Journal Name

ARTICLE

Crystallography of Supramolecular Host-Guest Complexes

Kari Rissanen[a]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

The crystallography of supramolecular host-guest complexes is reviewed and discussed as a part of small molecule crystallography. In these complexes the host binds the guests through weak supramolecular interactions, such as hydrogen and halogen bonding, cation-π, anion-π, C-H-π, π-π, C-H-anion and hydrophobic effect. As the guest often shows bad disorder, large thermal motion and low occupancies, the reliable crystallographic determination of the guest can be very demanding. Analysis of the host-guest interactions with tools such as Hirshfeld and cavity volume surface analysis will help to look closely at the most important host-gust interactions. The jewel in the crown of utilizing host-guest interactions in the solid-state is the recently developed *Crystalline Sponge Method* (CSM) by Makoto Fujita. This method, when successful, gives an accurate and unambiguous 3-D structure of the structurally unknown guest molecule from only micro- or nanograms of the guest molecule. In a case of an optically pure enantiomer, its absolute configuration can be determined.

Introduction

X-ray crystallography is by far the most powerful tool for the detailed structural analysis of crystalline supramolecular compounds, complexes and intermolecular interactions, provided that a good enough quality single crystal (indeed only one crystal is enough for a successful X-ray structure determination) of the target system is available. There has been an enormous boost in the number of X-ray structures deposited into the Cambridge Structural Database (CSD) compiled and distributed by the Cambridge Crystallographic Data Centre. At present (March 2017) the CSD[1] contains > 870 000 entries, with an annual increase of about 50,000 new structures. Before 1990's a single crystal X-ray diffraction study of a supramolecular complex was considered to be a non-trivial and time-consuming task performed by well-educated and experienced crystallography experts, often as a part of departmental service or via external collaborations. Due to the complex nature and instability of the crystals of supramolecular host-guest complexes the X-ray crystallography was not considered as a routine analytical tool for structural analysis. Yet the extremely fast development of personal computers, sensitive area detectors and automated structure solution methods in the 1990's have had a direct impact on the speed and ease of X-ray diffraction analysis. Contemporary, nearly fully automated, single crystal diffractometers are able to perform very fast and accurate data collections, processing and structure solution, leading to a situation where very large supramolecular structures (FW > 5000) can be measured and solved within only a few days.

[a] [a]*University of Jyvaskyla, Department of Chemistry, Nanoscience Center, Survontie 9 B, Jyvaskyla, 40014 Finland. Email: kari.t.rissanen@jyu.fi*

Supramolecular Crystallography can be defined as the crystallography of any single crystalline system which has been defined as supramolecular, *viz.* classical host-guest complexes, metallosupramolecular complexes, coordination cages, dendrimers, gels (xerogels), etc. Covering even few most important expects of *Supramolecular Crystallography* is well beyond this concise review. Following the definition by Jean-Marie Lehn[2,3] of *Supramolecular Chemistry* as the "*chemistry beyond the molecule, bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces*" this review will focus on specific examples of host-guest complexes determined through single crystal X-ray crystallography. In these examples the guest molecule or molecules are fully encapsulated in a confined space, and the review solely focuses on the single crystal structural analyses of selected, here encapsulation, host-guest systems. The review deals with selected clathrate and the container molecule systems where the guest is bound inside the cavity of the host or pores, channels or cavities of the crystal structure by weak supramolecular interactions such as hydrogen and halogen bonding, cation-π, anion-π, C-H-π, π-π, C-H-anion and hydrophobic effect. In most of the cases when the guest in trapped inside a confined space it is a very demanding task to determine accurately the structure of both the host and the guest, the latter in many cases imposes a true challenge. This due to the fact that the guest which is bound inside the host with very weak interactions, tends very often to be very difficult to reliable determine solely on crystallographic techniques due to the guest disorder, large thermal motion and low occupancies of the guest (*viz.* a 1:1 complex can in reality be a 1:0.5 complex, etc.).

The key component of a successful single crystal X-ray crystallographic study is the good quality single crystal, which in many (larger) supramolecular systems is nearly impossible to

obtain. The good quality of a crystal is determined by its diffraction power (well-diffracting), small thermal movement and full occupancy of all the atoms with no disorder (of the host, guest or the solvent molecules). The weak intermolecular interactions which form the supramolecules, *viz.* host-guest complexes or supramolecular assemblies, are the same as those that act in the formation of a crystal, thus a link between supramolecular chemistry and crystal growth becomes apparent. This concept was taken to the crystallographic extreme by Jack Dunitz[4,5] as he referred organic crystals as "supermolecule(s) *par excellence*". The development of the concept of supramolecular interactions within crystals in the 1980's and 1990's by prominent crystallographers such as Gautam Desiraju and Michael Zaworotko has merged the supramolecular interactions with classical crystallography to a research area called *Crystal Engineering*, and is now considered a mature field.[6-10] The term "*Crystal Engineering*" appears in proceedings of the American Physical Society Meeting (as abstract) in 1955[11], and it became generally accepted after being used by G. M. J. Schmidt[12] in 1971. In the Schmidt article[12], crystal engineering was used for the first time as an explicit term, also the article postulated that, under suitable conditions, molecular recognition events, *viz*. self-assembly, could be the major factor leading to crystal formation. Occasionally *Crystal Engineering* has also been called as *Solid-State Supramolecular Chemistry*, yet this particular area of crystallography is outside of the scope of this review.

The present concise review is not intended to make readers experts on single crystal crystallography nor give a thorough account on all the very nice X-ray structures of multitude of supramolecular systems, but to look at some appealing X-ray structures of host-guest complexes through the eyes of a supramolecular chemist, yet being aware of the crystallographic difficulties often encountered in these systems. To study the theoretical basis of X-ray crystallography in detail, the reader is encouraged to read some excellent X-ray crystallography text books to become fully acquainted with the theory involved at introductory[13], intermediate[14] or advanced[15] levels. Based on selected examples of host-guest complexes this review highlights the difficulties encountered in some host-guest systems and reflects author's own personal view on the crystallography of them. It also briefly reviews the most recent breakthrough in crystallographic methods*,* namely the *"Crystalline Sponge Method"* (*CSM*)*,* a method still in its early development phase. The structural details of the host-guest interactions are discussed through Hirshfeld and cavity volume surface analysis, while the packing coefficient PC developed by Julius Rebek[16] is used as a general feature which can be used to discuss well-defined host-guest systems, such clathrates and container molecules (*viz.* molecules with cavities).

Reliable and accurate determination of the structures of all the components of supramolecular inclusion complexes and supramolecular assemblies has gained a lot of attention in supramolecular chemistry and crystallography, especially after the publication from 2013 by Makoto Fujita on the revolutionary "post-crystallization" method[17], now generally known as *"Crystalline Sponge Method"*. This method relies on the robust enough porous frameworks, typically metal-organic frameworks (MOFs), pores of which the target molecules are trapped and "post-crystallized" and thus the structure of the entrapped target, *viz.* guest molecule can be determined from a standard single crystal data collection with an in-house instrument and routine structure solution methods. The method, when successful, gives an accurate and unambiguous 3-D structure of the guest molecule, from only micro- or nanograms of it. If the target molecule (guest) is an optically pure, its absolute configuration can be determined.

The Crystalline Sponge Method has its roots in the classical host-guest complexes, viz. clathrates[18], well-known single crystalline materials which contain channels, pores or cavities into which the guest molecules are tightly entrapped. As defined by IUPAc (http://goldbook.iupac.org/C01097.html) "*clathrates are inclusion compounds in which the guest molecule is in a cage formed by the host molecule or by a lattice of host molecules"*. The molecular counterparts of the clathrates are the container molecules[19-22], either macrocyclic or macropolycyclic molecules or self-assembled capsular entities, which have an isolated cavity encapsulating the guest molecule(s). Based on the above IUPAC definition the solid-state container molecules and also crystalline sponge crystals, when encapsulating a guest, can defined as clathrates.

Detailed information about the weak intermolecular interactions that are responsible for the guest entrapment inside the host channels, pores or cavities is crucial in order to understand how the guest interacts with the host, *i.e.* the channel/pore/cavity walls and how these interactions can be further utilized in order to develop crystalline supramolecular host systems. These host-guest systems should be capable, not only entrapping, but also ordering the guest inside the confined space so that it is: easily entrapped; is non-disordered; has small thermal movement; and resides in the confined space with full occupancy. If this can be achieved it will allow even more general use of confined spaces for accurate guest structure determination through single crystal X-ray crystallography. Analysing the quest's interactions with the host with the classical metric analysis, *viz.* by measuring the shortest guest-to-host contact distances is a common practise. However more holistic and visual view of these interactions can be obtained by inspecting the Hirshfeld[23] surface plots if the X-ray structure host-guest complex is available. The Hirshfeld surface analysis reveals details on the interaction distances between the guest and the host using a colour coding, red indicating distances shorter than the VDW contact (*viz*. distance shorter than the sum of the *van der Walls* radii of the interacting atoms), white at the VDW contact distance and blue longer that VDW contact distance. Those readers not familiar with Hirshfeld surfaces and the CrystalExplorer[24] software are recommended to visit the web site http://hirshfeldsurface.net.

A popular method to discuss the host-guest complexes is so called 55% rule[16] developed by Julius Rebek which is based on the

ratio of the volume of the guest and the volume of the cavity where the guest is encapsulated. The general difficulty with the 55% rule, also called as packing coefficient (PC), is that the researcher has to decide how to estimate both the guest and cavity values. There is some controversy how to calculate molecular volumes, *viz.* which method to use, the same applies also to the calculation of the cavity volume. For the sake of clarity the packing coefficients (PC) discussed in this review follow the definition by Rebek.[16]

Several tests for the volume calculation of a simple guest, tetramethylammonium (TMA) cation with different levels of theory (SPARTAN'16,[25] from MM to DFT/6-311+G(2df,2p)/M06-2X levels of theory) indicates that MM level calculations gives only very slightly (1.5 Å^3) larger guest volume. Yet, as the guest generally is a small molecule, it is advisable to calculate the volume of it with highest level of theory that is still acceptable with available CPU time. Traditionally the cavity volume is calculated by using a 1.2 Å probe, *viz.* the VDW radii of a hydrogen atom.

As the packing coefficient (PC) is just the ratio between the volume of the guest and cavity and does not give any info about the possible host-guest interactions the Hirshfeld surface[23] analysis offers a very good and fast method for the interaction analysis. The only limitation is that it can be done only when full 3-D coordinates in crystallographic information file (cif) format are available. Another visual way to inspect the solid-state guest-to-host interactions from an X-ray structure is to use a graphics tool to visualise the shape and size of the calculated cavity volume (e.g. Connolly surfaces with the program MSRoll[26]) as a semi-transparent cavity volume surface (CVS) and simultaneously showing the guest molecule inside with van der Walls (VDW) radii of atoms (or CPK model) using X-Seed, a software tool for Supramolecular Crystallography by Len Barbour.[27-28] The results are visually very similar with the Hirshfeld surface plots, as the short contact distances appear as punctures in the cavity volume surface.

The principal difference between the clathrates and the container molecules when compared to the crystalline sponge crystals[17] is that the former are formed in-situ from all the components by crystallization from solution, while the crystalline sponge crystals are pre-formed and have to go through a soaking phase where the pore-included solvent molecules are completely or partially exchanged to the target guest molecules. The clathrates and the container molecules have tightly closed internal cavities, from which, in general, it is impossible to remove or exchange the guest without breaking the whole crystal. Another, yet as important, aspect is that after removing the guest molecules and then calculating the void volumes of these three types of crystals, it is evident that the void volumes of the crystalline sponge crystals are typically much bigger that those in clathrates and container molecules. This results in that the PCs of the crystalline sponges tend to be smaller than in clathrates and the container molecules, also the PC values are much more difficult to evaluate as the guests and solvent molecules in the crystalline sponges are often disordered and not with full occupancy. However, the Hirshfeld and cavity volume surface analysis can be utilized to the cavities used in the *Crystalline Sponge Method*, at least to the guest and solvent molecules with full occupancy.

Clathrates and Container Molecules

Analysing the thiourea-bromocyclohexane clathrate[29] (CCDC code DAVVIH[1]) both using the Hirshfeld surface and cavity volume surface analysis reveal a tightly encapsulated row of bromocyclohexane guests in a channel formed by the H-bonded helically ordered thiourea molecules. One β–H at the same side as the Br-atom of the guest shows a clear but weak C-H…S=C hydrogen bond [H···S = 2.88 Å, C-H···S angle 143.1°], while the other β–H interacts weakly with one of the nitrogen atoms in the thiourea molecule. The stronger of these interactions is clearly seen as a bright red spot on the Hirshfeld surface (Figure 1, top) and as a puncture of the cavity volume surface (Figure 1. bottom, center of

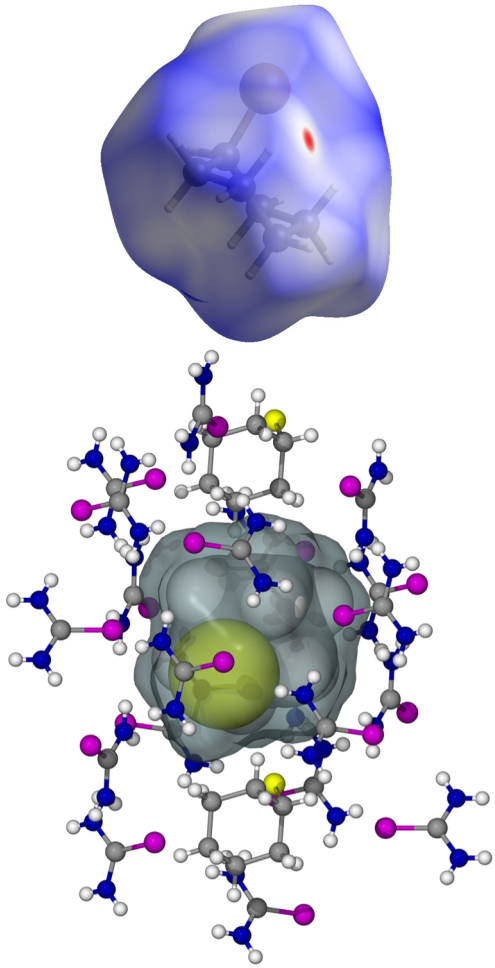


Figure 1. The Hirshfeld[24] surface plot (top) of the bromo-cyclohexane guest in the thiourea channel.[29] The ball&stick view of the lattice of the DAVVIH[1] structure (bottom), one of the encapsulated guest with CPK style and the cavity volume surface[26-28] in transparent grey (1.2 Å probe).

the figure). The cavity volume is 234.5 Å^3 and the guest volume = 129.8 Å^3 [DFT/6-311+G(2df,2p)/M06-2X] leading to PC = 55.1%. The PC value is in nearly perfect agreement with the Rebek 55% rule and supports the weak guest-to-host interactions. The governing interactions are the hydrogen bonds between the adjacent thiourea molecules.

One of the topical areas of Supramolecular Chemistry are the self-assembled dimeric[30-45] and hexameric[46-53] capsules obtained by connecting suitably shape molecules (normally macrocycles) through metal coordination or hydrogen or halogen bonds. The single crystal X-ray crystallographic studies of the capsular assemblies have provided a lot of information about how the guests are bound inside the cavitites of these capsular assemblies. Crystallizing a π-basic bowl-shaped resorcinarene molecule from moist ethanol solution together with tetramethylammonium halides (TMAX, X = Cl, Br) results in a dimeric capsule[35] in the solid-state (CCDC code XUSZIU[1]). The Hirshfeld surface and cavity volume surface analysis reveals a tightly encapsulated TMA cation as a guest inside the cavity of the capsule. The capsule is formed by two resorcinarene molecules which are held together by hydrogen bonds to the counter anions and solvent molecules. The cavity has a volume of 156.7 Å^3 and the TMA cation has a volume of 103.7 Å^3 [DFT/6- 311+G(2df,2p)/M06-2X] leading to PC of 66.2%. This is clearly larger than the expected 55%, yet the interactions between both the upper and lower part of the π-basic resorcinarene benzene ring are evident from the Hirshfeld surface analysis (red and white colours dominate, Figure 2, top). The strongest are the two C-H-π interactions [H···C(arom) = 2.65 Å C-H···C(arom) angle 146.2°] between two of TMA methyl groups and two of the resorcinarene benzene ring at the opposite sides of the capsule (due to the symmetry of the capsule). These are clearly seen as a bright red spot on the Hirshfeld surface (Figure 2, top) and as the punctures of the cavity volume surface (Figure 2 bottom, center and left in the figure). Due to the tight packing into the cavity the TMA guest is very well ordered and very reasonable (small) thermal motion.

The hemicucurbiturils[54-63] are macrocyclic host molecules that have electron-deficient cavities capable encapsulating suitably sized anion in solution and in solid-state. When a chiral (all-*R*)-cyclohexanohemicucurbit[8]uril (**cycHC[8]**) is mixed with tetrabutylammonium hexafluoroantimonate (TBASbF$_6$) in methanol a very stable (K > 10^5) 1:1 host-guest complex is formed.[63] Slowly evaporating the solvent single crystal **cycHC[8]**:TBASbF$_6$ emerge. The guest anion is found to be very tightly encapsulated into the roughly octahedral cavity of **cycHC[8]** and the Hirshfeld and cavity volume surface analysis (Figure 3) manifest strong interactions, this time through C-H-anion interactions. The deep red spots in Hirshfeld surface (Figure 3, top) and the large punctures of the cavity volume surface (Figure 3, bottom) correlate well with the eight shorter than the VDW contact of H- and F-atoms (2.67 Å), these C-H…anion (F) contact distances range from 2.3 – 2.65 Å. The cavity volume is 139.4 Å^3 and the volume of the SbF_6^- anion is 85.3 Å^3 [DFT/6-311+G(2df,2p)/M06-2X] giving PC = 61.2%. Actually this value is very likely underestimated as the cavity extends until the portals of the **cycHC[8]** (Figure 3, bottom) and therefore the occupied volume (volume of the Hirshfeld surface) of 110 Å^3 calculated by the CrystalExplorer program[23] would be a better estimate for the true cavity volume and would give the PC as 77.5%. This is supported by the exact fit of the

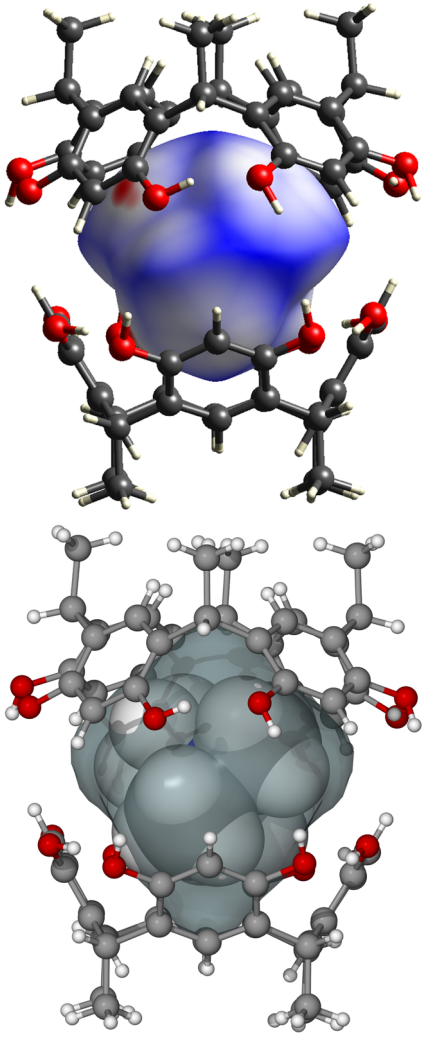


Figure 2. The Hirshfeld[24] surface plot (top) of the TMA guest in the cavity of the capsule.[35] The ball&stick view of the capsule XUSZIU[1] structure (bottom), the encapsulated guest with CPK style and the cavity volume surface[26-28] in transparent grey (1.2 Å probe). Counter anions and solvent molecules are excluded for clarity.

octahedral anion into the octahedral cavity of the **cycHC[8]** with a lot of strong C-H…anion interactions. Furthermore the SbF_6^- anion shows very small thermal movement with no disorder.

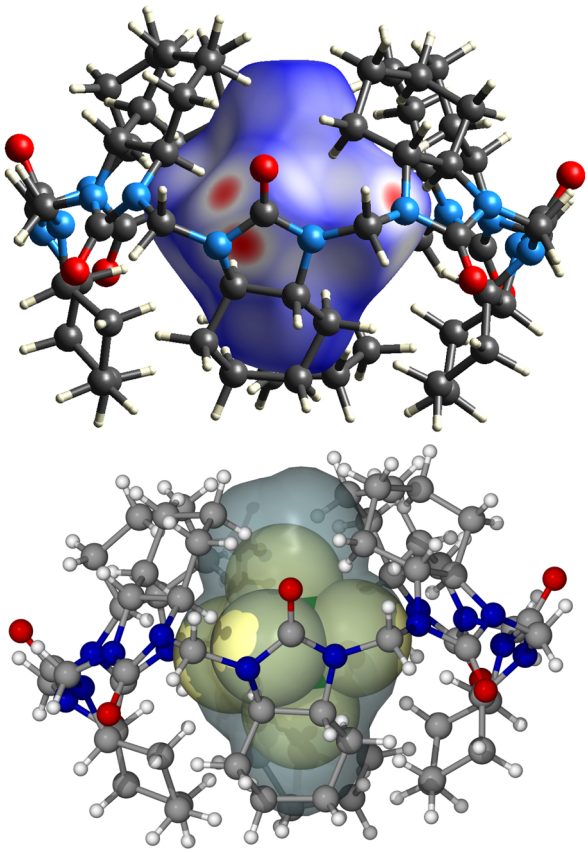


Figure 3. The Hirshfeld[24] surface plot (top) of the SF_6^- guest in the cavity of the macrocycle.[63] The ball&stick view of the ECADOE[1] structure (bottom), the encapsulated guest with CPK style and the cavity volume surface[26-28] in transparent grey (1.2 Å probe). Counter cations and solvent molecules are excluded for clarity.

Encapsulation either extremely reactive (pyrophoric) or poorly soluble highly symmetrical guest molecules inside the cavities of host molecules imposed two severe difficulties, first how to get the guest inside the host intact or at all, and secondly being able to grow good enough quality single crystal for the structure determination of the host-guest complex. Two different examples of these systems are given.

Mixing the sub-components of a metallo-organic cage with white phosphorus (P_4) in water (the highly pyrophoric P_4 has to be stored under water in order to prevent it from igniting).[64] The vapor diffusion of 1,4-dioxane into an aqueous solution of the 1:1 complex of the metallocage and P_4 leads to formation of moderate quality crystal, which reveal the P_4 to be completely incarcerated inside the cavity of the metallocage (Figure 4). The tetra-anionic

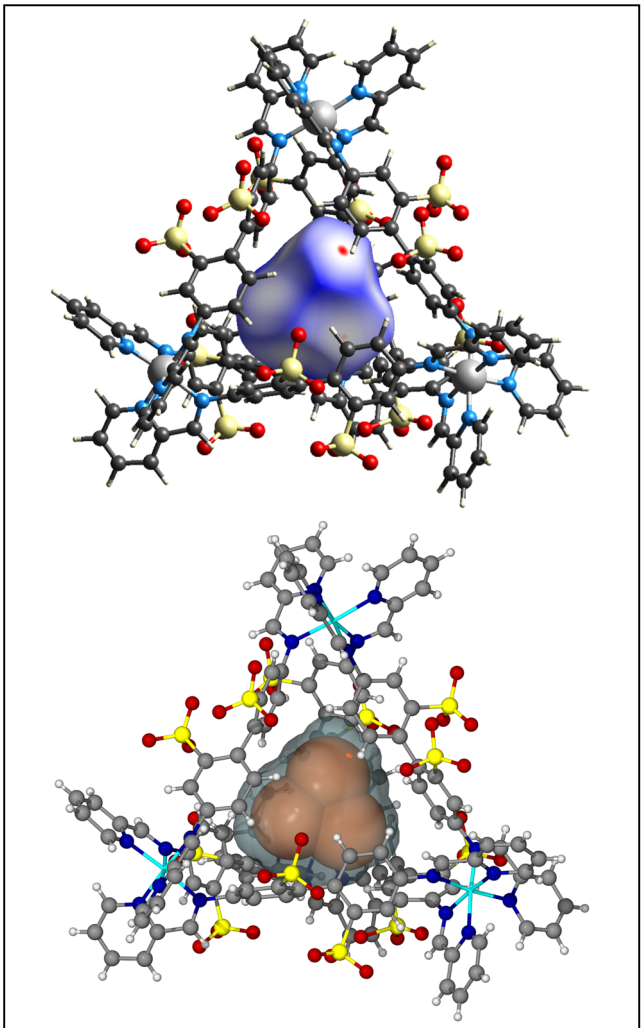


Figure 4. The Hirshfeld[24] surface plot (top) of the P_4 guest in the cavity of the metallocage.[64] The ball&stick view of the COSZOA[1] structure (bottom), the encapsulated guest with CPK style and the cavity volume surface[26-28] (1.2 Å probe) in transparent grey. Counter cations and solvent molecules are excluded for clarity.

cage has a very hydrophobic cavity volume of 151.2 (1.2 Å probe) and the calculated volume of P_4 is 80.8 $Å^3$ [DFT, 6-3111+G(2df,2p), MO6-2X]. This gives PC = 53.4% which is very close to the Rebek's 55% optimum. When inspecting both the Hirshfeld (Figure 4, top) and the cavity volume surfaces (Figure 4, bottom), it is clear that the interactions between the P_4 molecule (which shows a slight 95:5 disorder inside the tetrahedral cavity) and the cavity walls, manifests weak interactions between the host walls and the guest, indicating that the hydrophobic effect is the most likely cause of the encapsulation. The P_4 molecule is "leaning" against the cavity walls at the VDW contact distance, with only a few of them being slightly shorter and can be visually seen as red spots in the Hirshfeld surface (Figure 4, top) and as tiny punctures of the cavity volume surface (Figure 4, bottom).

Encapsulating fullerenes, C_{60} or C_{70}, into the cavity of the same molecular capsule[65] offers a possibility to observe if the differently

sized and shaped, yet chemically similar, quest will show different behaviour, *viz.* differences in the interactions, and if it will affect both the cavity size (host breathing) and the packing coefficient. Either using solution or mechanochemical complexation peptide-embedded resorcinareces form dimeric capsules encapsulating either C_{60} or C_{70} in 1:1 (capsule:guest) stoichiometry.[65] Fascinating in this work is the fact that the same capsule forms complexes both with C_{60} or C_{70}. The Hirshfeld and the cavity volume surface analysis both show that the C_{60} (CCDC refcode NADKOV[1]) is very loosely trapped inside the cavity of the capsule. While the Hirshfeld surface shows some weak red spots (Figure 5, top), the majority of the surface has blue colour, indicating longer that VDW contact distances. This is more clearly visible when inspecting the cavity volume surface (Figure 5, bottom) as there is no punctures though the surface indicating that no real contacts shorter than 3.4 Å exist. The cavity volume is 831.9 $Å^3$ for the C_{60}-capsule. The volume of C_{60} is given[65] as 549 $Å^3$, thus giving PC as 66.0%. This is surprisingly large value, when comparing to the other PC's discussed above in connection with the analysis Hirshfeld and cavity volume surfaces. However, if the volume of C_{60} is estimated form the X-ray structure, so that the VDW radii of carbon is taken into account, gives the diameter of C_{60} as 7 Å + 1.7 Å = 8.7 Å, giving radius of 4.35 Å, then we get V_{C60} = 345 $Å^3$. Using this as the guest volume the PC value is more realistic, *viz.* PC = 41.5%. Maybe the correct value in this case is ca. 50%, *viz.* lower than the optimal 55%.[16] Also the thermal displacement parameters of the C_{60} atoms are so large that the authors could not do a proper unrestrained anisotropic refinement. Very interestingly in the C_{70}-capsule (CCDC refcode NADKUB[1]) the capsule is the same, but now the guest is definitely bigger, *viz.* C_{70} *vs* C_{60}. The volume of C_{70} is not available but based on the X-ray structure (NADKUB[1]) the C_{70} is a regular ellipsoid and similarly as in the case of C_{60}, we can get the estimated C_{70} volume as 390 $Å^3$. The cavity volume is 853.2 $Å^3$ (notice: it was 831.9 $Å^3$ for the C_{60}-capsule) and thus the PC = 45.7%. In the C_{70}-capsule the guest shows much more interactions, visible in the Hirshfeld and cavity volume surface plot as red dots (Figure 6, top) and surface punctures (Figure 6, bottom), respectively. As with the C_{60} the PC seems not to reflect the host-guest interactions visible both in the Hirshfeld and cavity volume surface analysis shown in Figure 6, which both show shorter than VDW contacts between the host and the guest.

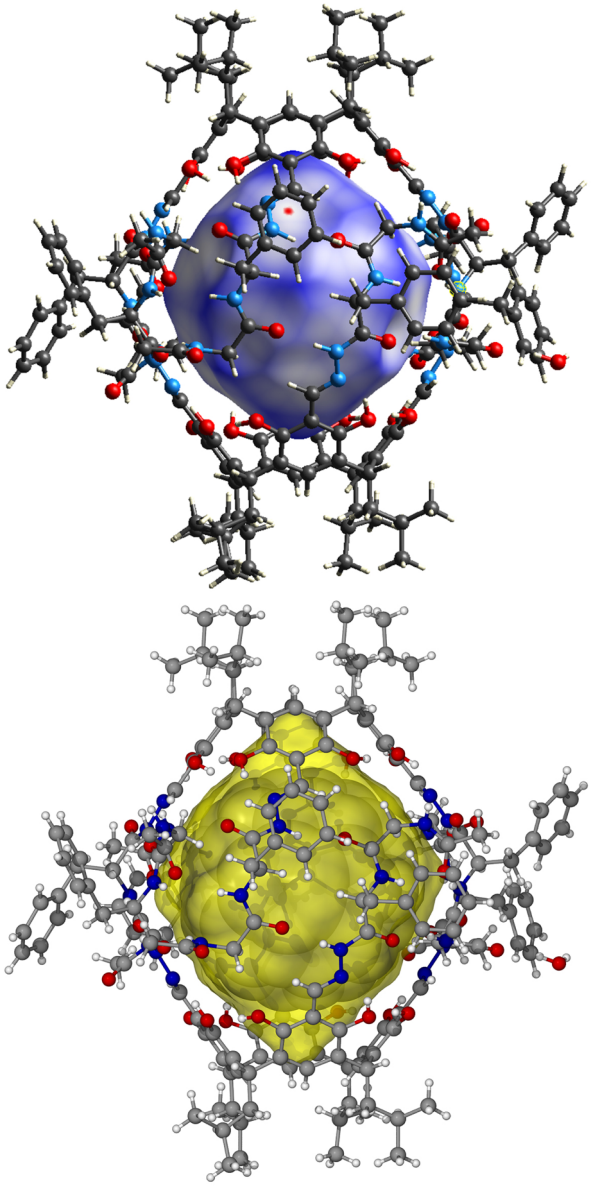


Figure 5. The Hirshfeld[24] surface plot (top) of the C_{60} guest in the cavity of the dimeric capsule.[65] The ball&stick view of the NADKOV[1] structure (bottom), the encapsulated guest with CPK style and the cavity volume surface[26-28] (1.2 Å probe) in transparent yellow. Solvent molecules are excluded for clarity.

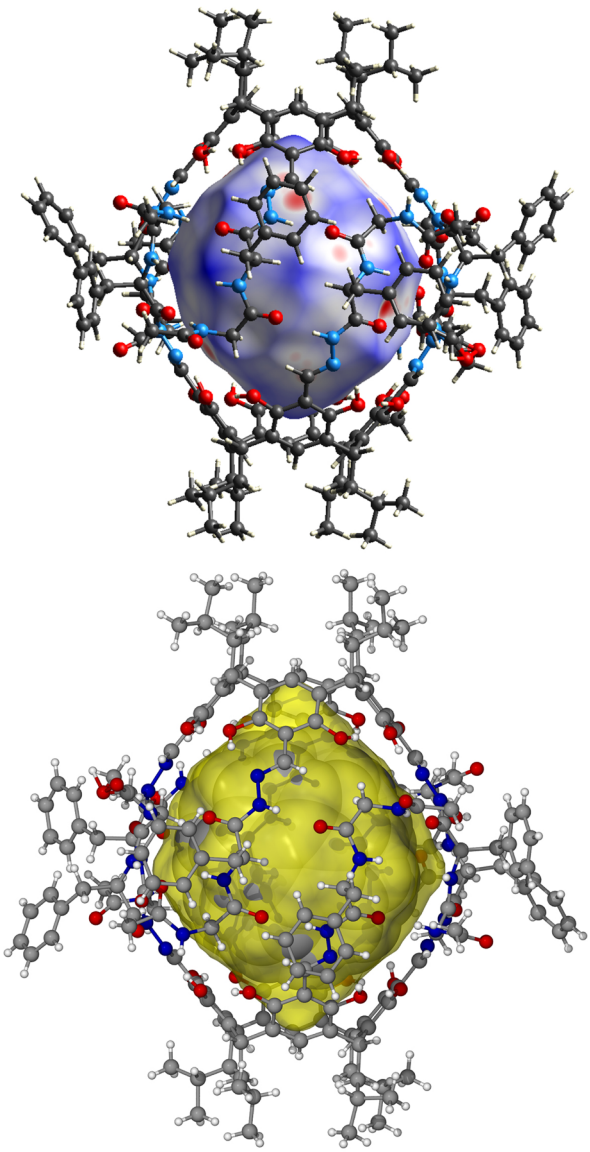
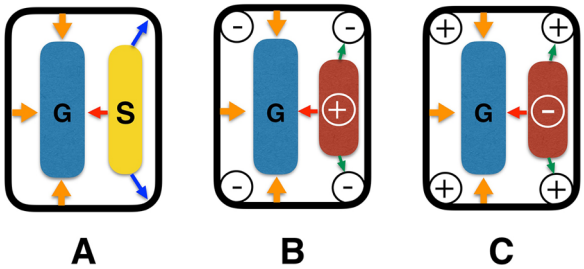


Figure 6. The Hirshfeld[24] surface plot (top) of the C_{70} guest in the cavity of the dimeric capsule.[65] The ball&stick view of the NADKUB[1] structure (bottom), the encapsulated guest with CPK style and the cavity volume surface[26-28] (1.2 Å probe) in transparent yellow. Solvent molecules are excluded for clarity.

The Crystalline Sponge Method

The *Crystalline Sponge Method* (CSM) is a very ingenious way, conceptualized in 2013 by Makoto Fujita,[17] of exploiting the large enough pores, channels or cavities of a pre-formed *sponge* crystal, so that by soaking the sponge crystal into an inert solvent containing the target compound (the guest), it will exchange itself with the solvent molecules in the pores, either completely or partially. If the guest is a liquid and available in reasonably large amounts (in ml), then the soaking can be done in the neat guest solution in order to maximize the guest-solvent-exchange.[66] The CSM works reliably if the sponge crystal has pore, channel or cavity walls, *viz.* confined spaces, that are able to interact strongly enough with the guest molecules via weak supramolecular interactions, the same that were mentioned in the introduction above. These interactions between the guest and pore, channel or cavity walls direct and entrap the guest in a particular position leading to *post-crystallization*[67] of the guest inside the already existing crystal lattice. The CSM thus uses the same principles as the clathrates and container molecules discussed above when binding the guest. The strength of the host-guest, in CSM, the MOF walls-to-guest, interactions define how well the guest will be ordered inside the pre-formed sponge crystal. If the guest is well-ordered, has sufficiently high occupancy and reasonable thermal motion, then the X-ray crystallographic analysis and results of the sponge crystal do not differ from the similar work on host-guest complexes, as above discussed with the clathrate and container molecules.

The Scheme 1 shows a schematically the possible CSM systems. The presently used systems (see below) (Scheme 1, A) relies only the interactions between the sponge walls, guest and the possible solvent. The other possible CSM systems, which utilize charged sponge walls, either negative (Scheme 1. B) or positive (Scheme 1. C) have so far not being used. In these cases the anion/cation can't leave the sponge pores, channels or cavities, but



Scheme 1. The possible construction principles of crystalline sponges. Color coding: Black = the sponge walls; Orange = Wall-Guest interactions; Red = Guest-solvent interactions; Blue = Wall-Solvent interactions, Green = Anion/Cation-Wall interactions.

would offer additional interactions, that might fix the guest better inside the sponge crystal. The charged sponge walls would also allow anion and cation exchange if the guest would be charged, *e.g.* a cationic drug molecule.

The initial crystalline sponge method (Scheme 1. A) publication in Nature[17] caused both over-positive and over-negative responses, partly due to the fact that the used sponge crystal $[(ZnI2)_3(tpt)_2x(solvent)]_n$, tpt = 2,4,6-tris(4-pyridyl)-1,3,5-triazine, turned out to be disordered in the case of the determination of the absolute configuration of the marine natural product. This caused the authors to publish a correction[68] on this aspect of the original publication[17], yet highlighting the breakthrough nature of the method itself. Very recently a publication about the hidden transformations of the $[(ZnI2)3(tpt)2x(solvent)]_n$ crystalline sponge system has been published.[69] The initial difficulty to reproduce the soaking experiments led both Fujita and others to improve the protocols how the sponge crystals should be grown and selected, optimizing the soaking conditions and solvents used, and giving

guidelines about the actual data collection strategies with an in-house instrument[67,69-73] or synchrotron radiation.[66]

Until now (March 2017) CSM it has not yet been extensively used, mainly due to the expertise needed in the growing of the sponge crystals, in guest soaking and in the not trivial crystallography involved. The contemporary publications have reported the use of CSM in the previously impossible structural elucidations, most of them by Fujita himself. These success stories include the structural re-evaluation of the electrophilic hyper-valent iodine reagent for trifluoromethylthiolation[74], structural determination of the reaction products from the radical C-H functionalization of heteroarenes under electrochemical control[75], observation of palladium-mediated aromatic bromination reaction[76], the structural analysis of the position of the oxygen atom in α–humulene oxidation product[77], determination of absolute structures of axially and planar chiral molacules[78], determination of the absolute and regio-configurations of the cyclic product from phosphine-catalyzed β,γ-Umpolung Domino reaction of allenic esters[79], structure determination of *S*-(-)-Nicotine and other small organic molecules[80], determination of the absolute configuration of the pseudo-symmetric natural product Elatenyne[81], a saccharide-based crystalline sponge for hydrophilic guests[82], structure determination of Astellifadiene[83], confirmation of the syn-addition mechanism for metal-free diboration[84], the *in situ* observation of thiol Michael addition to a reversible covalent drug[85], high-resolution X-ray structure of methyl salicylate[86], differentiation of volatile aromatic isomers and structural elucidation of volatile compounds in essential oils[87], structure analysis of ozonides[88] and determination of absolute configuration and structural revision of Cycloelatanene A and B.[89]

As examples of Hirshfeld and cavity volume surface analysis some crystalline sponges are briefly discussed below. The most used crystalline sponge, the [(ZnI2)3(tpt)2x(solvent)]n MOF, crystallizes in many crystals systems, depending on the guest and also due to the framework flexibility.[69] The cavity volume surface analysis discussed above in the clathrates and container molecules section is not often feasible for large and partially filled pores, channels and cavities, in these cases the Hirshfeld surface analysis works well. The [(ZnI2)3(tpt)2x(solvent)] crystalline sponge has very large voids in its lattice, ca. 50 – 53% is void space if only the MOF framework is taken into account. To get the guest and the possible solvent molecules as well ordered as possible, they should fill the void space as completely as possible. This however does not rule out the possibility of the guest and solvent disorder. A good example of a [(ZnI2)3(tpt)2x(solvent)] sponge with only a few molecules in the asymmetric unit, actually one guest (= guaiazulene) and two solvent molecules (= chloroform), measured with the synchrotron radiation is shown in Figure 7. (CCDC refcode ZOQTAC[1]).[66] This sponge crystal has 50 % voids, yet they are not fully occupied by the guest and the solvents, ca. 17 % of the crystal is still void. In this case the use of synchrotron radiation results in a very well-resolved and well-behaving structure with some interesting features. The iodine atoms in the ZnI_2 moiety act as H-atom acceptors for one of the chloroform molecule, the electron-deficient tpt moieties interact with the guest guaiazulene as earlier reported by Fujita with the same guest.[17,67,70,71]

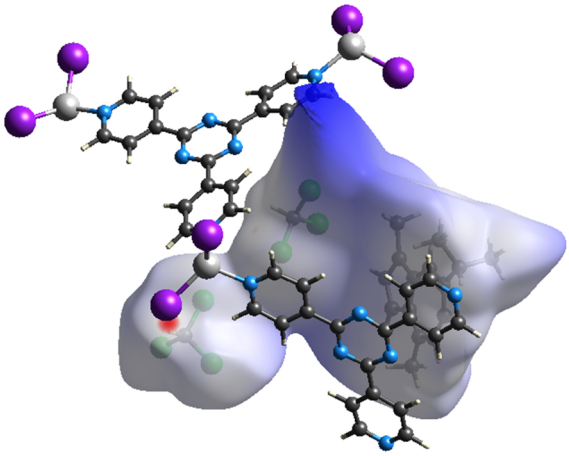


Figure 7. The Hirshfeld[24] surface plot of the guest in the asymmetric unit of a ZnI_2-tpt sponge structure ZOQTAC[1] from synchrotron radiation.[66]

A more complex structure (CCDC refcode IYOCUW[1]) based on the amount of guest molecules to be determined was reported recently by a Chinese group.[87] They used the same tpt ligand but now together with $ZnBr_2$ moiety. The soaking experiment from chloroform with carvacrol, a small monoterpenoid phenol (a structural isomer of thymol) resulted in crystals with unresolvable amount of solvent chloroform and five guest molecules. The badly resolved and ordered chloroform molecules were removed using the SQUEEZE protocol (note that SQUEEZE should be used with utmost care in CSM[67]) and asymmetric unit now contains five carvacrol molecules which form a large "supermolecule" inside the cavity of the MOF. The phenolic OH-group is able to acts as hydrogen bond donor and acceptor towards the adjacent molecules and the Hirshfeld surface analysis reveals these as red spots on the surface of the "supermolecule" (Figure 8).

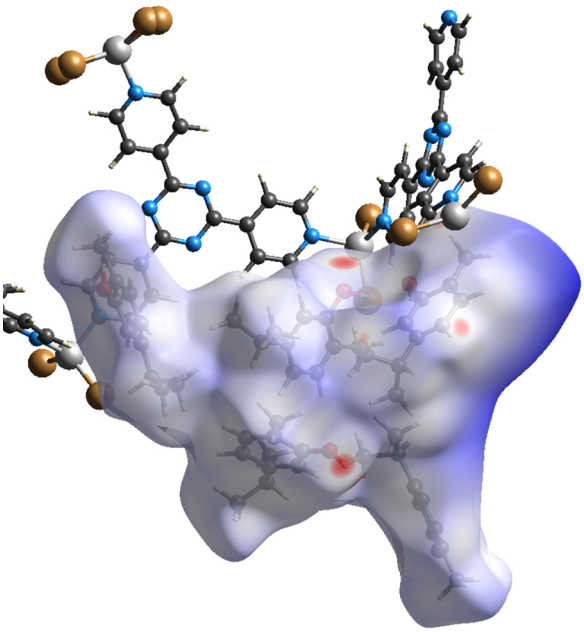


Figure 8. The Hirshfeld[24] surface plot of the guest in the asymmetric unit of a $ZnBr_2$-tpt sponge structure IYOCUW.[1,87]

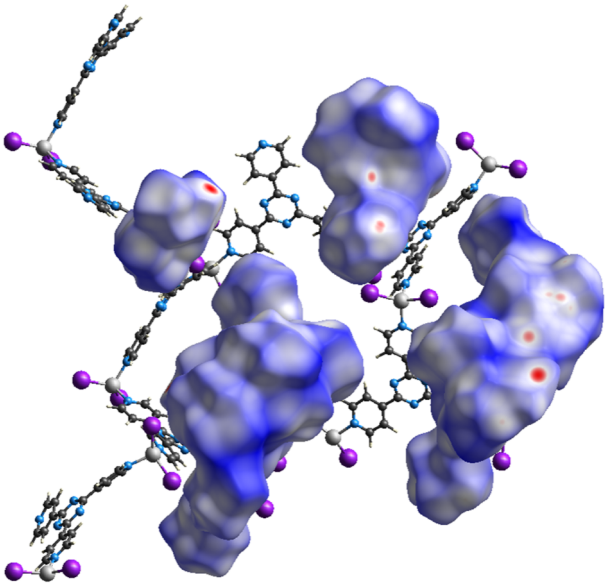


Figure 9. The Hirshfeld[24] surface plot of the guests and solvent molecules in the asymmetric unit of a ZnI_2-tpt sponge structure LABNAG.[1,35]

Fujita improved[35] the protocol for applying CSM with the [(ZnI2)3(tpt)2x(solvent)] sponge MOF to enantiomerically pure drug molecule santonin. Solving experiment with santonin leads to the transformation from the initially centrosymmetric crystal lattice (space group *C*2/c with unit cell volume of 15103 Å^3) to a chiral crystal lattice (space group $P2_1$ with unit cell volume of 16430 Å^3).

This lowering of symmetry increases the number of molecules in the asymmetric unit and after soaking the asymmetric unit cell contains five santonin and 13 cyclohexane solvent molecules (CCDC refcode LABNAG[1]). The santonin and the cyclohexane molecules are forming "clusters" which will fill up 99% the voids of the sponge cavities. The carbonyl oxygen of the santonin molecules act as hydrogen bond acceptors from the H-atoms of the walls of the sponge. The pyridinic ortho-H-atoms of the tpt ligand will be more acidic with the complexation of ZnI_2 and they will form quite strong 2.2 – 2.4 Å H-bonds (C-H…O=C) to the santonin carbonyl oxygen. These interactions are clearly visible from the Hirshfeld surface analysis (Figure 9) as large red spots. The cyclohexane molecules fill up the spaces between the santonin molecules creating a nearly "small molecule" level crystal structure. Due to the very good quality of the santonin sponge crystal it could be crystallographically treated as a small molecule data, and Fujita himself consideres this LABNAG structure as the benchmark for crystalline sponge method for chiral optically pure molecules.[35]

Finally a short account that also other MOF structures can and will act like crystalline sponges, and even though their use has not been reported as CSM, they manifest the same features as above described examples of the iconic $[(ZnX_2)_3(tpt)_2x(solvent)]$ sponge MOF's as well as those in the beginning of this review for clathrates and container molecules. This is to say that any porous single crystalline material which, by defined weak host-guest interactions, will bind and order guest molecules into its pores, channels or cavities can be regarded as a crystalline sponge. Keeping this in mind Fujita published[58] very recently an article about finding new crystalline sponges from the Cambridge Structural Database.[1]

Gas molecules such as CO_2, N_2, O_3, CH_4, etc. can be considered as special guests for the CSM. As they are gases the soaking phase is substituted either by a gas flow through the crystals or better by pressuring the crystals up to 80 bar of the guest gas. Achieving this requires a special technique for the crystallographic work, so called environmental gas cell developed by Len Barbour.[59] With this technique the Barbour group have studied simple MOF structures with very tiny pores, just big enough to encapsulate gases, most often CO_2. They have shown that hysteresis[60] occurs in the sorption of CO2 into the specific breathing MOFs, most interestingly they have used as simple Zn(II)-MOF as CSM and can achieve an *in situ* crystallographic visualization of CO_2 binding within the Zn(II)-MOF (crystalline sponge at high gas pressure) at 298 K.[61] Due to the very small pores, and the nature how the gas molecules are situated in the pores, allows both Hirshfeld and cavity volume surface analysis as for the clathrates and container molecules above. The Hirshfeld surface and cavity volume surface analysis (Figure 10) reveals the interactions with the encapsulated CO_2 molecule and the pore walls of the Zn(II)-MOF, giving a crystallographic proof for the MOF (crystalline sponge) to effectively bind the CO_2 molecules. The CO_2 molecule has a volume of 38.5 Å^3 [DFT/6-311+G(2df,2p)/M06-2X] and the cavity size, where the CO2 is residing is 73.0 Å^3 resulting in a PC of 52.7%. This is very close to the optimal 55%[24] (for single cavity hosts), and the interactions between the CO_2 and the wall of the MOF pore are very nicely visualized by the Hirshfeld surface analysis (Figure 10, top). The electron-deficient carbon of the CO_2

interacts quite strongly with the electron-rich oxygen atom of the carboxylate moiety in the MOF wall (Figure 10, top), the contact distance being 3.07 Å, definitely shorter that the VDW contact distance of carbon and oxygen (3.22 Å). This interaction is also see as a clearly visible puncture in the surface volume surface (Figure 10, bottom).

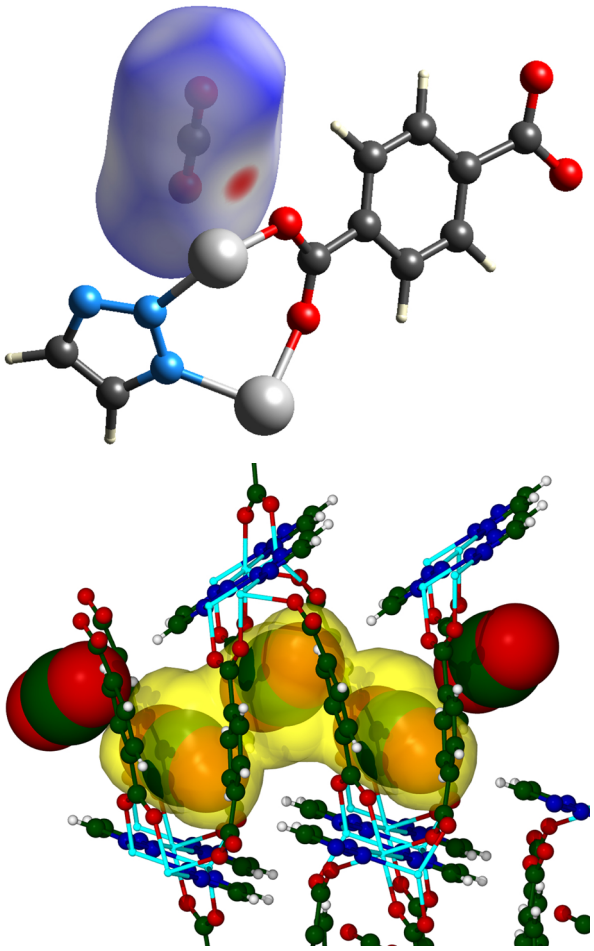


Figure 10. The Hirshfeld[24] surface plot (top) of the CO_2 guest in the pores of the Zn(II)-MOF (only asymmetric unit is shown).[61] The ball&stick view of the DAFSEL[1] structure (bottom), the encapsulated guest with CPK style and the cavity volume surface[26-28] (1.20 Å probe) in transparent yellow.

Conclusions

Single crystal X-ray crystallography offers the most accurate method of studying and analysing crystal and molecular structures and the supramolecular interactions which occurring between the components in the crystal structure. In Supramolecular Chemistry it often occurs that the studied single crystal contains a host-guest complex, either as a classical or molecular clathrate. In these crystal structures the guest molecule or guest molecules interact with the host via weak supramolecular interactions. Extracting structural details of these interactions and utilizing this knowledge is the essence of Supramolecular Chemistry. The detailed crystal structure studies can pave way to the design new more selective host systems active either in solution or in the solid-state. The most promising and certainly a revolutionary way of applying the supramolecular interaction is the *Crystalline Sponge Method* (CSM) which offers unprecedented possibilities for the X-ray crystallographic determination of unknown compounds. However CSM is still in its very early development phase and new more robust, selective, low-symmetry and easy-to-handle crystalline sponge systems, weather they are MOFs or other porous materials, have to be found and/or developed.

Only after three years *Crystalline Sponge Method* has produced amazing results and it will have a very bring future as a part of *Supramolecular Chemistry.*

Acknowledgements

The Academy of Finland (project no's 263256, 265328 and 292746) and the University of Jyväskylä are gratefully acknowledged for financial support.

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