capillary, and the vacuum was applied to reach 0.55 bar and kept for about 10 hours. At this rate, the structure, starting from crystalline, slowly collapses into the

amorphous state as the Bragg peaks lose intensity. The evolution plot clearly demonstrates the collapse into the amorphous phase, and as for the temperature experiment, there is a tendency toward higher angles (Figure 7.4). The vacuum acts by removing the guest molecules gradually in the cages, which inevitably turns back into the collapsed chain form.

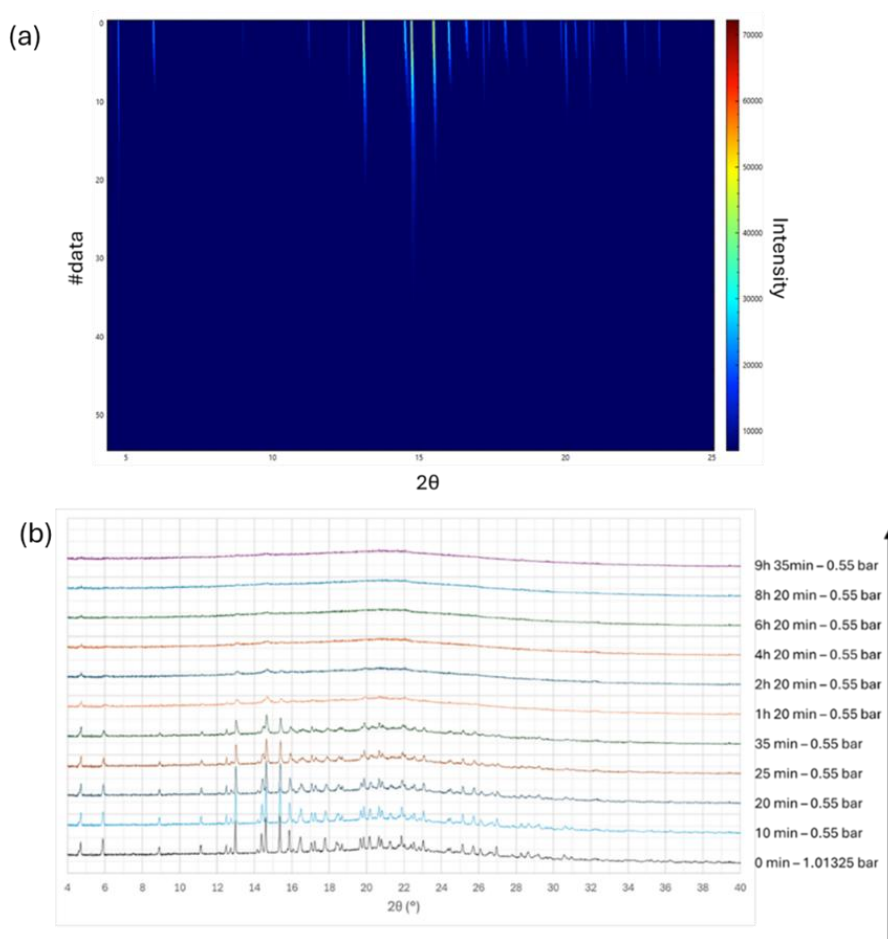


Figure 7.4 – a) Collection of all the P-XRD data into a 2D plot showing the evolution of the peaks;
b) P-XRD data from the evacuation experiment.

The effects of temperature and pressure on the material are fundamental to understand and predict the dynamic behaviour and to design the conditions for potential applications in the field of molecular recognition, drug delivery, gas storage and so on.

7.2 CLASSIC NMR study

For a clearer understanding of the behaviour of the material as microcrystalline powder in contact with an aromatic solution, the CLASSIC NMR technique is a powerful tool.^[94] The CLASSIC NMR experiment carried out at the High Field Solid-State NMR Facility in Warwick helped explore more deeply the *in-situ* guest inclusion phenomena. With this technique, it is possible to investigate the evolution of both the liquid and the solid state at the same time (Materials and methods for the experimental procedure). The pulse sequence was: 1) $^1\text{H} \rightarrow ^{13}\text{C}$ CP; 2) ^{13}C HPDEC; 3) ^1H . Several experiments were carried out using different ratios of *o*-dichlorobenzene as aromatic templating guest and methanol. The most representative experiment is the one with the highest ratio between *o*-DCB and TPB, as it is the most similar to the conditions done *ex-situ*. Still, the ratio carried out during the instant synthesis is too high (a large excess of *o*-DCB, *o*-DCB/TPB ~900) to be replicated in the small insert of the NMR rotor. The *in-situ* experiment is done by contacting the amorphous phase with a mixture of *o*-DCB/MeOH (77:23 v/v) in the insert, and the highest *o*-DCB/TPB ratio that could be achieved was 17.9. After a few minutes of the solid-liquid contact, the acquisition is started, and the pulse sequence cycle is carried out for a total measurement time of almost 14 hours. The experiment clearly showed an evolution where the *o*-dichlorobenzene and the methanol change the phase, and there is the presence of more chemical and physical environments. The measured spectra are collected in evolution plots as a function of time to show how the peaks change and gain information on the progress of the experiment (Figure 7.5 and Appendix 13.30, 13.31).

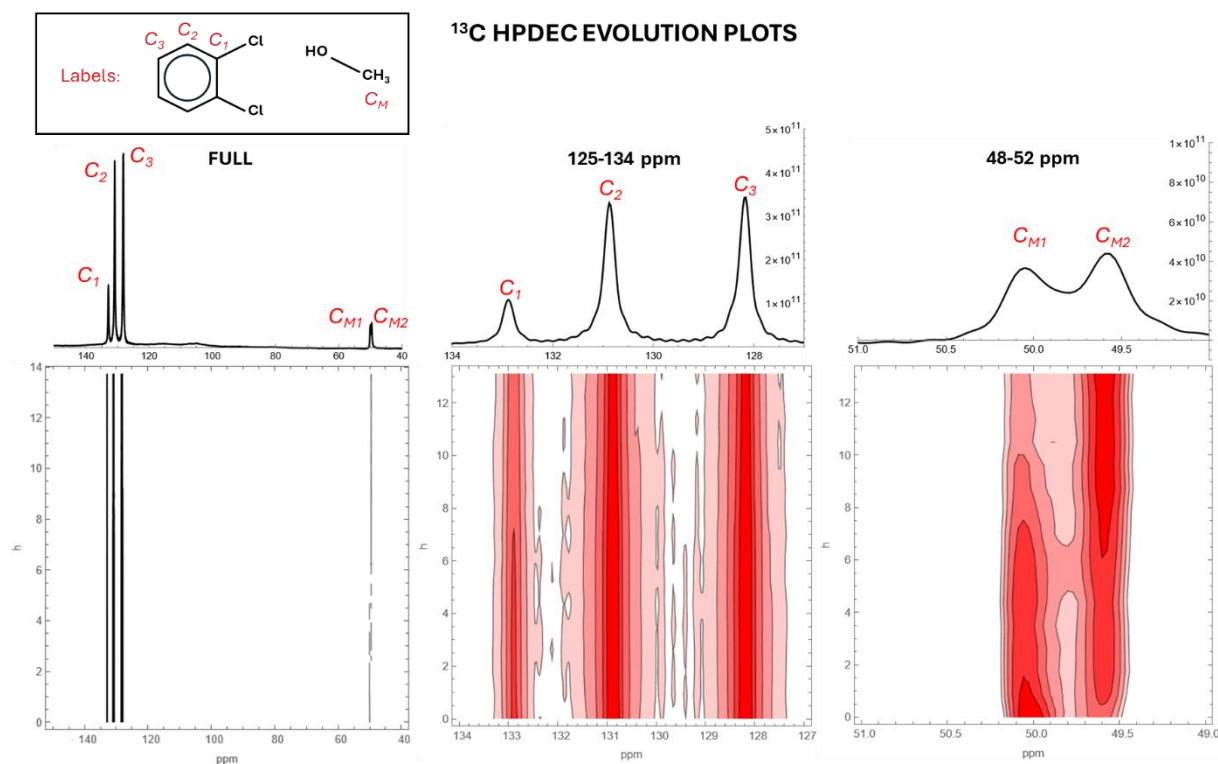


Figure 7.5 – Evolution plot of the ^{13}C HPDEC spectra collected over the course of the experiment. The spectra on the top represent the sum of all spectra of the corresponding evolution plot below.

^{13}C HPDEC can give combined information on the solid and liquid states. The spectra and evolution plot (Figure 7.5) show the *o*-DCB and methanol peaks. The *o*-DCB peaks are three, corresponding to the three carbons, where the carbon attached to the Cl is much weaker than the other two because of no direct contact with hydrogens for effective decoupling. Two main peaks at low ppm indicate the presence of two methanolic environments, one increasing and one decreasing.

The $^1\text{H} \rightarrow ^{13}\text{C}$ CP spectra and evolution plot (Appendix 13.30) show mainly the peaks of the solid phase present in the rotor. Broad peaks represent the main framework of the cage with spinning sidebands generated by a not fast enough Magic Angle Spinning. Interestingly, there is the presence of sharp peaks indicating a highly mobile environment, which was assigned to the carbons of the *o*-dichlorobenzene. The carbon of the *o*-DCB attached to the Cl is not present in the spectra, probably because the CP is not efficient enough. In the aliphatic range, there is the presence of methanol peaks. Here, different peaks are present, indicating the existence of different environments, where methanol molecules are present in different states in the cages. It is clear from the evolution plots that while one peak decreases, the other increases

in intensity, and in between these two peaks, there is another broad feature indicating another methanolic environment exchanging on a different timescale.

The ^1H measurement (Appendix 13.31) presents a complex behaviour which is still hard to analyse but probably indicates the contemporary presence of ordered and disordered methanol.

The P-XRD pattern of the sample after the NMR experiment matches the crystalline phase that is obtained when the crystalline (or even amorphous) phase is annealed up to 230°C (Section 7.1, *Temperature and pressure effects on the phase transition*). Probably, there was a rearrangement and transformation of phase, and this could also happen once the sample is taken out of the rotor and out of the insert.

Still, the data analysis is difficult as the dynamic behaviour, and more in general, the overall system, is quite complicated. A detailed analysis of $^1\text{H}\rightarrow^{13}\text{C}$ CP and ^{13}C HPDEC can give important information about the motional difference in the environments and ordered/disordered guest, even understanding which type of guest is the first to settle in the cage. The interpretation of the spectra and their evolution is still going on to clear all the doubts and try to give a definite mechanism.

8 Conclusions and outlook

This doctoral thesis reported the synthesis, characterisation, and functionalization of MOCs derived from the TPB ligand. The main focus was the self-assembly of TPB with Zn metal salts into $M_{12}L_8$ poly- $[n]$ -catenanes. Different synthetic (Chapter 3) approaches were used to obtain different products following kinetic and thermodynamic control. The $M_{12}L_8$ poly- $[n]$ -catenane is obtained in a crystalline phase using solution-based reactions (slow crystallisation or instant synthesis methods) or in the amorphous phase using grinding techniques. The slow crystallisation produces a mixture of two materials, the $M_{12}L_8$ interlocked nanocages (kinetic product) and a new coordination polymer (thermodynamic product). The instant synthesis allows to trap the kinetic product in the bulk state. In the solid-state, mechanochemistry produces the kinetic product as an amorphous powder, which can be transformed into the crystalline product by means of the guest templating effect *via* an amorphous-to-crystalline transformation. In this way, the $M_{12}L_8$ polycatenane can be obtained in a fast and easy way, with good yields and in total absence of solvent, ideal for scale-up purposes. DFT calculations allowed the rationalisation of the interaction energies in the entire structure, defining a hierarchy of energies from the host-host (*i.e.*, chain-chain interactions, 27 kcal/mol), host-guest (46 kcal/mol), to the mechanical bond energies (110 kcal/mol). All these energies contribute to the overall structure stabilisation.^[125] The combination of XRD, DFT calculations and NMR techniques allowed the complete elucidation of the 3D structure and exploration of its dynamic behaviour when exposed to external stimuli.

The $M_{12}L_8$ poly- $[n]$ -catenanes exhibit exceptional guest-uptake abilities, which were studied for molecular recognition applications (Chapter 3). Aromatic molecules and volatile organic compounds have been studied for guest inclusion and exchange studies. Gas-solid SCSC guest exchange experiments allowed the description of the dynamic behaviour that permits the guest inclusion and stabilisation in the $M_{12}L_8$ cages. It was possible to propose a mechanism where the pyridine moiety of the TPB acts as a nanorotor (*i.e.*, due to the low rotational energy (*ca.* 3kcal/mol)) and lets the guest enter and fix at specific positions. Thanks to DFT calculation, these spots were rationalised and defined as binding sites for aromatic guest molecules. Preferential inclusion of a series of aromatic guests was determined, which is important for molecular recognition applications. Even small molecules like methanol or

nitromethane could be trapped. The differences in behaviour when the cages trap aromatic or non-aromatic molecules were highlighted with a VT-SC-XRD study, proposing a swelling-like or breathing-like effect when the temperature is increased.

Next was the encapsulation of larger molecules, and a drug like paracetamol was chosen (Chapter 4). Using slow crystallisation, single crystals could not be obtained; thus, paracetamol was trapped in the amorphous phase of the $M_{12}L_8$ poly-[*n*]-catenane, which was prepared by mechanochemical methods. An experimental-computational combined approach has been applied to solve structures from low-quality P-XRD patterns coming from the inclusion of paracetamol in $M_{12}L_8$ cages. The controlled release in water was successfully proved, and the recovered TPB was reused for further synthetic reactions.

Another topic of this research was focused on the functionalization of the organic ligand TPB to explore how the diversifications have an impact on the coordination assembly mechanism and products (Chapter 5). Two new ligands (mTPB and extTPB) were synthesised, and their crystalline structure was determined by SC-XRD. These two structures were not reported yet in the Cambridge Structural Database, and thus, they were deposited. The mTPB derivative was coordinated with $ZnBr_2$, yielding a new 2D MOF, which suggested that the presence of the methyl group (steric and electrostatic effect) prevented the formation of the $M_{12}L_8$ cages. The extTPB was subjected to coordination with $ZnBr_2$, but there is no proof yet of the product obtained. Although poorly diffracting single crystals were obtained, the unit cell parameters could not be determined.

The other cornerstone of the research was the coordination of the TPB ligand into M_6L_4 cages using ethylenediamine Pd^{2+} end-capping groups (Chapter 6). The cages were synthesised self-assembling TPB and Pd^{2+} using ethylenediamine as end-capping groups in the solid state and in the solution state. Mechanochemistry produced the M_6L_4 cages in the powder state, as was confirmed by ^1H NMR analysis. This is very important because it is possible to obtain the material in the absence of a solvent and in rapid times. The structure was confirmed thanks to single crystals suitable for SC-XRD that were obtained by overcoming the challenging crystallisation process using a suitable templating agent. Solid-state DFT calculations described the binding energies of the $Pd_6(TPB)_4$ and of the $Pd_6(TPT)_4$ cages. Due to the intrinsic properties of the TPB ligand, the final product, though isostructural to Fujita's M_6L_4 , presents some differences, and the latter is more stable. In the case of the studied guest, 4 molecules could be stored in each cage in a very specific position at the border

of the cage, partially inside and partially outside. By means of titration experiments, it was possible to obtain information on the guest inclusion mechanism and the potential carrying of hydrophobic compounds into aqueous solutions.

The research on polycatenanes self-assembled of $M_{12}L_8$ MOCs was expanded through high-field *in-situ* NMR (UK High Field NMR facility in Warwick) and high-resolution P-XRD synchrotron (UK Diamond Light Source in Didcot) (Chapter 7). These studies were aimed to investigate the evolution in real time of the amorphous $M_{12}L_8$ poly-[*n*]-catenane in different conditions, giving preliminary insights for further understanding CO₂ capture potential and real-time assembly mechanisms.

Having achieved the results presented in this thesis, many new objectives are set for future research on these MOCs. The study of the amorphous phase of the $M_{12}L_8$ poly-[*n*]-catenane is not yet completed, but the use of powerful techniques like PDF analysis can reveal interesting information and patterns on the nature of the disordered catenanes. The CO₂ trapping (or other small volatile molecules) will be further explored, as evident results demonstrate the capability of inclusion of gas phase. The results obtained using the synchrotron source are a good starting point to analyse the phase transitions that occur when the material is exposed to thermal annealing or pressure drops. New phases could be discovered that possess interesting properties. The CLASSIC NMR approach gave plenty of preliminary results, but the data are quite complicated to interpret. Nevertheless, it is a powerful method, and it will be used for a deep understanding of the mechanism of guest inclusion in the cages. New applications can be investigated, for example, the use in the nanoreactor field, where guest molecules are trapped in cages and then subjected to external stimuli that induce chemical reactions on these molecules. $M_{12}L_8$ interlocked nanocages were obtained by the combination of TPB and ZnI₂, but what if the metal counterpart is changed? Interesting studies have already started exploring the self-assembly of TPB with other metal units (*e.g.* Cu, Ni, Co, Cd, Hg), moving on the periodic table around the Zn to find a connection between the atomic properties and the formation of interlocked metal-organic structures.

The 2D MOF obtained from the mTPB ligand will be characterised to understand its properties and its application in exfoliation treatments and electron conductivity. Ligand extTPB was not yet used in combination with ZnX₂ salts and can give large architectures resembling the $M_{12}L_8$ geometry. If a cage is not obtained, it means that the extension of the ligand arm prevents the coordination into pseudo-spherical assemblies, or that the structures have low thermodynamic stability. As in

the TPB case, it would be interesting to explore the assembly with other metal salts of the periodic table to check the formation of a new coordination product. Even with the ethylene diamine palladium salt, to test the possible formation of the M_6L_4 discrete octahedral cages.

Ligand TPB has been used for the first time for the synthesis of M_6L_4 octahedral cages, with end-capped Pd^{2+} ions. In the presence of suitable guest molecules, the elusive TPB M_6L_4 SC-XRD structure has been determined. The TPB M_6L_4 octahedral MOC showed that it can be used for carrying out host-guest chemistry experiments in the inclusion of aromatic guest molecules. Future studies will explore the inclusion of other molecules, maybe unstable in water, that are stabilised in this type of environment. This M_6L_4 cage structure can even be used to study chemical reactions in a nanoconfined space, where unusual reactions can be carried out. The study of these MOCs can help the research because they not only have interesting topologies and potential tunability, but also have properties open to a wide range of applications.

9 *Materials and methods*

Starting materials and solvents were purchased from commercial suppliers (Alfa Aesar, Apollo Scientific, Fluka, FluoroChem, Honeywell, Sigma Aldrich, TCI, iChemicals) and used without further purification, if not mentioned otherwise.

9.1 Analytical Instrumentation

Powder X-Ray Diffraction

Bruker D2-Phaser diffractometer equipped with Cu radiation ($\lambda = 1.54184 \text{ \AA}$) using Bragg Brentano geometry. The experiments were performed at room temperature.

Single Crystal X-Ray Diffraction

SC-XRD were performed at the NeXt GAME Laboratory of the Politecnico di Milano, co-founded by Regione Lombardia. Single crystal X-ray data were recorded using a XtaLAB Synergy-S, Dualflex, HyPix-6000HE diffractometer.

Synchrotron experiments

Synchrotron-based experiments were performed at Diamond Light Source facility, Didcot, UK. The beamtime was allocated at the I11 beamline (High Resolution Powder Diffraction). The energy of the beamline is set at 15 keV ($\lambda \sim 0.826 \text{ \AA}$) for all experiments. With the standard beamstop in position, the lowest accessible 2θ angle is ~ 3 degrees ($d \sim 15 \text{ \AA}$ at 15 keV). The diffractometer adopts a standard Debye-Scherrer (capillary) geometry. Instrument calibration was performed with a silicon standard sample from the National Institute of Standards and Technology (NIST; Gaithersburg, MD, USA). The beamline uses an integrated multi-analysing crystals

(MAC) detector (x5 MAC-arms with 45 MAC channels). Temperature calibration was performed with a silver standard at room temperature with 1 sec step scans.

Solution-state NMR

Bruker ARS (400 MHz) spectrometer, selecting an appropriate number of scans and relaxation time using several deuterium solvents depending on the compound to be analysed.

High-Resolution Solid-State NMR

BRUKER NEO spectrometer equipped with a commercial 4 mm MAS iProbe. The magnetic field strength was 11.74 T with a spinning speed of 12 kHz. The operative temperature was 298 K with 3600-4800 scans for an appropriate signal-to-noise ratio. The solid-state Nuclear Magnetic Resonance (NMR) analysis was conducted using samples packed into a 4 mm ZrO₂ rotor. The standard High-Power Decoupling (HPDEC) MAS NMR spectra were acquired using a 90° pulse of 3.8 µsec, a 10 sec repetition time, and 3,000 scans. The Cross-Polarisation (CPMAS) NMR spectra utilised a 2 msec contact time, a 4 sec repetition time, and 6,500 scans. Additionally, CPNQS (Non-Quaternary Suppression) experiments were performed to selectively suppress signals from carbons bonded to protons, relying on a preacquisition delay of 60 µsec without proton decoupling to dephase the magnetisation of non-quaternary carbons (i.e., carbons not bonded to any protons).

High-Field CLASSIC NMR

High-Field CLASSIC NMR experiments were performed at the UK High-Field Solid-State NMR Facility on an 850 MHz solid-state NMR system sited at the University of Warwick.

FT-IR

ATR (Attenuated Total Reflection) method using a Varian 640-IR spectrometer by Agilent Technologies equipped with a PIKE MIRacle single reflection ATR by PIKE Technologies. Spectra were taken in the wavelength range of 450 cm⁻¹ to 4500 cm⁻¹ with 128 scans.

GC-MS

An Agilent HP-6890 chromatograph provided with a 5973-mass detector and an Agilent HP-5MS column.

TGA

Thermo-Gravimetric analyses were determined with a Perkin Elmer Thermal Analysis instrument by the Laboratorio Analisi Chimiche at the Department of Chemistry, Materials and Chemical Engineering (Politecnico di Milano). The temperature ranged from 30 °C to 700 °C with a heating rate of 10 °C/min under nitrogen.

Elemental Analysis

The elemental analysis experiments were performed by the Laboratorio Analisi Chimiche at the Department of Chemistry, Materials and Chemical Engineering (Politecnico di Milano) using a Costech ECS mod. 4010.

9.2 General procedures

9.2.1 $M_{12}L_8$ interlocked MOCs

9.2.1.1 Synthesis

Slow crystallization

30 mg of TPB were dissolved in 8 mL of nitrobenzene (or another specified solvent quantity) and 2 mL of methanol, in a 25 mL round-bottomed flask, and the mixture was stirred at room temperature until a clear, homogeneous solution was obtained. Simultaneously, a specific amount of zinc halide metal salt (32.76 mg of $ZnBr_2$, 19.83 mg of $ZnCl_2$, or 46.43 mg of ZnI_2) was dissolved in 1 mL of MeOH in a separate vial. For the crystallisation step, the ligand solution was transferred to a test tube, and 3 mL of methanol was carefully layered on top to create a distinct phase separation. This was followed by the layering of the metal salt solution as the third layer. Finally, the test tube was sealed with Parafilm to prevent evaporation, and the desired yellowish, transparent crystals were formed after approximately one week.

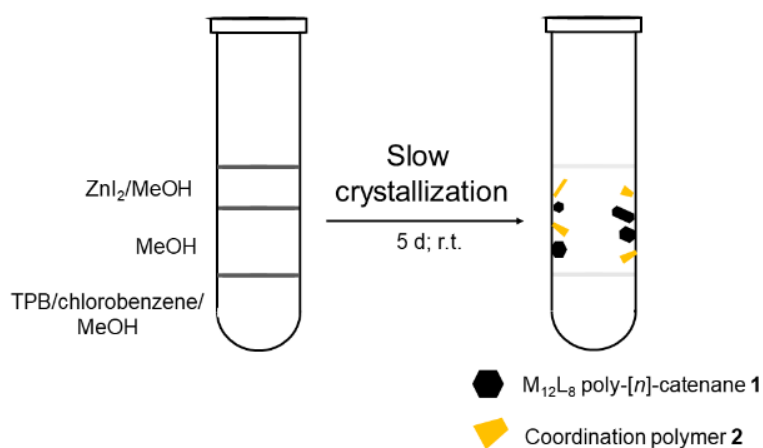


Figure 9.1 — Example of a slow crystallisation experiment: a test tube with the three layers and the growth of crystals.^[125]

The general formula of catenanes is $M_{12}L_8$, the ratio ligand to metal is 1:1.5.

30mg TPB (MW = 309.364 g/mol) = 0.097 mmol $\times$ 1.5 = 0.1455 mmol

ZnBr₂ (MW = 225.2 g/mol) = 32.767 mg

ZnCl₂ (MW = 136.3 g/mol) = 19.829 mg

ZnI₂ (MW = 319.2 g/mol) = 46.444 mg

Instant synthesis

The synthesis was performed by combining a ligand solution with a metal salt solution, with the immediate precipitation of the desired product. First, 30 mg of TPB were dissolved in a 25 mL round-bottomed flask with 8 mL of nitrobenzene (or another specified solvent) and 2 mL of methanol (MeOH), then stirred at room temperature until a clear solution formed. A precise amount of zinc halide salt (32.76 mg ZnBr₂, 19.83 mg ZnCl₂, or 46.43 mg ZnI₂) was dissolved in 1 mL of MeOH in a glass vial. The metal solution was then rapidly added to the ligand solution under vigorous stirring, causing an immediate formation of a white precipitate. This suspension was stirred for 15 minutes, then filtered and left exposed to the atmosphere to remove any residual volatile solvent from the surface of the microcrystalline powders.

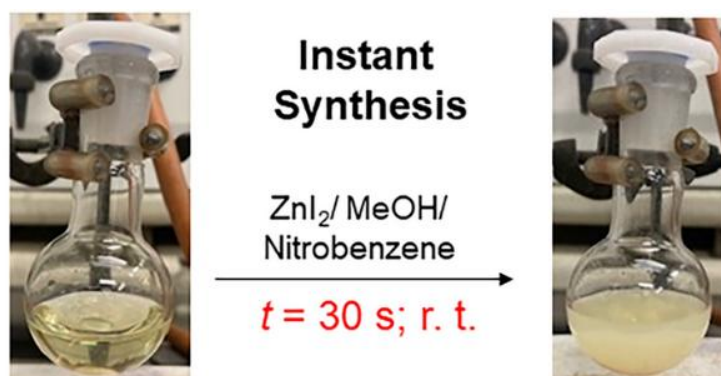


Figure 9.2 — Example of instant synthesis experiment: clear solution before adding the metal salt and instant precipitation after rapid addition of the salt.^[125]

Mechanochemical synthesis

30 mg of the ligand (TPB) and a quantity of the chosen zinc halide metal salt (32.76 mg ZnBr₂, 19.83 mg ZnCl₂, 46.43 mg ZnI₂) were ground in an agate mortar for a

minimum of 15 minutes, resulting in a white powder product. The product can be washed with a small amount of methanol and chloroform (~3 mL each) to remove any unreacted compounds, then dried and analysed at P-XRD and Elemental Analysis. The yield is ~80%.

In the case of Liquid Assisted Grinding, the milling is supported with two drops of methanol.

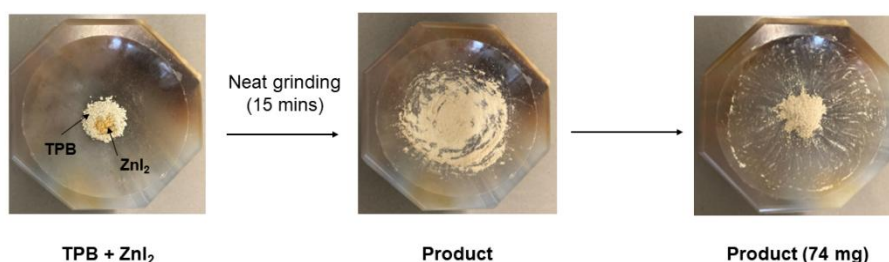


Figure 9.3 — Example of neat grinding experiment: agate mortar with the two reactants, product after grinding, product collected and weighted.^[125]

9.2.1.2 Characterizations

Guest inclusion

To incorporate the guest templating agent, 30 mg of the poly-[*n*]-catenane were placed in a round-bottom flask with 5 mL of the guest material solution. The resulting mixture was stirred for a given time, typically overnight. Following the stirring period, the solid was allowed to settle. The suspension was then filtered, and the resulting white solid was subsequently dried in open air before analysis.

SC to SC guest exchange

The gas-solid experiments were done by securing a suitable single crystal on a nylon loop for SC-XRD. The crystal was then placed inside a sealed chamber containing the volatile aromatic solvents. The entire experiment was conducted at room temperature.

Paracetamol study ^1H NMR and recyclability test

Paracetamol inclusion was conducted according to the procedure reported in the previous section (9.2.1.2, guest inclusion).

To quantify the paracetamol encapsulated within the M_{12}L_8 poly- $[n]$ -catenanes, a small amount of sample (*ca.* 5 mg) of the microcrystalline catenane was added to the NMR tube, with 0.5 mL of deuterium oxide and two drops of deuterated sulfuric acid. This acidic solution breaks down the catenane structure, causing the paracetamol and ZnX_2 components to dissolve in the water. TPB molecules are protonated and go into solution, resulting in a clear and transparent mixture for analysis. The concentration of paracetamol was determined by ^1H NMR spectroscopy, where the integrated intensity of the TPB singlet peak (two hydrogens at 7.5 ppm) was compared to the integrated intensity of one of the paracetamol doublet peaks (three hydrogens, around 5.5-6.5 ppm). By calculating the ratio between these integrated peaks and knowing that the M_{12}L_8 cage structure contains 8 TPB molecules, the exact number of paracetamol molecules per cage was calculated.

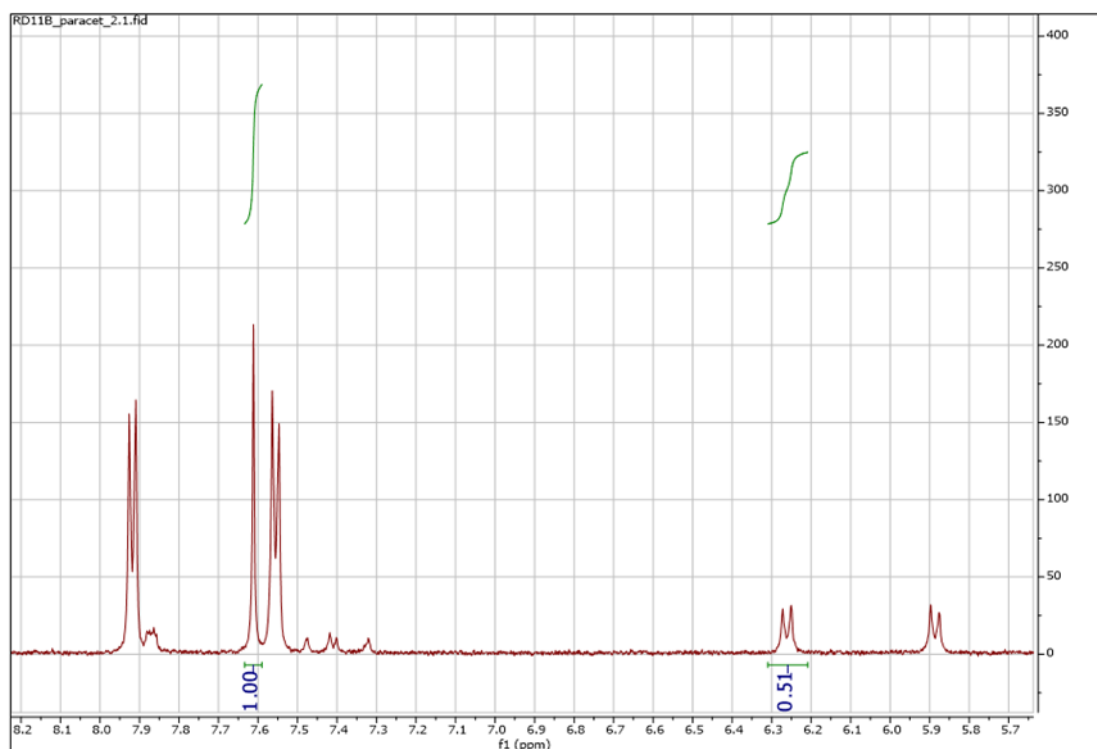


Figure 9.4 — ^1H NMR spectrum in a sample suspended in the saturated solution of paracetamol for 2d. The included paracetamol molecules per M_{12}L_8 cage are 6.12 according to the proton integrals.^[145]

The guest release and TPB recycle were conducted by dipping the crystalline phase in water and stirring for two days. The paracetamol is released and dissolved in water. The TPB molecule is not soluble in water, so it remains suspended and can be filtered. The filtrated TPB can be recrystallised in chloroform and then checked at P-XRD and ^1H NMR for purity. The ^1H NMR of TPB can be performed in deuterated chloroform.

Synchrotron thermal ramp experiment

The sample to be annealed was loaded in a quartz capillary of a diameter of 0.3 mm. The loaded capillary was sealed with super glue to a brass holder, then mounted on the base (Figure 9.4). The setup is mounted on the diffractometer for the experiment. A hot air blower (RT-1000 °C) ensures the control of the temperature. The experiment was carried out with a ramp starting from room temperature up to 500 °C (rate 12 °C/min), then cooling down to room temperature (rate -12 °C/min). Data were collected for the entire time of the thermal ramp.



Figure 9.5 — Brass holder and base for the capillary for a high-resolution P-XRD experiment at I11. (<https://www.diamond.ac.uk/Instruments/Crystallography/I11/status/capillaries.html>)

Synchrotron evacuation experiment

The sample to be exposed to a vacuum was loaded in a quartz capillary of a diameter of 1 mm. The loaded capillary is mounted on a gas cell (Figure 9.5a). The gas cell is connected to a gas pressure panel (Figure 9.5b). The vacuum was achieved through a vacuum pump that creates a certain pressure in the panel, then opening the valve connected to the sample, the pressure drops in the gas cell.

The evacuation was carried out keeping the pressure to 0.55 bar for about 10 hours, collecting data on the time of the vacuum.

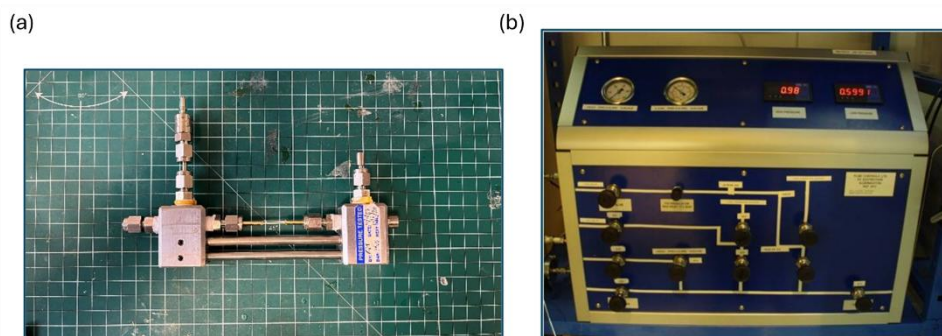


Figure 9.6 — a) High-pressure capillary gas cell; b) gas pressure control panel.
(<https://www.diamond.ac.uk/Instruments/Crystallography/I11/status/gascells.html>)

CLASSIC NMR experiments

The experiments required an insert to fit in the rotor that, with a screw, would avoid the spilling of any liquid.

According to the *ex-situ* experiment, the amount of *o*-DCB with respect to the amorphous cage is very large. Typically, 60 mg of the amorphous phase is left stirring in 16 mL of *o*-DCB (and some MeOH), which means the molar ratio *o*-DCB/TPB is around 730. Such a ratio can't be achieved, as the volume of liquid (for a very small amount of solid) would not fit in the insert. We try to put as much liquid mixture as possible in the insert and calculate the ratio we reach.

Preparation of *o*-dCB/MeOH (77:23) solution:

Table 9.1 — Calculations for the *o*-dichlorobenzene/methanol solution

	MW (g/mol)	mass (g)	moles	density (g/mL)	volume (mL)	Volume ratio	Molar ratio
<i>o</i> -DCB	147.01	1.002	0.006816	1.3	0.770769231	76.53%	53.84%
MeOH	32	0.187	0.005844	0.791	0.236409608	23.47%	46.16%

3.9 mg of an amorphous sample (**a1** phase, TPB + ZnCl₂, neat grinding) were weighted in the insert. 23.7 mg of the *o*-DCB/MeOH solution were carefully added to the insert using a Pasteur pipette. The insert was closed with its screw, put in the rotor and then the rotor was closed with its cap. The rotor was inserted in the probe, and the acquisition was started 7 minutes after the addition of the liquid phase.

Table 9.2 — Calculations for the actual *o*-dichlorobenzene/TPB experimental ratio in the rotor

	MW (g/mol)	mass (g)	moles	density (g/mL)	volume (mL)	Volume ratio	Molar ratio
<i>cage</i>	4110.56	0.0039	9.487E-07				
TPB			7.590E-06				
<i>o</i> -DCB	147.01	0.01997	0.0001358	1.3	0.01536	76.53%	53.84%
MeOH	32	0.003728	0.0001165	0.791	0.004713	23.47%	46.16%
<i>mix</i>		0.0237					

<i>o</i> -DCB/TPB	17.898
-------------------	--------

The acquisition is based on a script that repeats consequently: ¹H→¹³C CP, ¹³C HPDEC and ¹H NMR.^[94] The time for one set of measurements is 12.3 minutes, which was repeated (67 sets) for a total time of approximately 13.7 hours.

The acquisition parameters are:

- 1) ¹H→¹³C CP: SR=-111.46 Hz, d1=5 sec, 5 kHz MAS
- 2) ¹³C HPDEC: SR=-111.46 Hz, d1=5 sec, 5 kHz MAS
- 3) ¹H NMR: SR=-806.66 Hz, d1=5 sec, 5 kHz MAS

9.2.2 Ligand diversification

9.2.2.1 Suzuki-Miyaura Coupling

mTPB synthesis

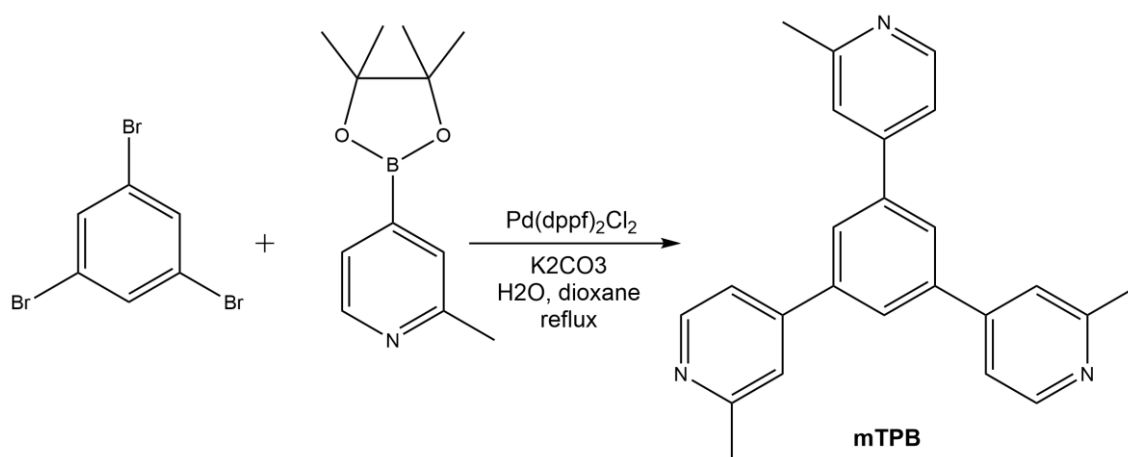


Figure 9.7 — Reaction scheme for the synthesis of mTPB via Suzuki coupling.

The synthesis of 1,3,5-tris(2-methylpyridin-4-yl)benzene was performed by a direct Suzuki-Miyaura coupling^[148] on the tribromobenzene, adapting the conditions from the paper by *Schmitt et al.*^[153].

In a 25 mL two-necked round-bottom flask, dioxane (6.4 mL) and a solution of Na₂CO₃ (504.9 mg, 4.76 mmol) in H₂O (6.3 mL) were added and degassed for 10 minutes. Then 1,3,5-tribromobenzene (50 mg, 0.158 mmol), 2-methylpyridine-4-boronic acid pinacol ester (139.2 mg, 0.635 mmol, 4 Eq), tricyclohexylphosphine (13.4 mg, 0.047 mmol, 0.3 eq), and [1,1'-bis(diphenyl-phosphino)ferrocene]palladium(II) chloride (25.9 mg, 0.032 mmol, 20 mol%) were added. The mixture was degassed under stirring for a further 10 minutes and then refluxed under a nitrogen atmosphere for 48 h. The completion of the reaction was checked by TLC (hexane : ethyl acetate in ammonia atmosphere), then the mixture was cooled to room temperature, and dichloromethane was added. The organic phase was separated and washed with H₂O, dried over Na₂SO₄, and the solvent was removed under reduced pressure to yield a dark brown oil. The crude was purified by flash column chromatography on silica

(gradient, eluent starting from Hex : EtoAc = 8 : 2 + 3%v/v TEA to 100% EtoAc + 3%v/v TEA) to yield 1,3,5-tris(2-methylpyridin-4-yl)benzene (mTPB) as a solid (Yield 45.4 mg, 81.3%). ^1H NMR (400 MHz, Chloroform- d) δ 8.62 (*dd*, J = 5.2, 0.8 Hz, 1H), 7.87 (*s*, 1H), 7.46 (*d*, J = 1.7 Hz, 1H), 7.40 (*dd*, J = 5.2, 1.7 Hz, 1H), 2.68 (*s*, 3H). ESI-MS (m/z): $[\text{M}+\text{H}]^+$ 352.2; $[\text{M}+\text{Na}]^+$ 374.1.

The product was also recrystallised in chloroform/methanol, and after slow evaporation, big crystals were obtained. The crystals were placed on a glass slide with mineral oil and examined under an optical microscope, then a suitable single crystal was chosen for SC-XRD.

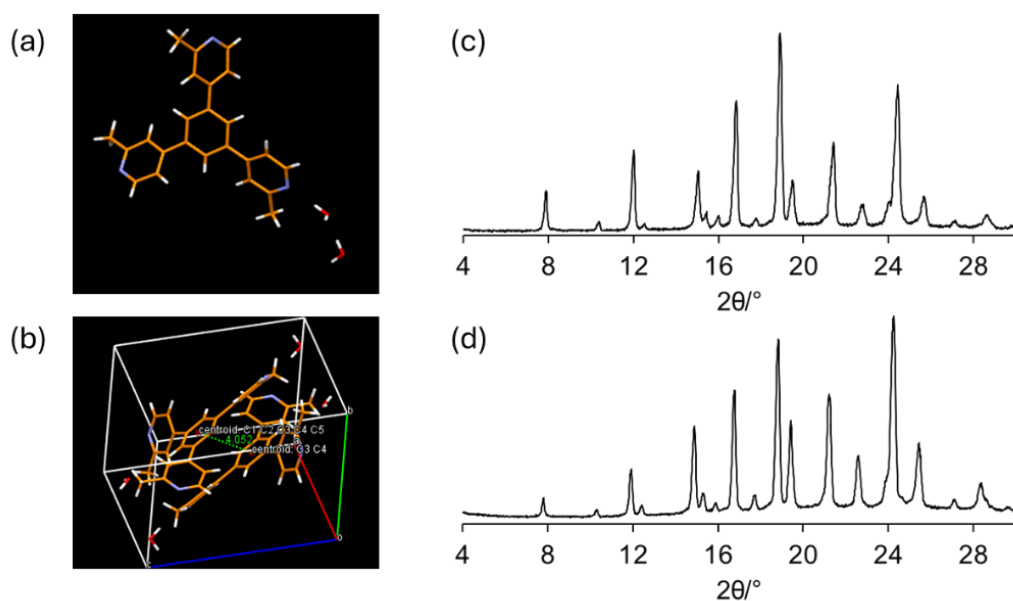


Figure 9.8 — a) SC-XRD asymmetric unit of mTPB; b) SC-XRD unit cell of mTPB; c) simulated P-XRD pattern of mTPB; d) experimental P-XRD pattern of synthesised mTPB.^[149]

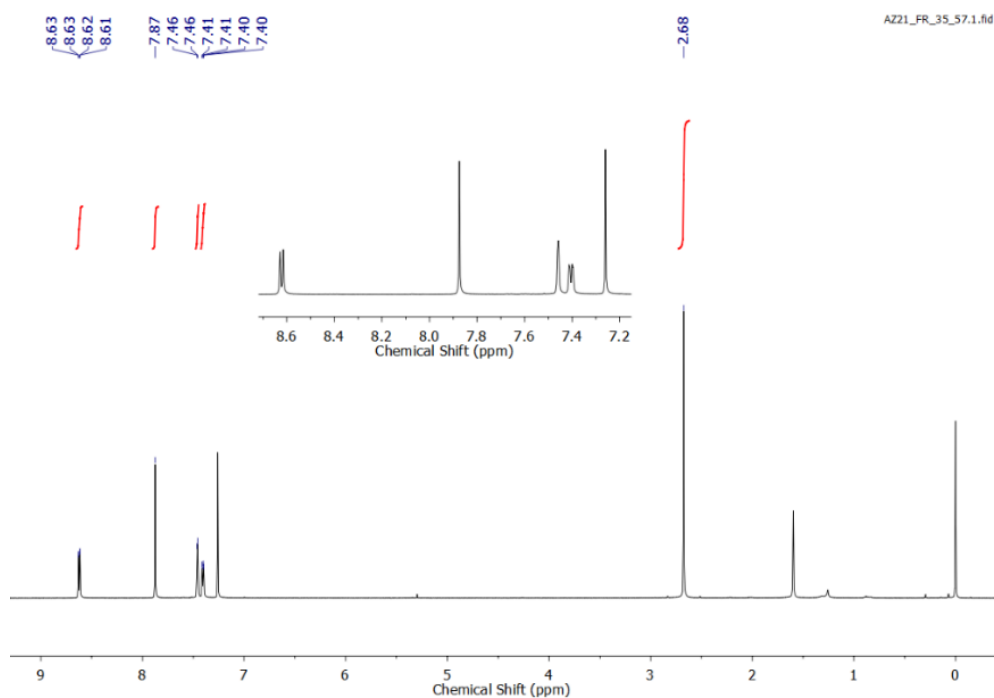


Figure 9.9 — ^1H NMR (400 MHz, Chloroform- d) δ 8.62 (dd, $J = 5.2, 0.8$ Hz, 1H), 7.87 (s, 1H), 7.46 (d, $J = 1.7$ Hz, 1H), 7.40 (dd, $J = 5.2, 1.7$ Hz, 1H), 2.68 (s, 3H).^[149]

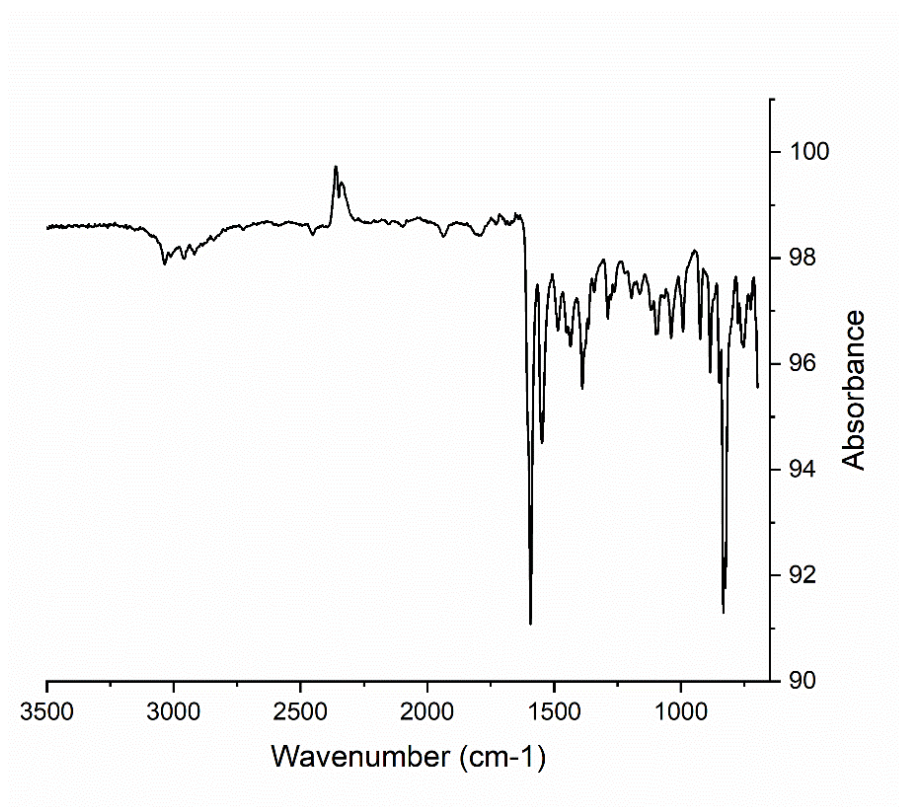


Figure 9.10 — ATR-FT-IR of synthesised mTPB.^[149]

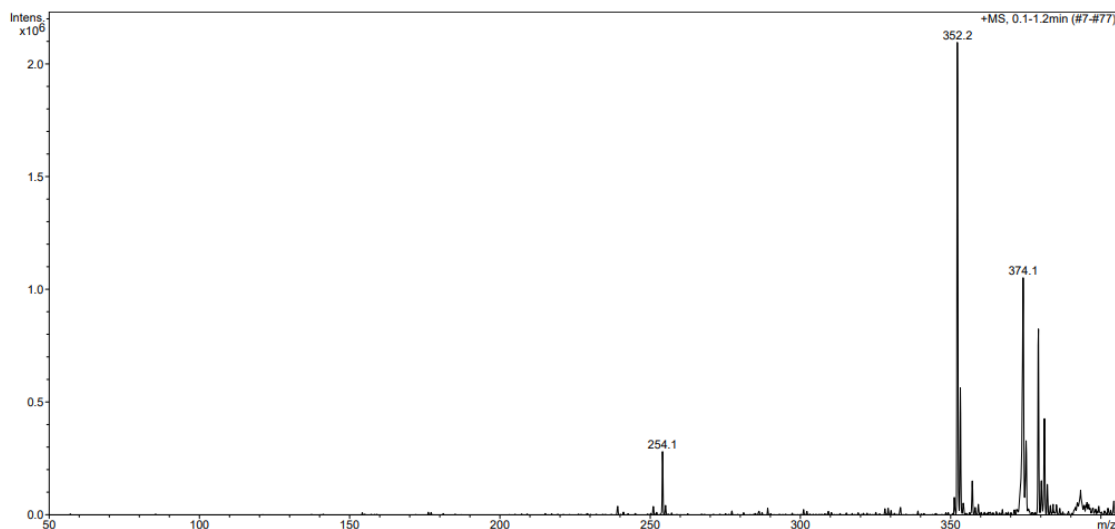


Figure 9.11 — ESI-MS of synthesised mTPB.

extTPB synthesis

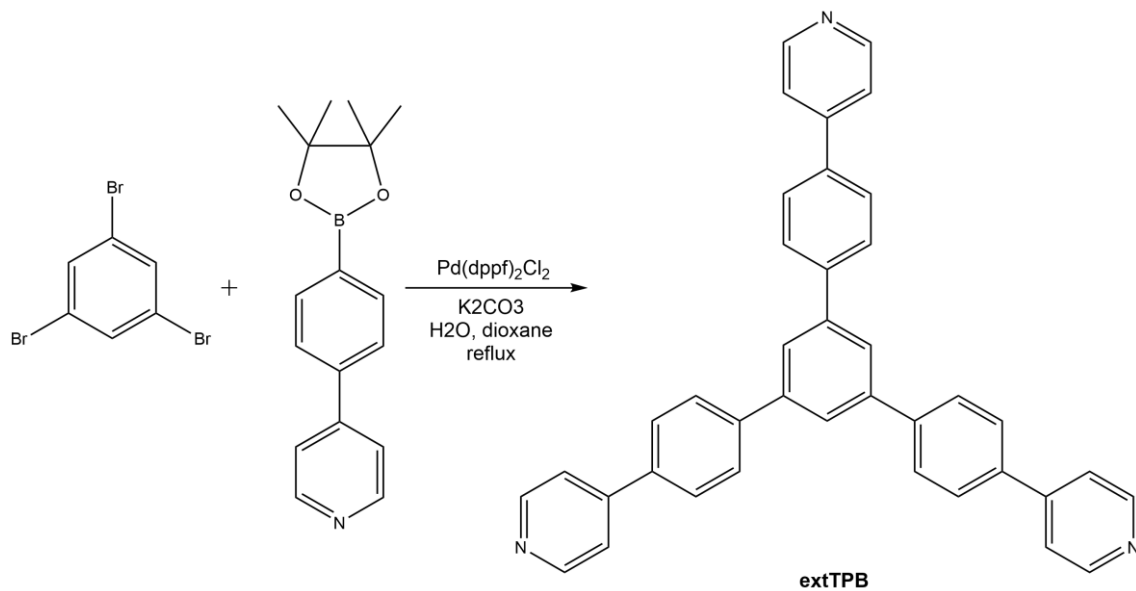


Figure 9.12 — Reaction scheme for the synthesis of extTPB via Suzuki coupling.

The synthesis of 1,3,5-tris(phenyl-4-pyridyl)benzene was performed very similarly to the mTPB synthesis.

In a 25 mL two-necked round-bottom flask, 9 mL of dioxane was added along with an aqueous solution of K_2CO_3 (659 mg in 3 mL of water). The solution was degassed for ten minutes. Subsequently, 200 mg of 1,3,5-tribromobenzene (0.477

mmol, 1 equivalent) and 402 mg of 4-(4-phenyl)pyridineboronic acid pinacol ester (1.431 mmol, 3 equivalents) are added to the flask with the catalyst system, tricyclohexylphosphine (40 mg, 0.143 mmol) and 1,1'-bis(diphenylphosphino)ferrocene]palladium(II)chloride (58.4 mg, 0.072 mmol, 15 mol%). The mixture was degassed for another ten minutes while stirring and then heated to reflux under a nitrogen atmosphere for 48 hours. The reaction was monitored by TLC (dichloromethane:methanol=9:1). At completion, the mixture was cooled and diluted with 100 mL of dichloromethane. The aqueous part was removed while the organic layer was collected, washed twice with 40 mL of water, and dried over Na₂SO₄. The solution was reduced using a rotary evaporator and then recrystallised in ethanol at 80°C for 24 hours. The product was characterised by ¹H NMR, mass spectrometry and P-XRD, matching the literature reports.

The product was also recrystallised in chloroform, and after slow evaporation, big crystals were obtained, suitable for SC-XRD.

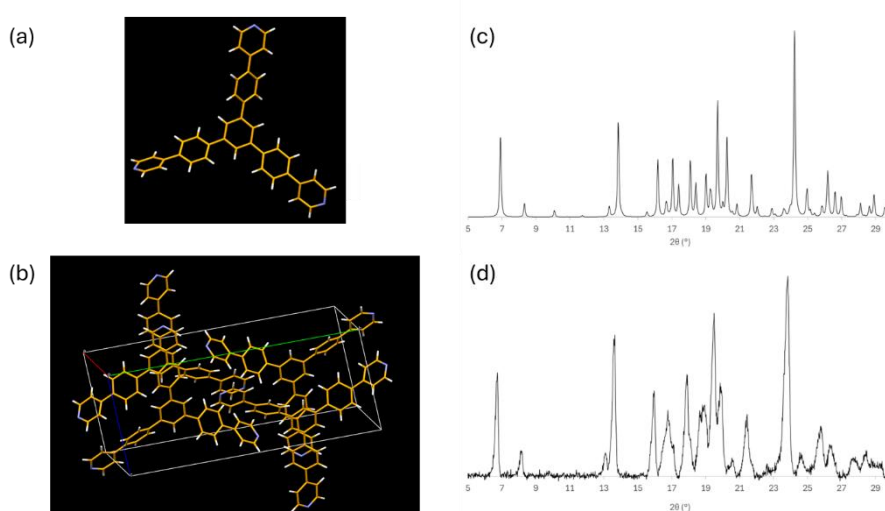


Figure 9.13 — a) SC-XRD asymmetric unit of extTPB; b) SC-XRD unit cell of extTPB; c) simulated P-XRD pattern of extTPB; d) experimental P-XRD pattern of synthesised extTPB.

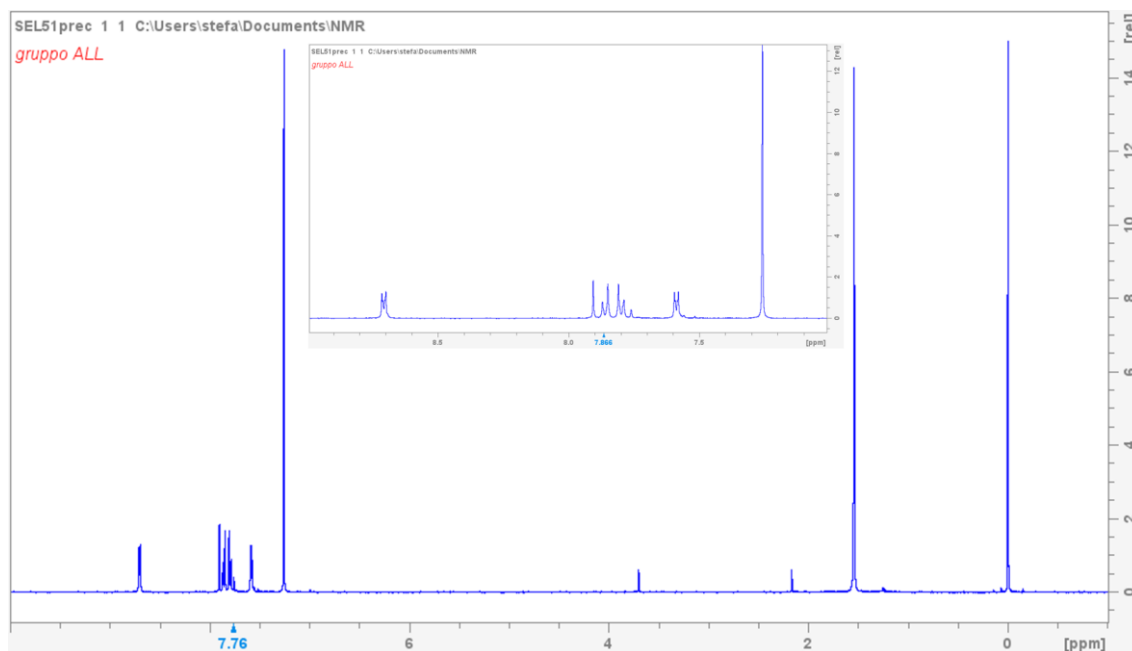


Figure 9.14 — ^1H NMR (400 MHz, Chloroform- d).

9.2.2.2 mTPB coordination polymer

Slow crystallization

mTPB (7.5 mg/0.021 mmol) is dissolved in a mixture of 1,2-dichlorobenzene and methanol (2:1 mL) and transferred to a test tube. Methanol is slowly added dropwise, layered on top of the ligand mixture. Then, a methanolic solution of ZnBr_2 (7.2 mg/0.032 mmol in 1 mL of MeOH) is layered dropwise as previously done with methanol to form a third layer. After *ca.* 3 days, crystals are formed on the walls of the test tube (**3**).

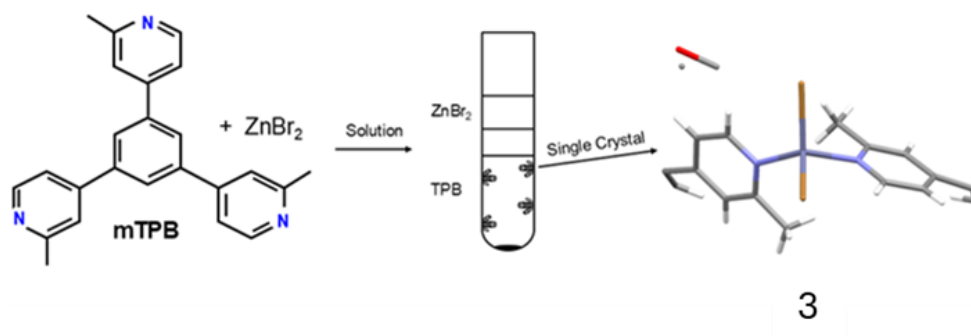


Figure 9.15 — Reaction scheme for the growth of **3** crystals and SC-XRD asymmetric unit content of **3**.^[149]

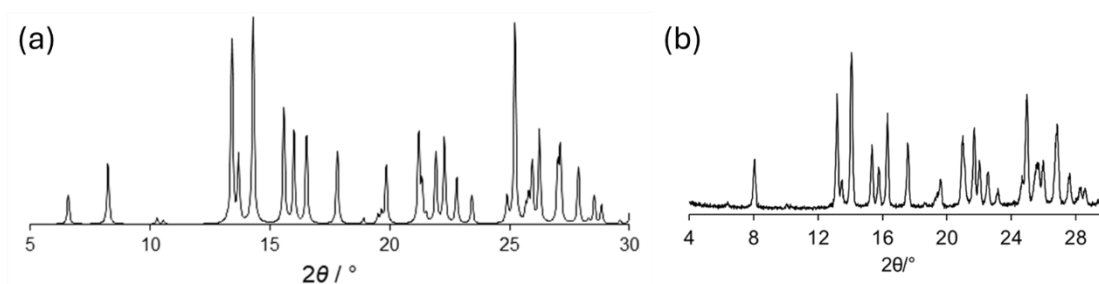


Figure 9.16 — a) simulated P-XRD pattern of **3**; b) experimental P-XRD pattern of filtered crystallisation tube.^[149]

Instant synthesis

In a 25 mL round-bottomed flask, 30 mg of mTPB (0.085 mmol) were suspended in 4 mL of 1,2-dichlorobenzene. Then, 1 mL of MeOH was added, and the mixture was stirred at room temperature until a clear homogeneous solution was obtained. Meanwhile, 28.8 mg ZnBr₂ (0.128 mmol) was dissolved in 1 mL of MeOH in a glass vial. The metal solution was quickly poured into the ligand solution under vigorous stirring. After the addition of the metal salt, a white precipitate immediately formed, giving a suspension which was left stirring for 15 minutes. The formed solid was filtered and left to equilibrate with the atmosphere to eliminate any solvent attached to the surface of the microcrystals (**3**).

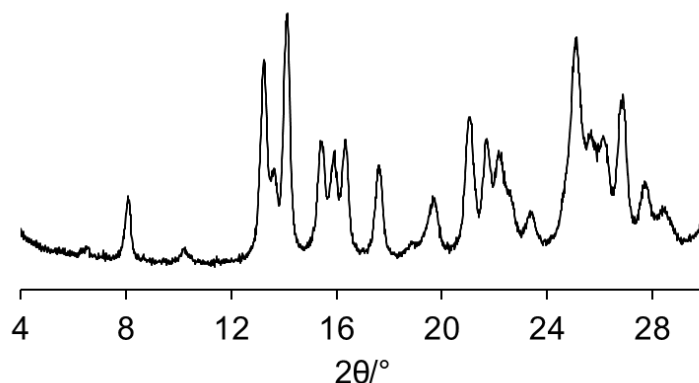


Figure 9.17 — P-XRD pattern of **3** obtained by instant synthesis method.

Mechanochemical synthesis

30 mg of mTPB (0.0967 mmol) and 28.8 mg ZnBr₂ (0.128 mmol) were ground in a mortar for at least 15 minutes to obtain a white powder (**a2**). The sample is transferred to filter paper to be washed with methanol and chloroform to remove any traces of mTPB or ZnBr₂ that have not reacted.

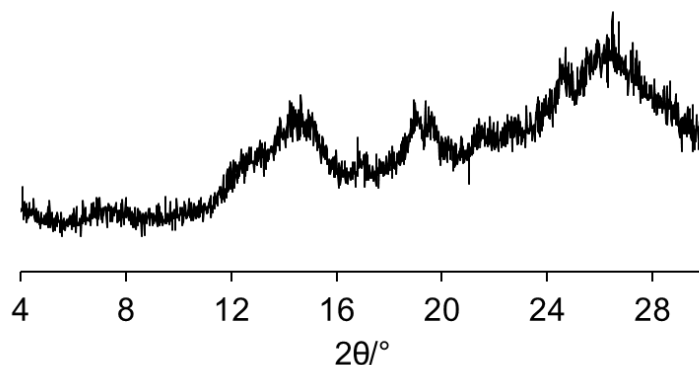


Figure 9.18 — P-XRD pattern of **a2** obtained by the neat grinding process.^[149]

Guest-inclusion experiments in 1,2-dichlorobenzene

30 mg of the neat ground sample (**a2**) were added to a round-bottom flask with 4 mL of 1,2-dichlorobenzene and 1 mL of methanol. The system was stirred overnight. Then, the stirring was stopped, and the solution was allowed to settle. The mixture was filtered, and the resulting off-white solid was dried in open air before the analysis (**3**).

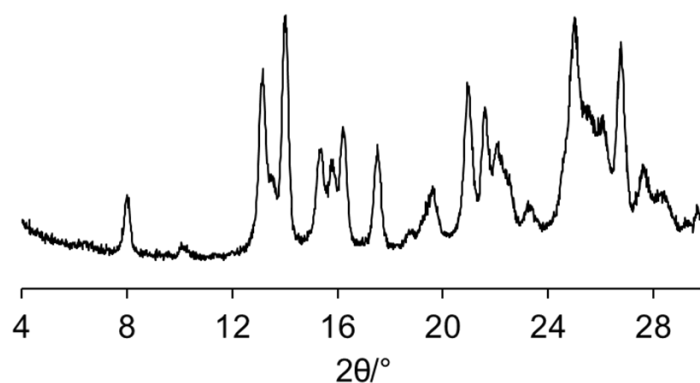


Figure 9.19 — P-XRD pattern of **3** obtained by guest inclusion on the amorphous sample **a2**.

Thermal annealing process

The amorphous sample obtained by neat grinding (**a2**) was heated up to 300 °C for one hour, then cooled down to room temperature for four hours to obtain the crystalline phase **3**.

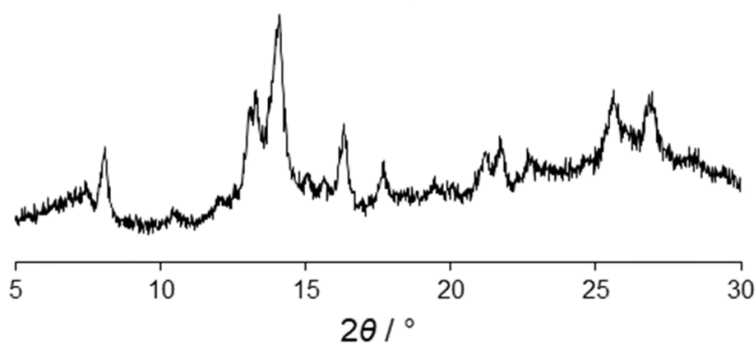


Figure 9.20 — P-XRD pattern of **3** obtained by thermal annealing of the amorphous sample **a2**.^[149]

9.2.3 M₆L₄ MOCs

9.2.3.1 Synthesis

enPd(NO₃)₂ synthesis

(ethylenediamine)palladium(II) dinitrate (*enPd(NO₃)₂*) was synthesised in the lab starting from the corresponding chloride salt. 218 mg (1 equivalent) of *enPdCl₂* and 312 mg (2 equivalents) of *AgNO₃* were added to a round-bottom flask with 10 mL of water. The mixture was first stirred for two hours at 60 °C, then for 24 hours at room temperature, with the flask always covered with aluminium foil. The result is a clear, yellow aqueous solution, with a grey precipitate corresponding to *AgCl*, which is separated by filtration. The clear solution was evaporated using a rotary evaporator, and the remaining traces of water were eliminated by drying under vacuum for several hours. The quality of the synthesised *enPd(NO₃)₂* product was confirmed using P-XRD (Figure 9.21).^[154]

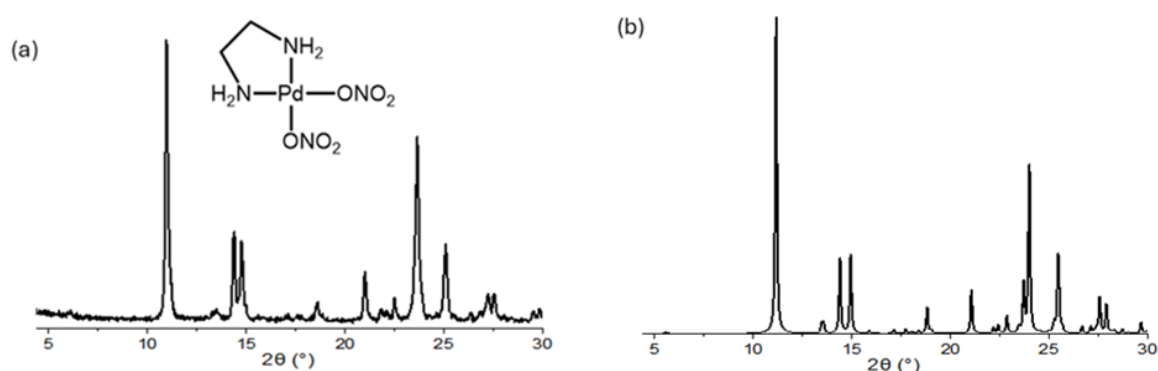


Figure 9.21 — Experimental P-XRD pattern of: a) synthesised (*en*)-Pd(NO₃)₂; b) simulated P-XRD from SC-XRD.^[150,154]

Solid-state M₆L₄ cage synthesis

In the solid-state approach, 70.4 mg of *enPd(NO₃)₂* and 50 mg of TPB were ground in an agate mortar with an agate pestle. Liquid-assisted experiments involved the use of a few drops of water, while neat grinding was in the total absence of solvent. NMR spectroscopy allowed the quality check and the estimation of the conversion,

sampling every 15 minutes of grinding. 45 to 60 minutes of grinding were necessary to complete the reaction and obtain a homogeneous brownish powder.

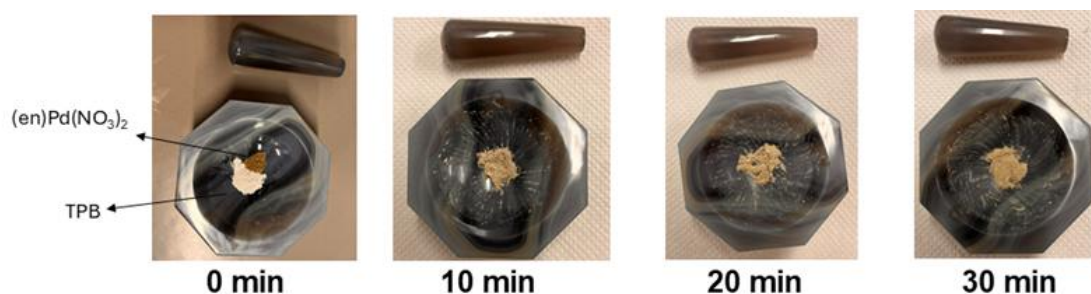


Figure 9.22 — Agate mortar and pestle with the reactants and the ground product at different times.

Solution-state M₆L₄ cage synthesis

A 2.4 mM aqueous solution of the M₆L₄ cages was synthesised by combining 30 mg of TPB and 42 mg of enPd(NO₃)₂ in 10 mL of water in a round-bottom flask. The mixture was stirred at 80 °C. The progress and quality of the synthesis were monitored using NMR spectroscopy (Appendix 13.23, 13.27). After 6-8 hours, the reaction was almost complete. To ensure optimal product formation, the reaction was left overnight for 18 hours. The solutions containing the M₆L₄ cages and the guests were left to slowly evaporate under ambient conditions for *ca.* 2 months without reaching complete evaporation.

9.2.3.2 Characterization

¹H NMR characterisation

The characterisation by ¹H NMR was done at room temperature using deuterium oxide.

For the solution state product, the NMR tube was prepared with 0.1 mL of the cage solution and 0.5 mL of deuterium oxide.

For the solid-state product, the characterisation was done by adding a very small quantity of the solid to the NMR tube, adding deuterium oxide and briefly sonicating for optimal dispersion. To be sure that the product is already formed and

that the reagents do not react in solution, one experiment involved the simple addition of the starting materials to deuterium oxide, and this does not result in the cage product. This demonstrates that the mechanical energy is essential for the self-assembly in the solid state.

The spectra are in the Appendix section.

Stability of M_6L_4 cages in water

To test the stability of the complex over time, an NMR tube of a solution of cages prepared as described before was monitored multiple times over the course of a month (Appendix 13.21). The cages present a good stability, and over the month, there are no significant changes in the spectrum that would indicate the return to the reagents. Also, the solid-state prepared sample seems stable, as an NMR at a distance of 8 months, despite the noise, clearly indicates the presence of the cage with no shift in the peaks.

Stability of M_6L_4 cages in acidic conditions

The stability of the cages to harsh environments was tested by adding 2.4 mg of citric acid to 0.5 mL of a 2.4 mM solution of M_6L_4 cages in the NMR tube. The NMR measurement does not indicate any drastic changes, thus suggesting the tolerance to moderate acidic environments by the cages (Appendix 13.22).

Guest inclusion and titration experiment

The guest inclusion experiment was done by the simple addition of a given quantity of 3-phenylpropionic acid (**G1**) to the 2.4 mM solution of the cages. The quantity depends on the desired host:guest ratio. It must be noted that the guest **G1** is not highly soluble in water, but upon entering the complex, the dispersion in water is assured.

For a precise study of the host:guest relationship, a titration is the best practice.^[120]

A titration was set up, keeping the concentration of the host fixed and gradually increasing the concentration of the guest.

First, a stock solution of 2.4 mM of **G1** in water is prepared. 36 mg of **G1** were added to a 100 mL volumetric flask and filled up with water.

For each experiment, the following mixtures were prepared, adding the cage solution to the stock guest solution in a sealed vial and letting it equilibrate.

Table 9.3 — Titration experimental amount.

<i>RATIO</i>	<i>mmol_{cage}</i>	<i>mmol_{guest}</i>	<i>V_{cage}</i> (mL)	<i>V_{guest}</i> (mL)	<i>V_{tot}</i> (mL)
1:1	0.0024	0.0024	1	1	2
1:2	0.0024	0.0048	1	2	3
1:3	0.0024	0.0072	1	3	4
1:4	0.0024	0.0096	1	4	5
1:5	0.0024	0.012	1	5	6
1:6	0.0024	0.0144	1	6	7
1:7	0.0024	0.0168	1	7	8
1:8	0.0024	0.0192	1	8	9
1:9	0.0024	0.0216	1	9	10
1:10	0.0024	0.024	1	10	11
1:11	0.0024	0.0264	1	11	12
1:12	0.0024	0.0288	1	12	13

12 different NMR tubes are prepared: 0.3 mL of each solution and 0.3 mL of D₂O. For the internal standard, dimethylcarbonate was used (shift in D₂O = 3.69 ppm). In this case, 0.1 mL of a 10 mM solution was added to the NMR tube. The tubes were sealed with parafilm.

The spectra are in the Appendix section (Appendix 13.27).

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11 List of abbreviations

MOFs	Metal-Organic Frameworks
MOCs	Metal-Organic Cages
CP	Coordination Polymer
XRD	X-ray Diffraction
SC-XRD	Single Crystal X-ray Diffraction
P-XRD	Powder X-ray Diffraction
NMR	Nuclear Magnetic Resonance
CP	Cross Polarization
HPDEC	High-Power Decoupling
MAS	Magic Angle Spinning
CLASSIC NMR	Combined Liquid- And Solid-State In-situ Crystallisation NMR
NG	Neat Grinding
LAG	Liquid-Assisted Grinding
TPB	2,4,6-tris(4-pyridyl)benzene
TPT	2,4,6-tris(4-pyridyl)-1,3,5-triazine
mTPB	2,4,6-tris(2-methylpyridin-4-yl)benzene
extTPB	2,4,6-tris(phenyl-4-pyridyl)benzene
enPd	Dinitrato(ethylenediamine)palladium(II)
M₆L₄	TPB-enPd octahedral cages (M = metal, L = ligand)
M₁₂L₈	TPB-enPd icosahedral cages (M = metal, L = ligand)
a1	M ₁₂ L ₈ poly-[<i>n</i>]-catenane amorphous phase
a2	mTPB-ZnBr ₂ coordination polymer, amorphous phase
1	M ₁₂ L ₈ poly-[<i>n</i>]-catenane crystalline phase
2	TPB-ZnI ₂ coordination polymer
3	mTPB-ZnBr ₂ coordination polymer, crystalline phase
G1	3-phenylpropionic acid
G2	1-adamantanecarboxylic acid
<i>o</i>-DCB	<i>ortho</i> -dichlorobenzene
NB	Nitrobenzene
NM	Nitromethane
BA	Benzaldehyde
PC	Paracetamol
Tol	Toluene
<i>o</i>-xy	<i>ortho</i> -xylene
<i>m</i>-xy	<i>meta</i> -xylene
<i>p</i>-xy	<i>para</i> -xylene
MeOH	Methanol
EtOH	Ethanol
<i>i</i>-PrOH	<i>iso</i> -propanol
<i>t</i>-BuOH	<i>tert</i> -butanol
1'<i>o</i>-DCB	M ₁₂ L ₈ poly-[<i>n</i>]-catenane single crystal with guest <i>o</i> -DCB (first inclusion)
1''NB	M ₁₂ L ₈ poly-[<i>n</i>]-catenane single crystal with guest NB (second inclusion)

1'''NB	M ₁₂ L ₈ poly-[<i>n</i>]-catenane single crystal with guest NB (third inclusion)
1'''<i>p</i>-xy	M ₁₂ L ₈ poly-[<i>n</i>]-catenane single crystal with guest <i>p</i> -xy (third inclusion)
1'''NB-2	M ₁₂ L ₈ poly-[<i>n</i>]-catenane single crystal with guest NB (third inclusion)
1·NM	M ₁₂ L ₈ poly-[<i>n</i>]-catenane single crystal with guest NM
1·BA	M ₁₂ L ₈ poly-[<i>n</i>]-catenane single crystal with guest BA
1·PC	M ₁₂ L ₈ poly-[<i>n</i>]-catenane crystalline powder with guest PC

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13 Appendix

TPB and Zn-based metal salts (Chapter 3)

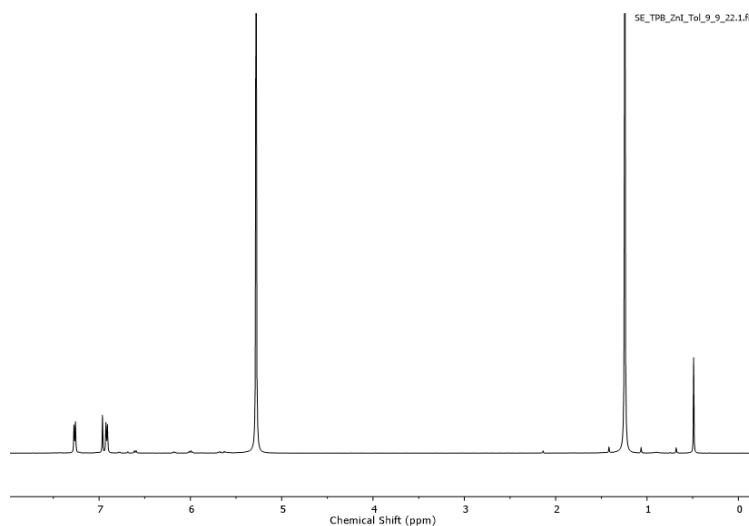


Figure 13.1 — ^1H NMR of the sample **a1** obtained by instant synthesis after being immersed in toluene/methanol. The ^1H NMR plot shows that no nitrobenzene nor methanol is present, but toluene.^[125]

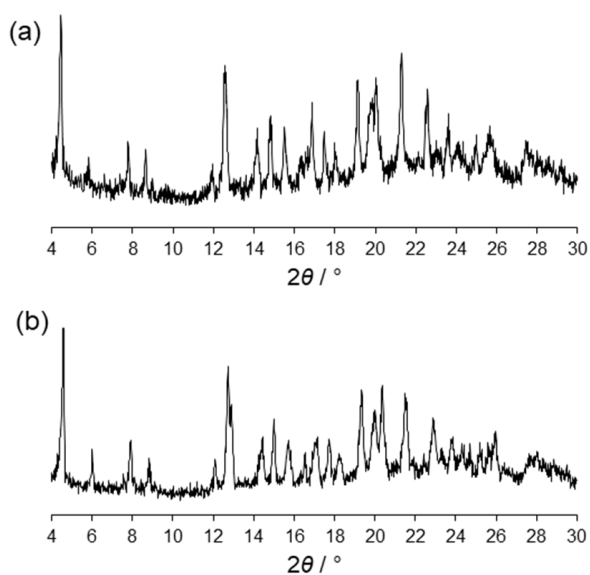


Figure 13.2 — a) Experimental P-XRD pattern of the solid product obtained from the instant synthesis of TPB and ZnI_2 using chlorobenzene as templating aromatic solvent measured after the synthesis; b) The same sample measured after one month kept in the vial at room temperature.^[125]

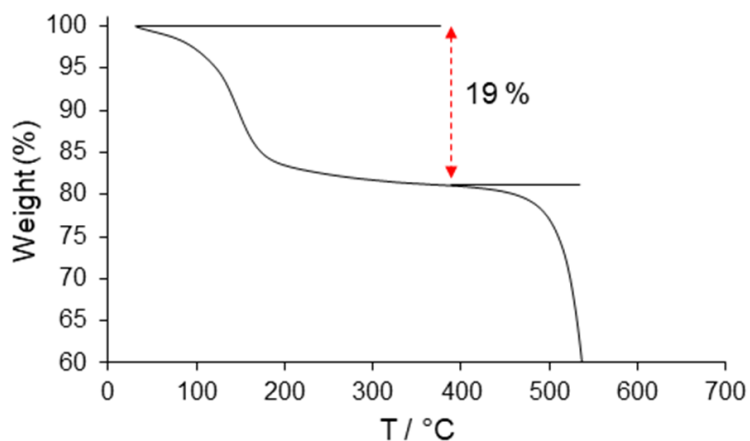


Figure 13.3 — TG corresponding to the sample obtained upon instant synthesis using chlorobenzene as a templating agent was measured after one month of its synthesis.^[125]

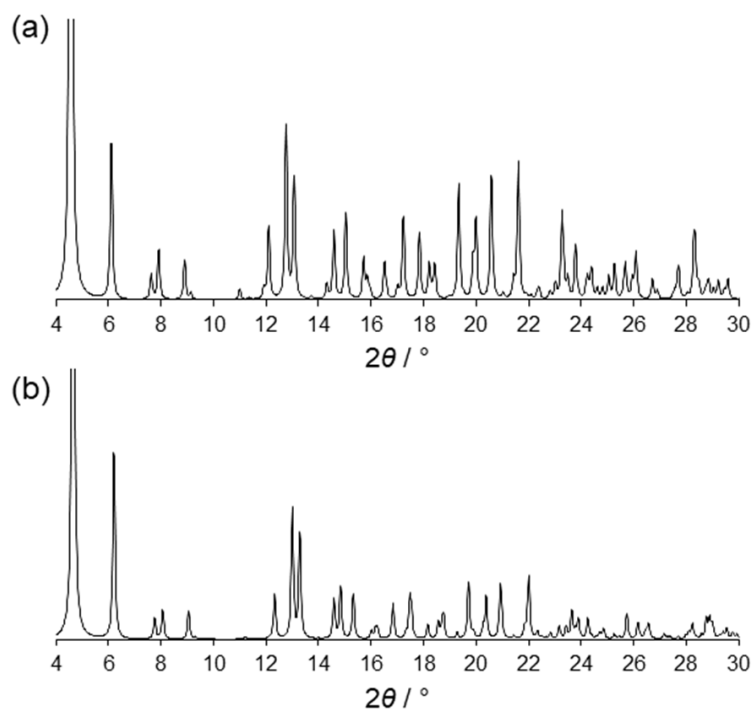


Figure 13.4 — a) Simulated P-XRD pattern of TPB-ZnI₂ synthesised using slow crystallisation with nitrobenzene. The structure is the poly-[n]-catenane **1**. (b) Simulated P-XRD pattern of the TPB-ZnBr₂ M₁₂L₈ poly-[n]-catenane, including para-chlorotoluene as guest whose SC-XRD structure was measured at 100 K.^[125]

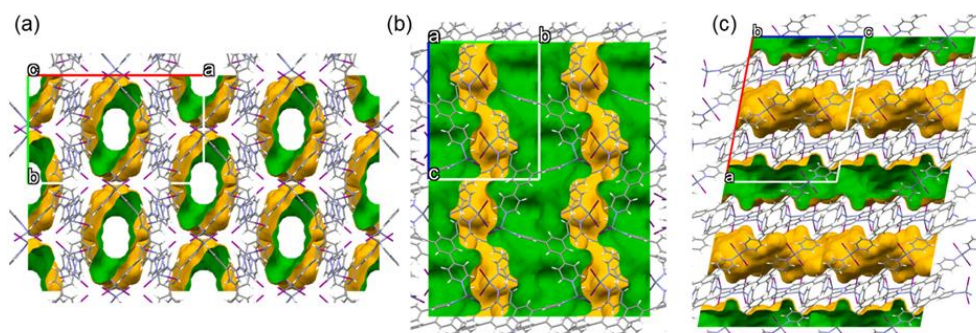


Figure 13.5 — Picture showing the 1D channels viewed along the three crystallographic directions of **2**. The void space corresponds to 30% of the total unit cell volume.^[125]

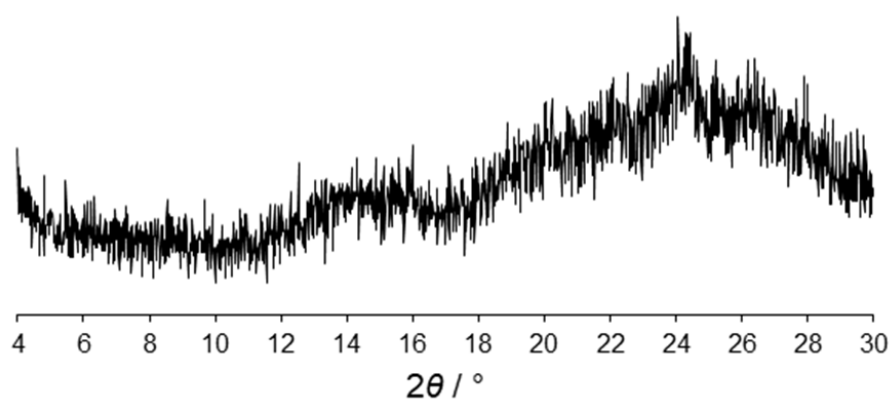


Figure 13.6 — Experimental P-XRD pattern of the amorphous phase (**a1'**) obtained upon neat grinding TPB and ZnI_2 .^[125]

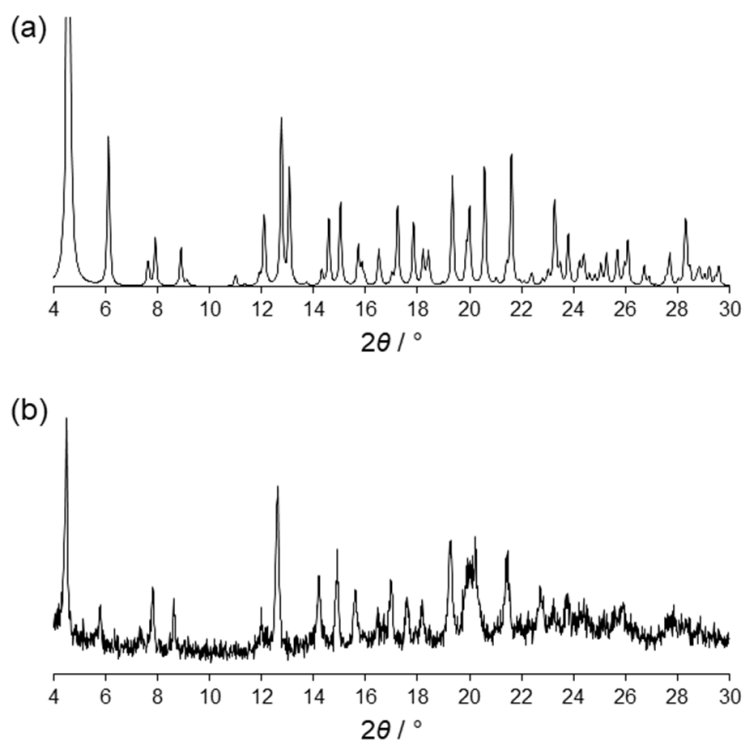


Figure 13.7 — (a) Simulated P-XRD pattern of **1** at room temperature. (b) Experimental P-XRD pattern obtained after immersing the amorphous phase **a1'** obtained upon neat grinding in toluene/methanol overnight, measured at room temperature.^[125]

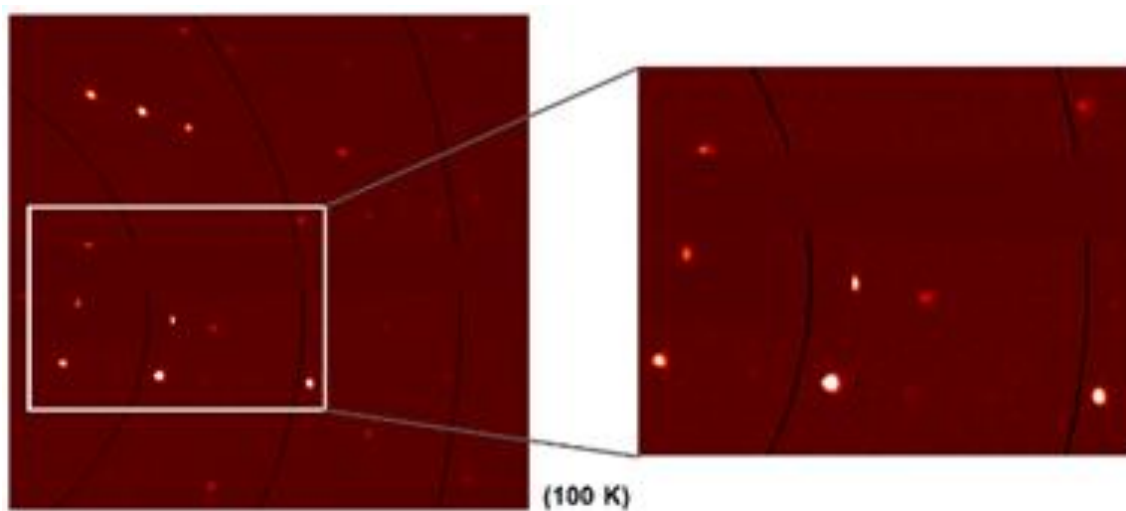


Figure 13.8 — SC-XRD (100 K) frame after 17 days of guest exchange.^[142]

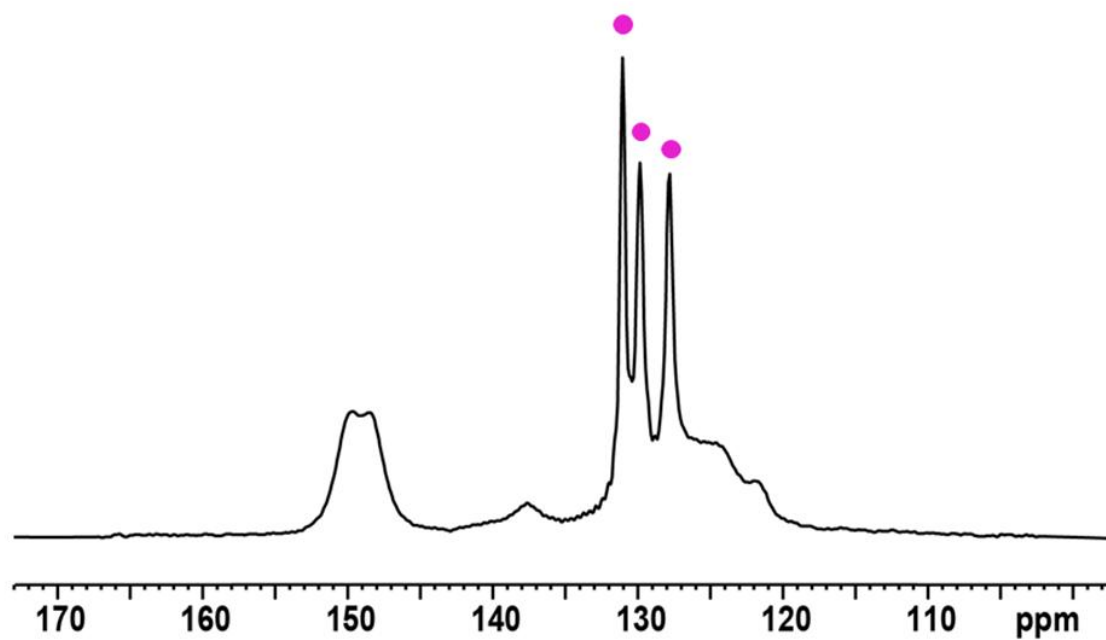


Figure 13.9 — Solid-state ^{13}C NMR HPDEC spectra (298 K) of a microcrystalline sample of TPB- ZnI_2 , including dichlorobenzene obtained by instant synthesis. *o*-DCB peaks are indicated with a pink star. The sharp lines of *o*-DCB indicate the high mobility of the guests.^[142]

Table 13.1 — Crystal data and structure refinement for 1.^[142]

Identification code	1	
Empirical formula	C ₂₆₄ H ₂₄₀ I ₂₄ N ₂₄ Zn ₁₂	
Formula weight	7578.83	
Temperature	173(2) K	
Wavelength	1.54184 Å	
Crystal system	Trigonal	
Space group	R -3	
Unit cell dimensions	$a = 38.8631(6) \text{ Å}$ $b = 38.8631(6) \text{ Å}$ $c = 16.2355(3) \text{ Å}$	$\alpha = 90^\circ$. $\beta = 90^\circ$. $\gamma = 120^\circ$.
Volume	21235.9(8) Å ³	
Z	3	
Density (calculated)	1.778 Mg/m ³	
Absorption coefficient	22.043 mm ⁻¹	
F(000)	10872	
Crystal size	0.100 x 0.080 x 0.070 mm ³	
Theta range for data collection	3.783 to 79.080°.	
Index ranges	-47 ≤ h ≤ 46, -49 ≤ k ≤ 46, -15 ≤ l ≤ 19	
Reflections collected	45003	
Independent reflections	9784 [R(int) = 0.0710]	
Completeness to theta = 67.684°	99.8 %	
Absorption correction	"multi-scan"	
Max. and min. transmission	1.00000 and 0.50103	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	9784 / 34 / 391	
Goodness-of-fit on F ²	1.059	
Final R indices [I > 2σ(I)]	R1 = 0.0712, wR2 = 0.2039	
R indices (all data)	R1 = 0.0829, wR2 = 0.2165	
Extinction coefficient	n/a	
Largest diff. peak and hole	2.360 and -2.358 e/Å ³	

Table 13.2 — Crystal data and structure refinement for **1'-o-DCB**.^[142]

Identification code	1'-o-DCB	
Empirical formula	$\text{C}_{204} \text{H}_{144} \text{Cl}_{12} \text{I}_{24} \text{N}_{24} \text{Zn}_{12}$	
Formula weight	7186.86	
Temperature	173(2) K	
Wavelength	1.54184 Å	
Crystal system	Trigonal	
Space group	R -3	
Unit cell dimensions	$a = 38.3737(6)$ Å	$\alpha = 90^\circ$.
	$b = 38.3737(6)$ Å	$\beta = 90^\circ$.
	$c = 15.5927(3)$ Å	$\gamma = 120^\circ$.
Volume	19884.7(7) Å ³	
Z	3	
Density (calculated)	1.800 Mg/m ³	
Absorption coefficient	23.483 mm ⁻¹	
F(000)	10116	
Crystal size	0.100 × 0.080 × 0.070 mm ³	
Theta range for data collection	3.131 to 73.285°.	
Index ranges	-35 ≤ h ≤ 46,	
	-47 ≤ k ≤ 37,	
	-18 ≤ l ≤ 19	
Reflections collected	39355	
Independent reflections	8370 [R(int) = 0.0623]	
Completeness to theta = 67.684°	99.4 %	
Absorption correction	"cylinder"	
Max. and min. transmission	0.2086 and 0.1081	
Refinement method	Full-matrix least-squares	
	on F ²	
Data / restraints / parameters	8370 / 58 / 409	
Goodness-of-fit on F ²	1.243	
Final R indices [I > 2σ(I)]	R1 = 0.0916, wR2 = 0.2839	
R indices (all data)	R1 = 0.1063, wR2 = 0.3033	
Extinction coefficient	n/a	
Largest diff. peak and hole	4.199 and -1.786 e/Å ³	

Table 13.3 — Crystal data and structure refinement for 1''·NB.^[142]

Identification code	1''·NB	
Empirical formula	C ₂₀₄ H ₁₅₀ I ₂₄ N ₃₀ O ₁₂ Zn ₁₂	
Formula weight	7043.57	
Temperature	173(2) K	
Wavelength	1.54184 Å	
Crystal system	Trigonal	
Space group	R -3	
Unit cell dimensions	$a = 38.6444(6)$ Å	$\alpha = 90^\circ$.
	$b = 38.6444(6)$ Å	$\beta = 90^\circ$.
	$c = 16.0924(2)$ Å	$\gamma = 120^\circ$.
Volume	20812.5(7) Å ³	
Z	3	
Density (calculated)	1.686 Mg/m ³	
Absorption coefficient	22.480 mm ⁻¹	
F(000)	9936	
Crystal size	0.300 × 0.280 × 0.200 mm ³	
Theta range for data collection	3.963 to 76.665°.	
Index ranges	-48 ≤ h ≤ 46,	
	-45 ≤ k ≤ 46,	
	-12 ≤ l ≤ 19	
Reflections collected	24572	
Independent reflections	8855 [R(int) = 0.0738]	
Completeness to theta = 67.684°	98.6 %	
Absorption correction	"multi-scan"	
Max. and min. transmission	1.0000 and 0.3820	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8855 / 0 / 424	
Goodness-of-fit on F ²	1.028	
Final R indices [I > 2σ(I)]	R1 = 0.0766, wR2 = 0.2116	
R indices (all data)	R1 = 0.0841, wR2 = 0.2190	
Extinction coefficient	n/a	
Largest diff. peak and hole	3.600 and -2.705 e/Å ³	

Table 13.4 — Crystal data and structure refinement for 1''·NB.^[142]

Identification code	1''·NB	
Empirical formula	C₂₀₄ H₁₅₀ I₂₄ N₃₀ O₁₂ Zn₁₂	
Formula weight	7043.57	
Temperature	173(2) K	
Wavelength	1.54184 Å	
Crystal system	Trigonal	
Space group	R -3	
Unit cell dimensions	$a = 38.6274(11)$ Å	$\alpha = 90^\circ$.
	$b = 38.6274(11)$ Å	$\beta = 90^\circ$.
	$c = 16.1327(5)$ Å	$\gamma = 120^\circ$.
Volume	20846.3(14) Å ³	
Z	3	
Density (calculated)	1.683 Mg/m ³	
Absorption coefficient	22.444 mm ⁻¹	
F(000)	9936	
Crystal size	0.200 × 0.200 × 0.100 mm ³	
Theta range for data collection	3.041 to 76.226°.	
Index ranges	-47 ≤ h ≤ 37,	
	-48 ≤ k ≤ 44,	
	-19 ≤ l ≤ 13	
Reflections collected	23850	
Independent reflections	8881 [R(int) = 0.1056]	
Completeness to theta = 67.684°	98.2 %	
Absorption correction	"sphere"	
Max. and min. transmission	0.2158 and 0.1140	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8881 / 56 / 425	
Goodness-of-fit on F ²	1.046	
Final R indices [I > 2σ(I)]	R1 = 0.1133, wR2 = 0.3120	
R indices (all data)	R1 = 0.1251, wR2 = 0.3222	
Extinction coefficient	0.000015(5)	
Largest diff. peak and hole	3.472 and -2.105 e/Å ³	

Table 13.5 — Crystal data and structure refinement for $1''' \cdot p\text{-xy}$.^[142]

Identification code	$1''' \cdot p\text{-xy}$	
Empirical formula	$\text{C}_{216} \text{H}_{180} \text{I}_{24} \text{N}_{24} \text{Zn}_{12}$	
Formula weight	6941.87	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Trigonal	
Space group	R -3	
Unit cell dimensions	$a = 38.8279(11)$ Å	$\alpha = 90^\circ$.
	$b = 38.8279(11)$ Å	$\beta = 90^\circ$.
	$c = 16.0050(4)$ Å	$\gamma = 120^\circ$.
Volume	20896.5(13) Å ³	
Z	3	
Density (calculated)	1.655 Mg/m ³	
Absorption coefficient	22.338 mm ⁻¹	
F(000)	9828	
Crystal size	0.200 × 0.200 × 0.100 mm ³	
Theta range for data collection	3.944 to 76.677°.	
Index ranges	-47 ≤ h ≤ 48, -38 ≤ k ≤ 47, -19 ≤ l ≤ 17	
Reflections collected	24306	
Independent reflections	8866 [R(int) = 0.1164]	
Completeness to theta = 67.684°	98.0 %	
Absorption correction	"sphere"	
Max. and min. transmission	0.2162 and 0.1142	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8866 / 75 / 405	
Goodness-of-fit on F ²	1.202	
Final R indices [I > 2σ(I)]	R1 = 0.1195, wR2 = 0.3139	
R indices (all data)	R1 = 0.1409, wR2 = 0.3354	
Extinction coefficient	n/a	
Largest diff. peak and hole	4.207 and -1.241 e/Å ³	

Table 13.6 — Crystal data and structure refinement for **1'''·NB-2**.^[142]

Identification code	1'''·NB-2	
Empirical formula	C ₂₀₄ H ₁₅₀ I ₂₄ N ₃₀ O ₁₂ Zn ₁₂	
Formula weight	7043.57	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Trigonal	
Space group	R -3	
Unit cell dimensions	$a = 38.7713(12)$ Å	$\alpha = 90^\circ$.
	$b = 38.7713(12)$ Å	$\beta = 90^\circ$.
	$c = 15.9904(5)$ Å	$\gamma = 120^\circ$.
Volume	20816.6(14) Å ³	
Z	3	
Density (calculated)	1.686 Mg/m ³	
Absorption coefficient	22.476 mm ⁻¹	
F(000)	9936	
Crystal size	0.200 × 0.200 × 0.100 mm ³	
Theta range for data collection	3.950 to 76.561°.	
Index ranges	-46 ≤ h ≤ 44, -30 ≤ k ≤ 48, -19 ≤ l ≤ 19	
Reflections collected	23573	
Independent reflections	8808 [R(int) = 0.0919]	
Completeness to theta = 67.684°	98.2 %	
Absorption correction	"sphere"	
Max. and min. transmission	0.2161 and 0.1142	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8808 / 11 / 379	
Goodness-of-fit on F ²	1.481	
Final R indices [I > 2σ(I)]	R1 = 0.1324, wR2 = 0.3708	
R indices (all data)	R1 = 0.1542, wR2 = 0.3892	
Extinction coefficient	n/a	
Largest diff. peak and hole	5.238 and -1.729 e/Å ³	

Paracetamol inclusion (Chapter 4)

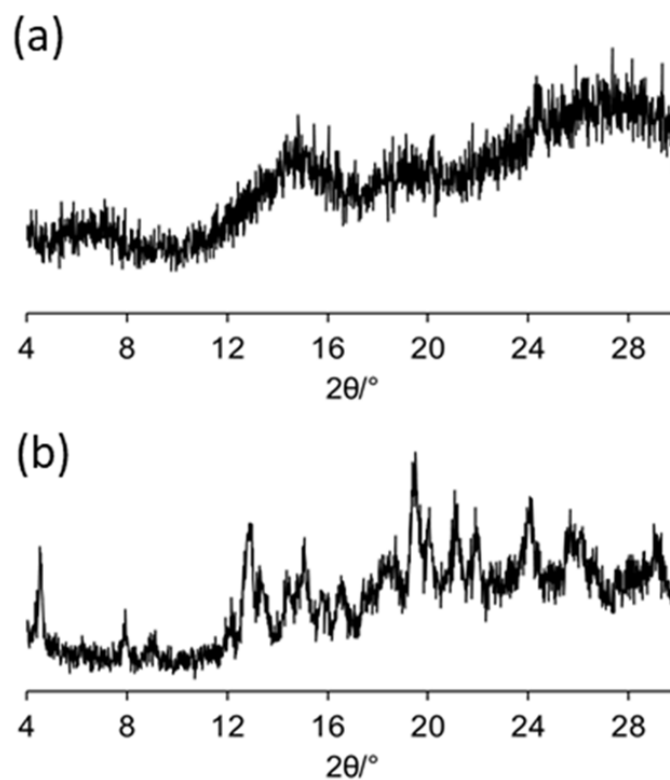


Figure 13.10 — P-XRD patterns of a) the amorphous *a2*; b) after being suspended in a saturated methanol solution of paracetamol overnight (12h).^[145]

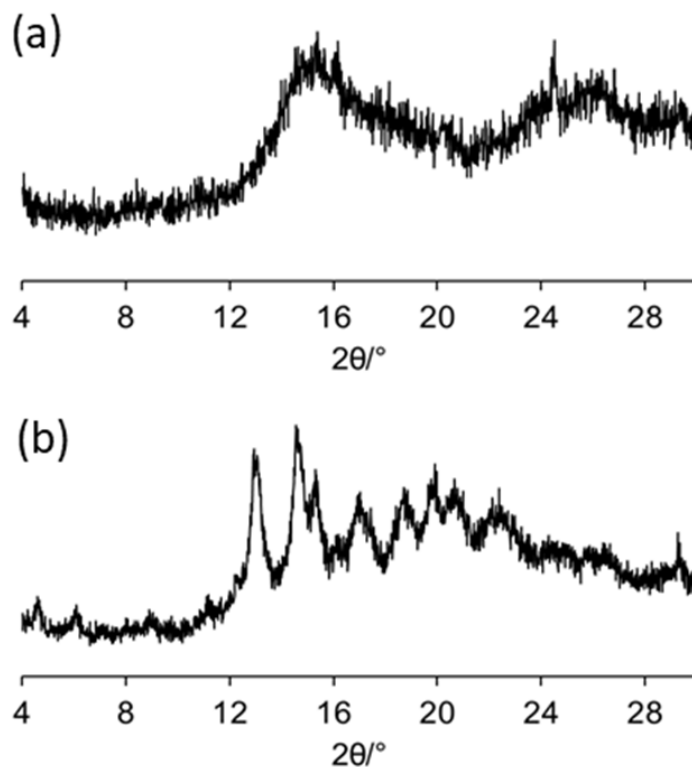


Figure 13.11 — P-XRD patterns of: a) the amorphous **a3**; b) after being suspended in a saturated methanol solution of paracetamol overnight (12h).

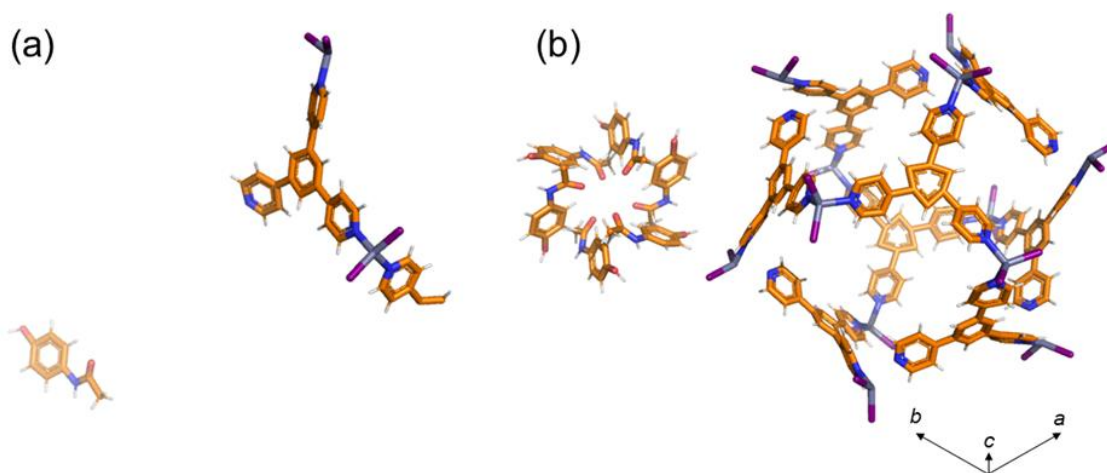


Figure 13.12 — a) Crystal structure of **1·PC** obtained from DASH showing the asymmetric unit; b) “almost” formed $M_{12}L_8$ cages including paracetamol. Note that one of the pyridine rings is not bonded to the Zn, and the symmetry-generated benzene ring is not an ideal hexagonal aromatic ring.^[145]

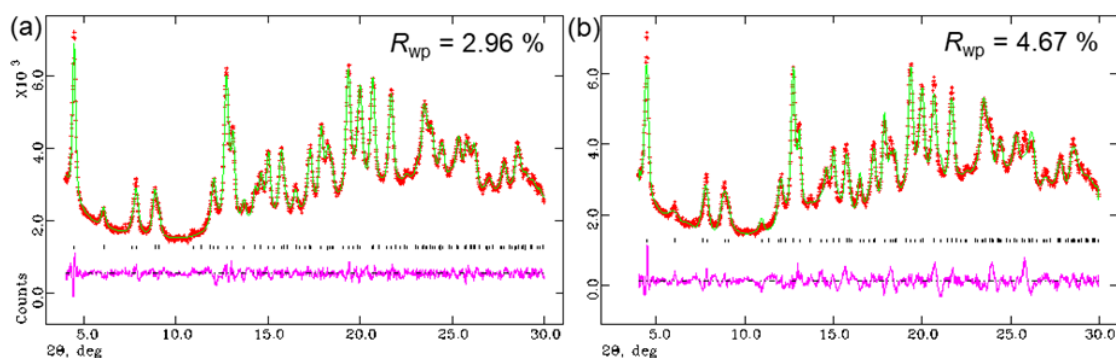


Figure 13.13 — LeBail (a) and Rietveld (b) refinements of $1'\cdot\text{PC}$.^[145]

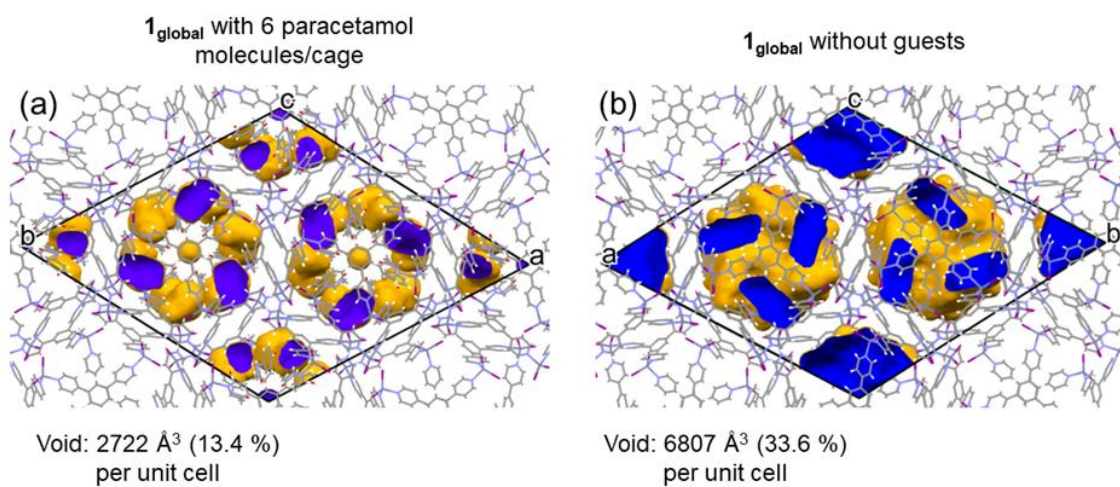


Figure 13.14 — View of the voids left in $1'\cdot\text{PC}$ with 6 paracetamol molecules per cage (a) and the total void per cell after manually removing the guests (b). The voids have been calculated using Mercury version 2022.1.0 using a 1.2 Å probe radius.^[145]

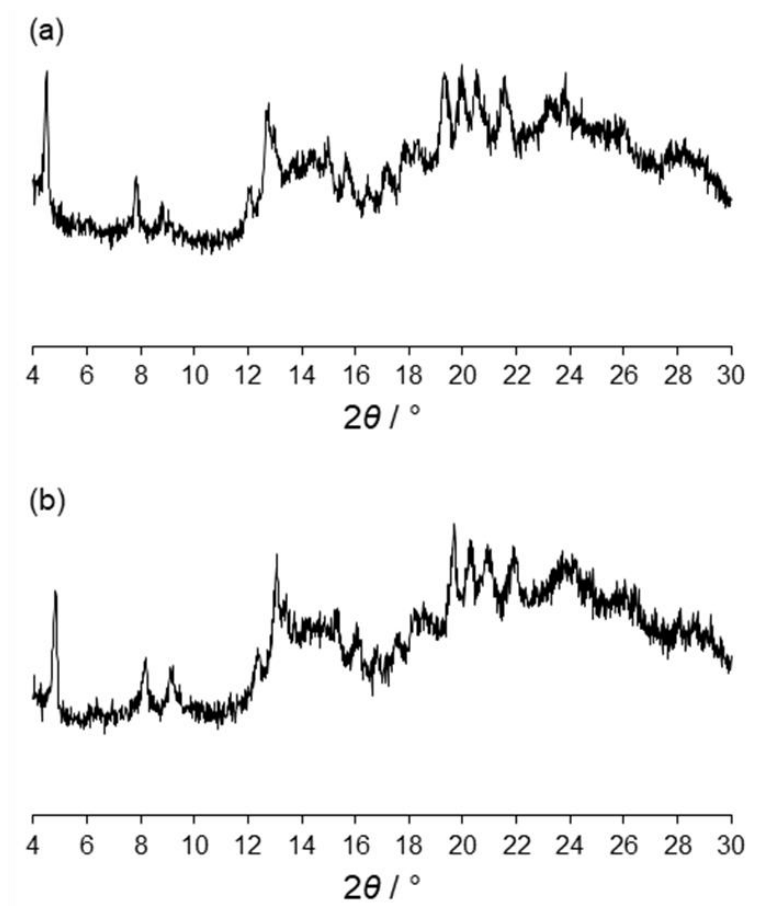


Figure 13.15 — Diffractograms of **1IS-1** (a) and **1IS-2** (b) measured on the dry products obtained upon the two instant synthesis experiments carried out using paracetamol in the TPB solution.^[145]

Ligand diversification (Chapter 5)

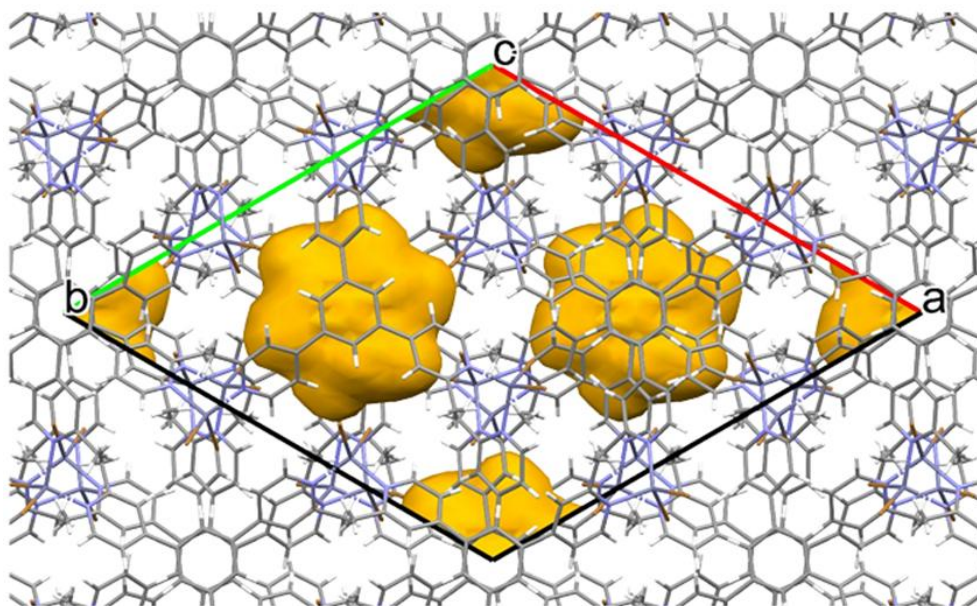


Figure 13.16 — View of three pockets (yellow) per unit cell occupied by the guest molecules in **1**.^[149]

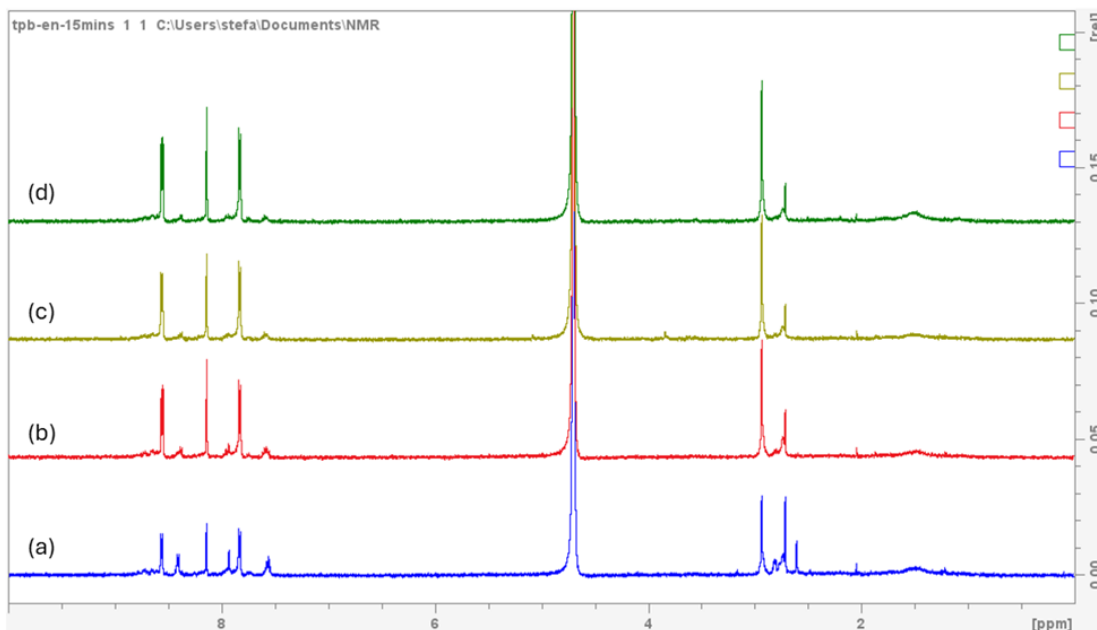
M₆L₄ cage (Chapter 6)

Figure 13.17 — ^1H NMR spectrum (303 K, 400 MHz, D_2O) of the solvent-free grinding reaction of TPB and Pd^{2+} at ambient conditions after 15 minutes (a), 25 minutes (b), 40 minutes (c) and 50 minutes (d).^[150]

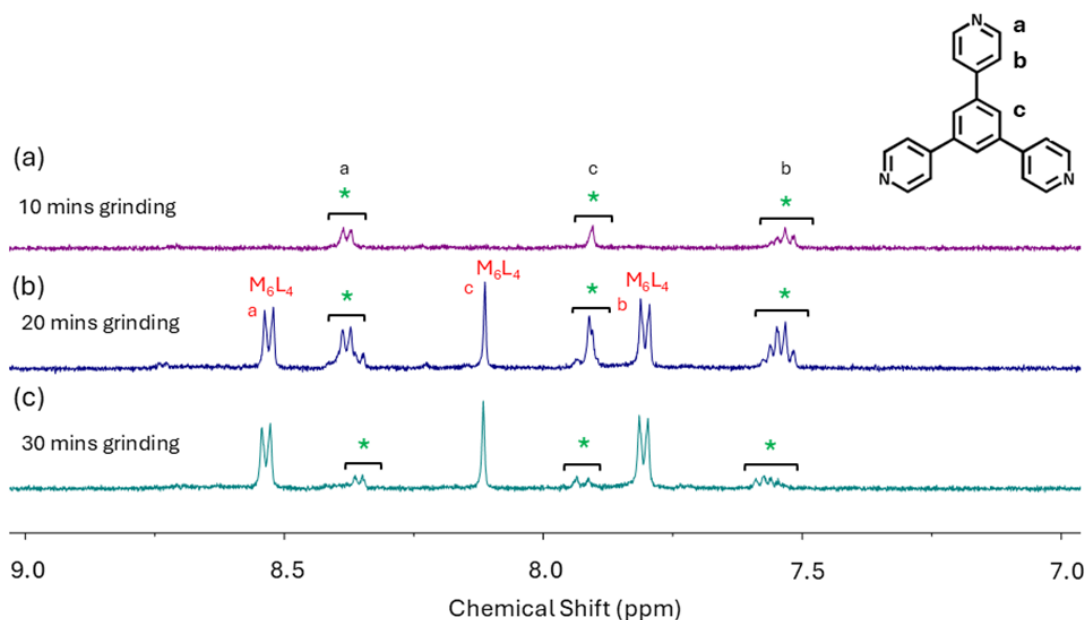


Figure 13.18 — Zoom of the aromatic region of ^1H NMR spectrum (303 K, 400 MHz, D_2O) of the solvent-free grinding reaction of TPB and Pd^{2+} at ambient conditions after 10 minutes (a), 20 minutes (b), 25 minutes (c) and 30 minutes (d). The presence of unknown side products is indicated with the green asterisk.^[150]

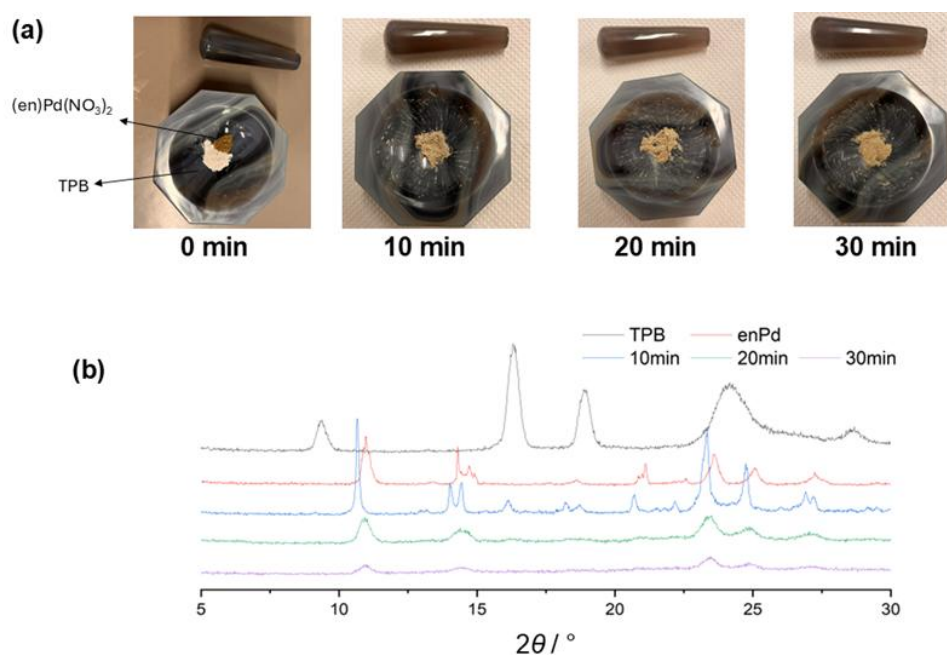


Figure 13.19 — (a) Pictures of the mortar and pestle used to carry out the neat grinding of TPB and the end-capping Pd^{2+} group in the synthesis of $Pd_6(TPB)_4$. (b) P-XRD patterns of reagents (TPB and $(en)Pd(NO_3)_2$) at different times of the solid-state reaction.

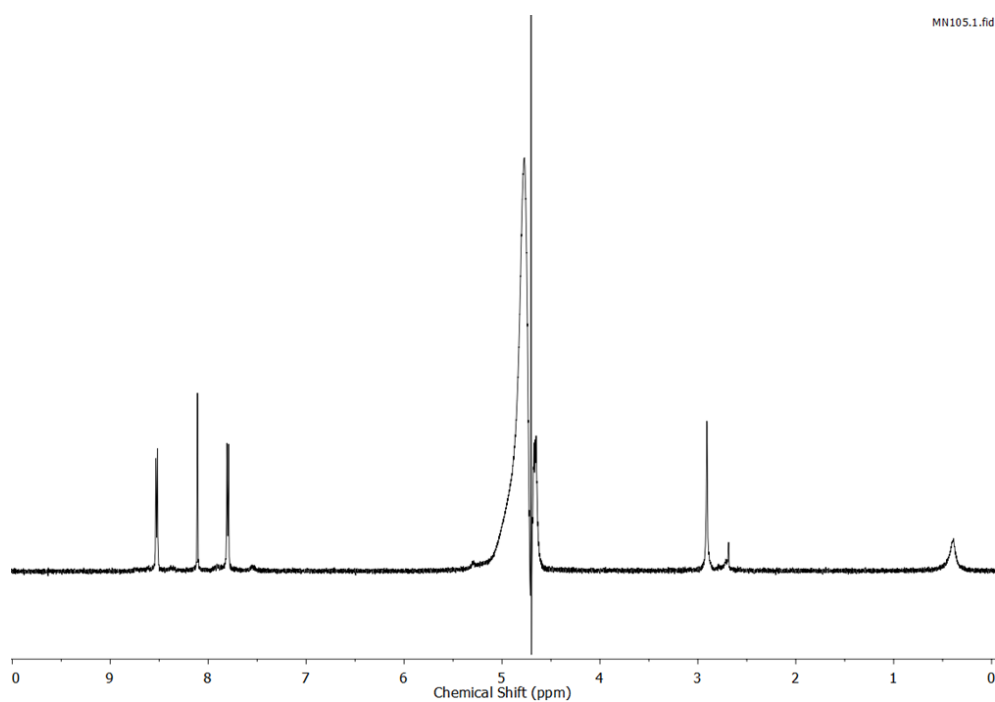


Figure 13.20 — ^1H NMR spectrum (400 Hz, D_2O , 303 K) of $Pd_6(TPB)_4$ synthesised in the solution state showing the aromatic region.^[150]

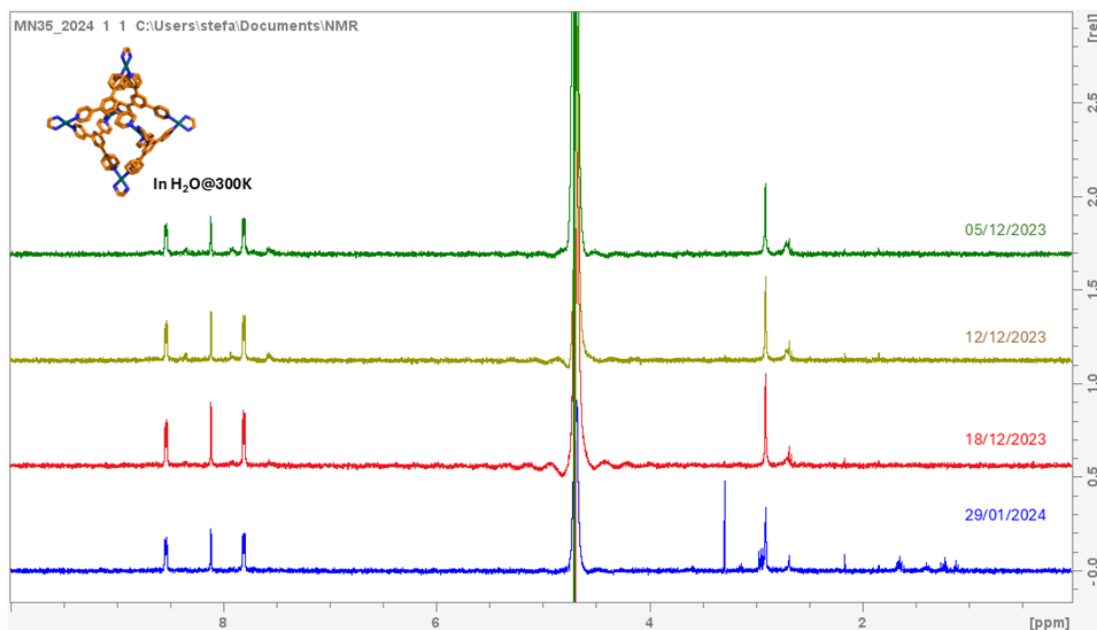


Figure 13.21 — ^1H NMR spectra (400 Hz, D_2O , 303 K) of $\text{Pd}_6(\text{TPB})_4$ in H_2O monitored for nearly one month.^[150]

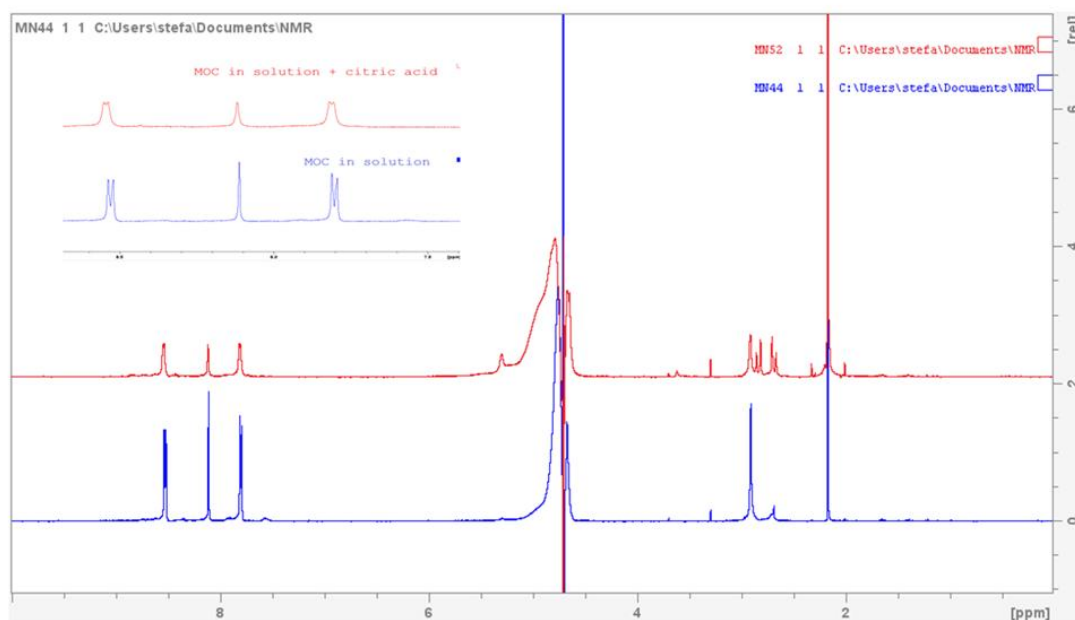


Figure 13.22 — ^1H NMR spectra (400 Hz, D_2O , 303 K) of $\text{Pd}_6(\text{TPB})_4$ in H_2O in the presence of citric acid.^[150]

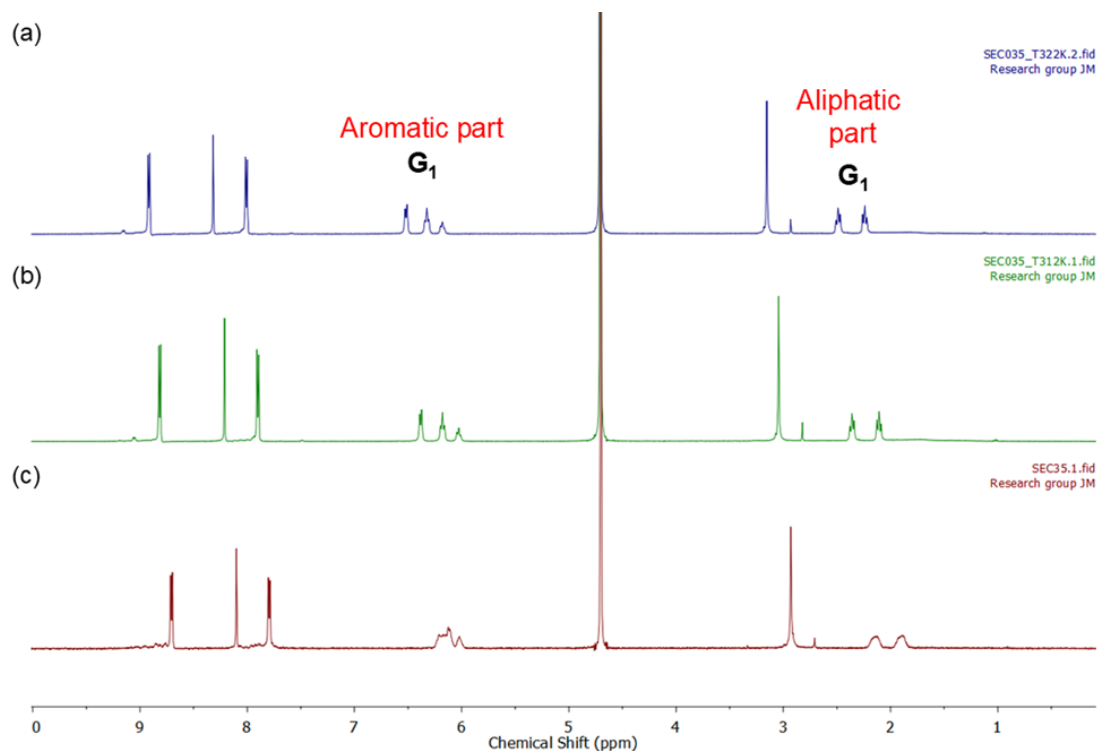


Figure 13.23 — ^1H NMR spectrum (400 Hz, D_2O) showing of $\text{Pd}_6(\text{TPB})_4$ including G_1 at 322 K (a), 312 K (b) and at 303 K (a). The displacement in the chemical shift is due to the different temperatures at which the NMR spectra were measured.^[150]

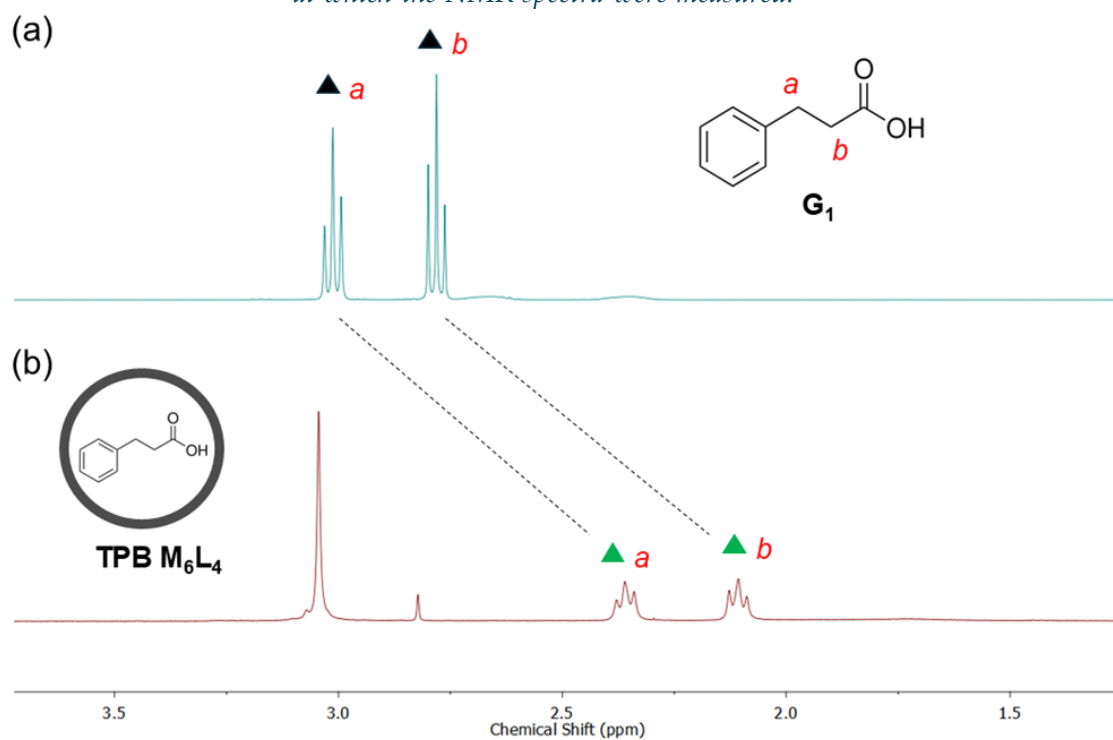


Figure 13.24 — (a) ^1H NMR (400 Hz, D_2O , 312 K) of G_1 in absence of the M_6L_4 cages. (b) ^1H NMR spectrum showing the aliphatic region with the two peaks corresponding to G_1 with lower mobility compared to free G_1 .^[150]

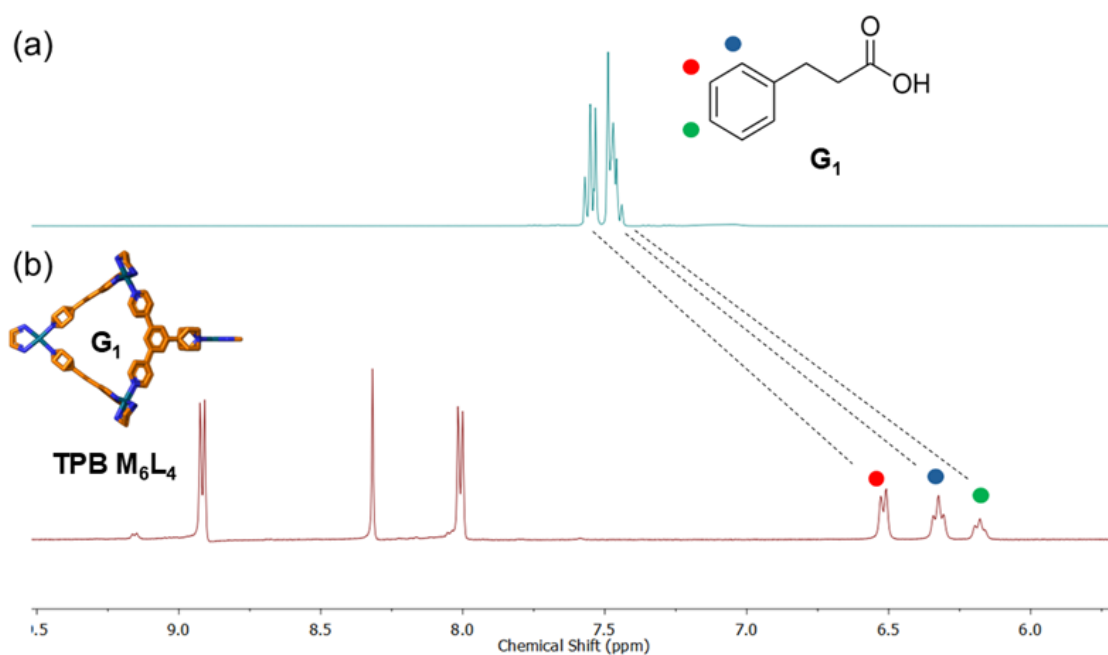


Figure 13.25 — ^1H NMR spectrum (400 Hz, D_2O) plot carried at 322 K of G_1 (a) and with G_1 included in $\text{Pd}_6(\text{TPB})_4$ (b) showing the separation and peak shift of the aromatic H in G_1 .^[150]

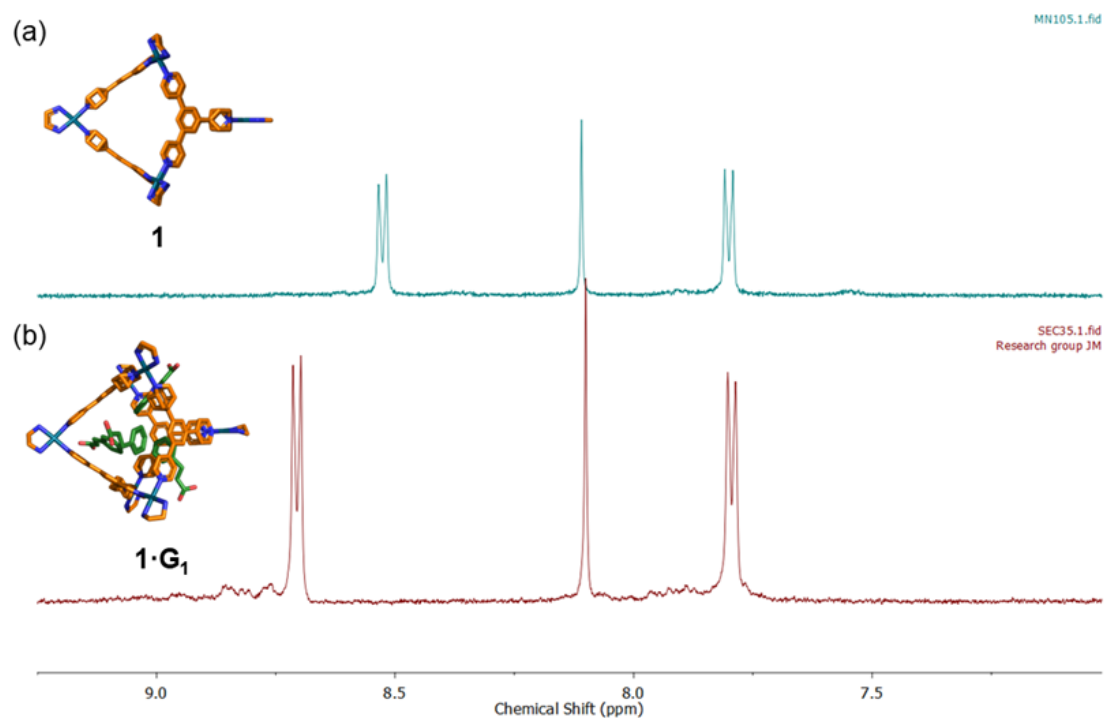


Figure 13.26 — ^1H NMR spectrum (400 Hz, D_2O , 303 K) of $\text{Pd}_6(\text{TPB})_4$ (a) and $\text{Pd}_6(\text{TPB})_4$ including G_1 (b) showing the aromatic part with the pyridine proton PyH_α showing downfield shift.^[150]

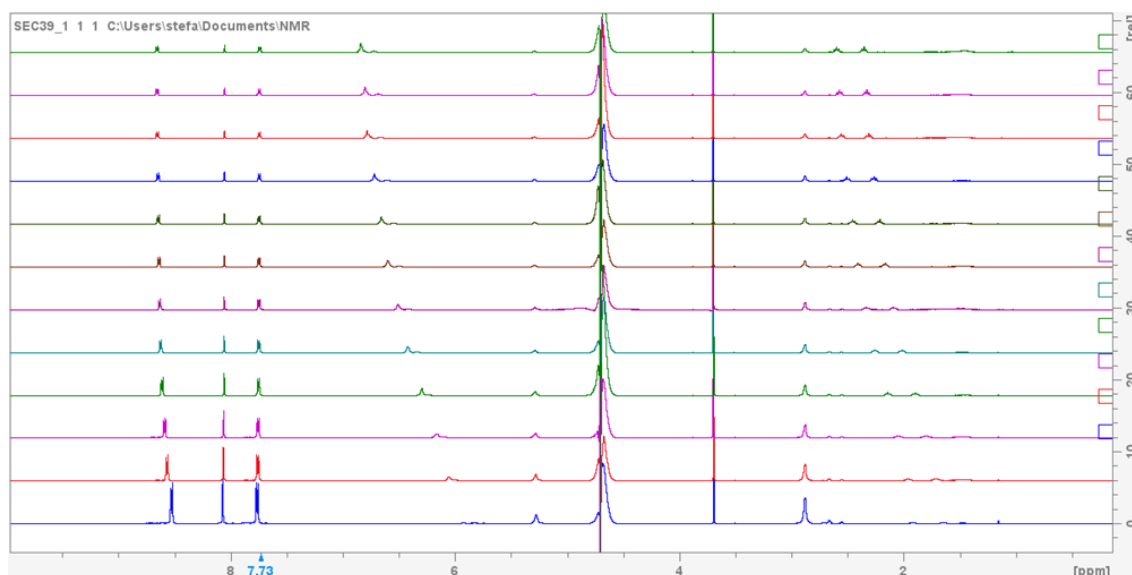


Figure 13.27 — ^1H NMR spectra (303 K, 400 MHz, D_2O) showing spectral changes during the progressive titration of **G1** into a solution of $\text{Pd}_6(\text{TPB})_4$. The bottom spectrum is 1:1 guest:host ratio, and the green spectrum on the top is a 12:1 guest:host ratio.^[150]

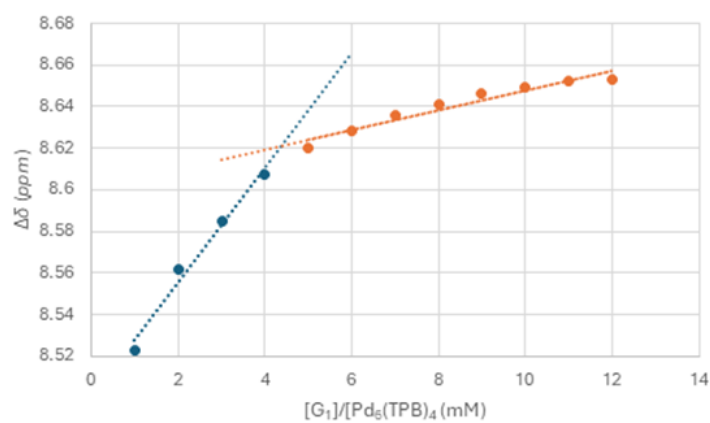


Figure 13.28 — Stoichiometric mole-ratio method.^[150]

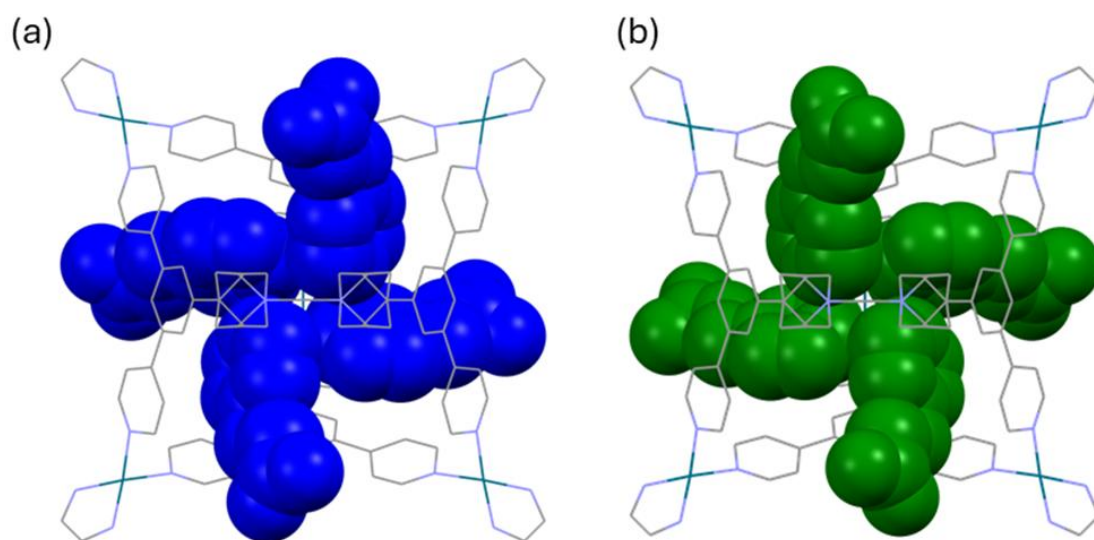


Figure 13.29 — (a) View of a single M_6L_4 cage (stick model) including four blue guests (space filling model) in blue with 0.5 occupancy factor. (b) View the other four green guest molecules (space filling model) with 0.5 occupancy factor filling the symmetry-related positions within the M_6L_4 (stick model) without the host frame showing efficient packing. For the sake of clarity, hydrogen atoms are not shown.^[150]

Further works (Chapter 7)

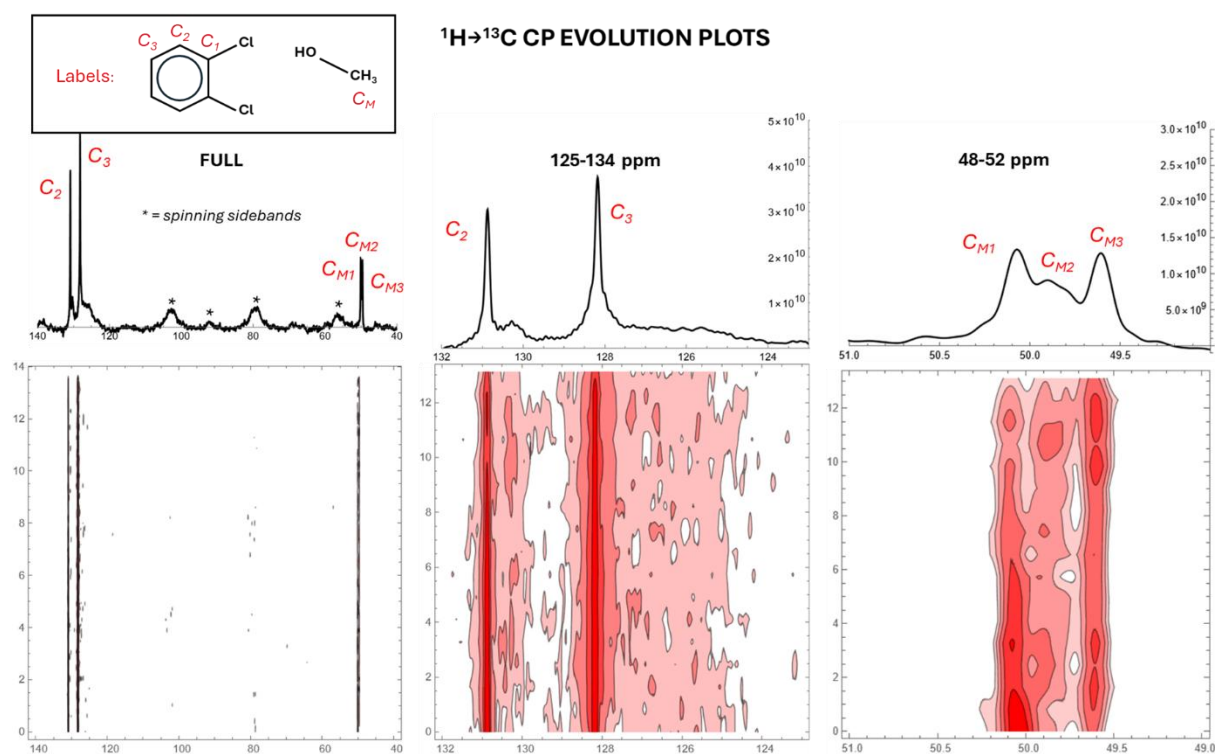


Figure 13.30 — Evolution plot of the $^1\text{H} \rightarrow ^{13}\text{C}$ CP spectra collected over the course of the experiment. The spectra on the top represent the sum of all spectra of the corresponding evolution plot below.

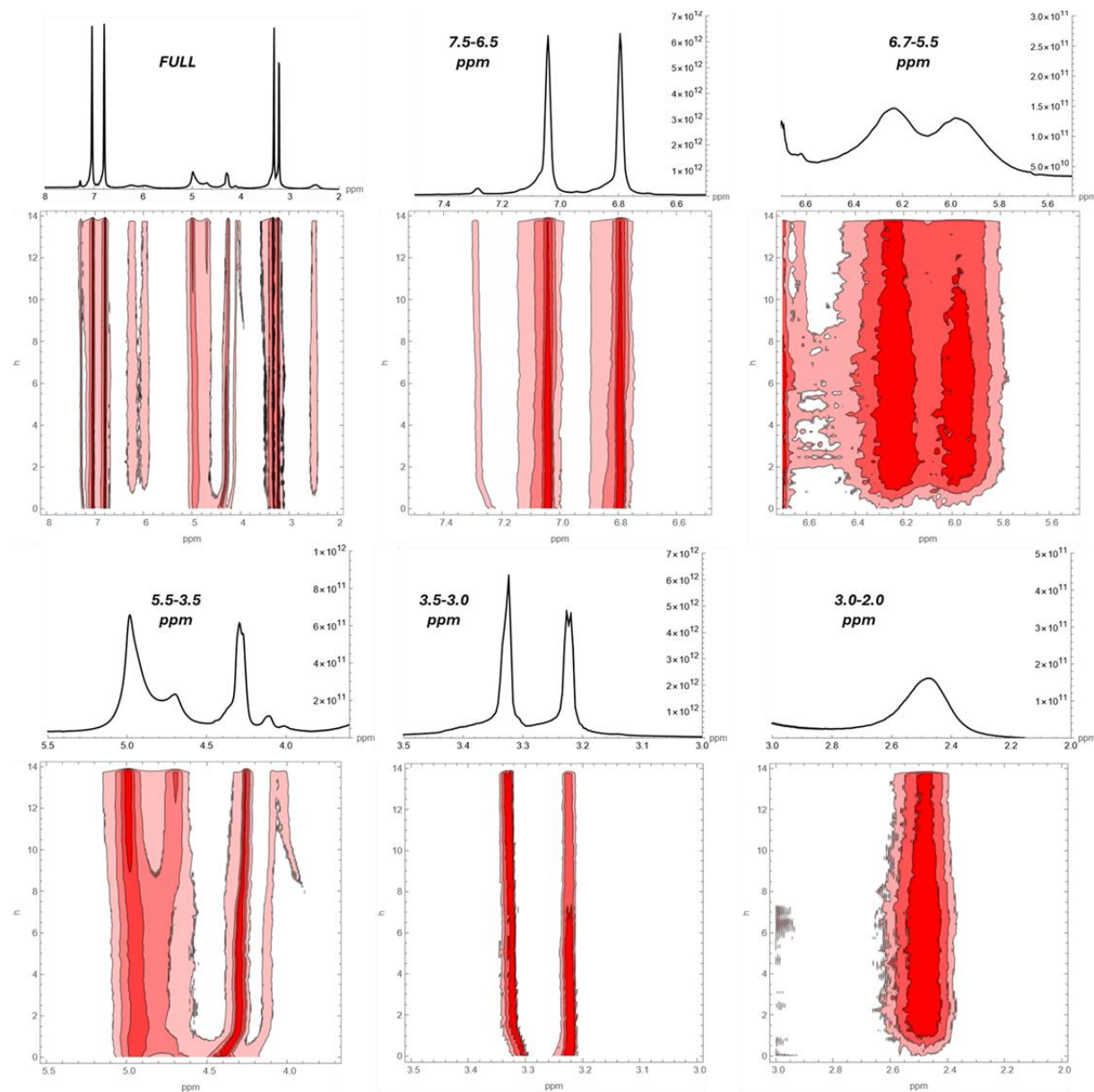


Figure 13.31 — Evolution plot of the ^1H spectra collected over the course of the experiment. The spectra on the top represent the sum of all spectra of the corresponding evolution plot below.