The Crystalline Sponge Method in Water

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Abstract: The crystalline sponge method entails the elucidation of the (absolute) structure of molecules from a solution phase using single-crystal X-ray diffraction and eliminates the need for crystals of the target compound. An important limitation for the application of the crystalline sponge method is the instability of the available crystalline sponges that can act as host crystals. The host crystal that is most often used decomposes in protic or nucleophilic solvents or when guest molecules with Lewis basic substituents are introduced. Here we disclose a new class of (water) stable host crystals based on f-block metals. We show that these hosts not only increase the scope of the crystalline sponge method to a wider array of solvents and guests, but that they can even be applied to aqueous solutions containing hydrophilic guest molecules, thereby extending the crystalline sponge method to the important field of water-based chemistry.

Single-crystal X-ray diffraction is the method of choice for determining the structure and absolute configuration of molecules. This method requires suitable crystals of the target compound, which can be a severe bottleneck. The crystalline sponge (CS) method, introduced by Fujita et al.,^[1] provides a promising solution by eliminating the need for crystals of the target compound. Instead, the target compound is absorbed into a porous metal-organic framework (MOF), the host crystal, and subsequently adapts an ordered structure inside the pores, when there is a good match between host and guest. By applying single-crystal X-ray diffraction to the host-guest complex, structure elucidation of the target compound becomes possible.^[1-2]

There are important factors that limit the successful application of the CS method. As one may expect, there is no universal CS that can host the large variety of possible target compounds. The choice of host depends on the size, shape, coordination properties and specific reactivity of the guest compound and a successful host-guest combination is generally difficult to identify. As an example, for the optimal uptake and ordering of hydrophilic guest compounds other host systems will be required than for hydrophobic guests.^[2f]

Another problem is the ordering of guest molecules inside the host framework. Up to now, successful host-guest combinations relied on two kinds of host-guest interactions. One of those involves weak Van der Waals interactions of the guest molecules with the pore walls, as is the case with the MOF host

introduced by Fujita et al.^[1] This may give rise to ordering of the guest molecules, but may also lead to different levels of disorder that hamper a proper structure determination.^[2a] The second interaction consists of coordination of the guest molecules to the metal, as shown in the MOF introduced by Yaghi et al.^[2g] Metal coordination allows for a rigid anchoring site, which can enhance structure solution, especially for the molecular part close to the metal. However, disorder is still possible in the crystal structure if the compound of interest can coordinate to the metal in more than one way, or, in the case of flexible molecules, may occur further away from the anchoring site. Despite many reported successes of the CS method, ordering of guest molecules inside the host framework is rather unpredictable and in principle requires the availability of several suitable host compounds to optimize the host-guest combination.

The instability of the MOF host also determines the range of molecules that can be investigated using this method.^[3] The most frequently used ZnI_2 -tpt MOF introduced by Fujita et al. consists of ZnI_2 with 2,4,6-tri(pyridin-4-yl)-1,3,5-triazine linkers. This MOF host easily decomposes when it comes into contact with solvents or (high concentrations of) guest molecules containing Lewis basic or protic substituents.^[3b] Therefore, there is a clear need for more stable MOFs that can withstand a wider array of solvents and functional groups. Moreover, crystals of the host compound must be of sufficient size and quality. Easy, fast and reproducible synthesis of suitable host compounds is therefore one of the challenges in the further development and optimization of the CS method.^[3a]

We have conducted more than 10.000 crystallization experiments using combinations of metals, solvents, counter ions, and ligands under various conditions. These experiments yielded a number of porous f-block-based MOFs, consisting of lanthanide metals linked with carboxylic acid containing ligands (Figure 1), as promising and stable hosts for the CS method. To demonstrate the suitability of these hosts we have performed tests with several common solvents and guest molecules to provide proof of principle, and additionally used aqueous solutions of the guest compounds 2-pyrrolidone and ϵ -caprolactam for guest exchange.

Figure 1. Chemical structure of the ligands. 1,3,5-benzenetribenzoic acid (H_3BTB) (1), and 4,4',4''-(1,3,5-triazine-2,4,6-triyl)tribenzoic acid (H_3TATB) (2) used in the synthesis of the MOF hosts (called RUM-X) investigated here.

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By using ligands **1** and **2** three different lanthanide-based MOF topologies (**RUM-1**, **RUM-2** and **RUM-3**) were obtained that proved to be suitable for application of the CS method (Figure 2). In many instances the lanthanide metal can be replaced by a different lanthanide metal in the synthesis of the MOFs, without changing the resulting MOF topology. A different f-block metal may influence the crystalline stability, as is illustrated by the differences in the stability of **RUM-3** when Ce is replaced by Dy (Table 1). It is envisioned that lanthanide metals with a higher number of electrons give more stable MOFs, due to the greater effective nuclear charge of the metal. Crystals of **RUM-2** of a size suitable for single-crystal X-ray diffraction were only obtained by adding a crown-ether modulator to the crystallization solution, which is, to the best of our knowledge, the first example of the modulating effect of crown-ethers on the crystallization of MOFs (see SI-2 for more details).

Both hydrophilic and hydrophobic guests were introduced into the hosts. The first MOF (**RUM-1**) shows only Van der Waals interactions with the guest molecules, while **RUM-2** and **RUM-3** allow for coordination of the guest molecules to the metal site, in which the guest molecule (partly) replaces a coordinated solvent molecule. Additionally, ordered guests were encountered in **RUM-2** and **RUM-3** that only have Van der Waals interactions with the host. This clearly shows that **RUM-2** and **RUM-3** allow for both types of host-guest interactions that were described before.

Figure 2 Schematics for applying the crystalline sponge method using the lanthanide-based MOFs (called RUM). The MOFs with pores filled with DMF are made by layering solutions containing the lanthanide salt and the ligand. Target molecules are introduced into the pores by soaking the host crystals in (solutions containing) the target compound, e.g. ϵ -caprolactam in water. The blow-up (marked purple) shows the resolved structure of caprolactam coordinated to the lanthanide metal side via the ketone lone-pair.

The versatile RUM hosts enable structural elucidation of guest molecules bound to the metal, but also of isolated guest molecules present in the pores of the host crystal. The topologies of **RUM-1** and **RUM-2** have been described for different metals,^[4] or for different solvents coordinated to the metal.^[5] However, the **RUM-3** topology is new. Related MOFs described in literature are usually obtained via solvothermal synthesis, which in our

experience does not yield crystals of suitable size and quality for single-crystal diffraction, and subsequent application of the CS method. Our liquid diffusion procedure, in which a modulator can be used, does provide crystals of a size suitable for the CS method, and as a result of the better crystal quality, we could also resolve the host structures in more detail.

Figure 3 Optical microscopy photographs of the RUM host crystals. RUM-1 (a), RUM-2 (b), and RUM-3 (c) host crystals (highlighted by the arrows).

The synthesis of the RUM host crystals is simple and reproducible, analogous to the crystallization technique employed by Fujita et al. (for details see SI-2). The crystallization occurs in a highly controlled environment in terms of temperature and pressure and yields crystals suitable for single-crystal X-ray diffraction using lab equipment (see Figure 3). The solvothermal method employed by Yaghi et al. yields rather small crystals (which we could reproduce) and synchrotron radiation is required to obtain single-crystal diffraction data of acceptable resolution for these crystals.

One key aspect of the new CS hosts is their stability, which determines the scope for application of the CS method. The new RUM hosts were therefore exposed to various solvents for one day, to investigate their stability to different chemical functionalities (alcohol, aldehyde, thiol, etc). The results are summarized in Table 1. If a host crystal structure could still be determined after exposure to a solvent this is indicated by a green +, while if the crystal was damaged, making structure elucidation impossible, a red - is shown. For comparison the ZnI_2 -tpt MOF was also examined in the same way.

Table 1 Summary of the stability of the MOFs. Stability for the MOF introduced by Fujita et al.^[1], and the new MOF hosts (RUM-1, RUM-2 and RUM-3). †Under influence of the solvent the crystals converted into a different non-porous structure: refcode IZUVAB^[6] in the CSD. *RUM-3 finally decomposes in pure water, but did allow for the elucidation of ϵ -caprolactam, which was introduced from an aqueous solution.

	RUM-1	RUM-2	RUM-3 (Ce)	RUM-3 (Dy)	Fujita-MOF
MeOH	+	+	+	+	-†
H ₂ O	+	+	-	+/-*	-
DMF	+	+	-	-	-
CHCl ₃	+	+	-	-	+
acetonitrile	+	+	-	+	-†
DMSO	-	+	-	-	-
nitrobenzene	+	+	+	+	+
pyridine	+	+	-	+	-
acetic acid	-	-	-	-	-†
dodecanethiol	+	+	+	+	+

Especially **RUM-1** and **RUM-2** outperform the Zn_{12} -tpt host in terms of stability. This difference can be explained by the different bonding character of the RUMs compared to the Zn_{12} -tpt MOF, *i.e.* strong carboxylic acid to f-block metal bonds versus the less stable nitrogen lone-pair coordination to a d-block metal, respectively. The crystal quality of **RUM-1** deteriorates only after longer exposure to solvents. This slow decomposition can most likely be attributed to its crystal structure, since it comprises a two-dimensional coordination network in two crystallographic directions, which leaves these crystals prone to delamination. Fortunately, even though the crystals eventually deteriorate, they proved sufficiently stable for application of the CS method. **RUM-2** and **RUM-3** do not show deterioration after longer exposure to solvents. Clearly, the better stability of the RUM host crystals extends the scope of the CS method significantly.

In order to test the suitability of these new hosts for structure determination using the CS method, different solvents and guest compounds were introduced. The results of these measurements are summarized in Figure 4 and SI-3. Carvone was resolved (only bound through Van der Waals interactions with **RUM-2**) from a 99% pure (–)-carvone solution. If a single enantiomer is incorporated in an ordered way inside the pores of **RUM-2**, the space group should change to a Sohncke space group. However, we observed a retention of the centrosymmetric space group ($C2/c$). This means that enantiomeric pairs consisting of (–)-carvone, and of (+)-carvone (a contamination) have ordered inside the pores of **RUM-2**. Therefore, soaking these crystals with the 99% pure (–)-carvone solution would allow for enhancing the enantiomeric excess of the remaining solution. We previously observed the same phenomenon, the ordering of enantiomeric pairs for α -pinene and camphene, in the Zn_{12} -tpt host,^[2] which also has a centrosymmetric space group.

Finally, **RUM-3** was used to resolve the structures of ϵ -caprolactam (Figure 2), and *N*-methylcaprolactam (SI-3). Both molecules coordinate to the metal through a lone pair of the ketone group. ϵ -Caprolactam and 2-pyrrolidone are solids and therefore need to be dissolved in order to apply the CS method. Both compounds are freely soluble in water, which is why this solvent was selected for guest exchange. To the best of our knowledge this is the first time that the CS method is applied in water. Figures 2 & 5 illustrate the extended scope of the applicability of the CS method.

In summary, this proof-of-principle opens the way to the use of the CS method for a much wider range of solvents and guest compounds and for application in water-based media. MOFs with larger or differently shaped pores will be required for larger molecules, which can in principle be realized by using extended carboxylate ligands in combination with lanthanide metals. By adapting the ligands, other stable lanthanide containing MOFs could be created with different topologies and pore architectures, adapted to the needs of different guest compounds.

Figure 4 X-ray structures and structural formulas for the different guest compounds determined with the CS method. Guests (sometimes coordinated to a metal site) resolved using RUM-1 (a-c), RUM-2 (f-j), and RUM-3 host crystals (d-e), respectively. Guest molecules are: 2,6-dimethylaniline (a), pyridine (b), chloroform (c), ϵ -caprolactam (d), *N*-methylcaprolactam (e), methanol (f), pyridine (g), carvone (h), 1-methyl-2-pyrrolidone (i), and 2-pyrrolidone (j).

Figure 5 Schematics showing possible guest exchange mechanisms. Guest exchange mechanisms for the lanthanide crystalline sponges. Top: replacement of coordinating DMF molecules with methanol, followed by replacement of coordinated methanol by pyrrolidone from an aqueous solution. Bottom: replacement of DMF inside the cavity for liquid carvone. The blow-ups marked in purple show the resolved structure of the guest compounds.

Data availability

CCDC 1880732-1880745 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Experimental Section

The crystallization of the RUM hosts and the guest exchange procedure are described in detail in SI-2. In general, host crystal synthesis was achieved by liquid diffusion of a salt solution into a solution containing **1** or **2** (Figure 1). The host crystals were soaked in a solution or neat solvent for at least one day to achieve guest exchange.

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Keywords: Crystalline sponge method • Structure elucidation • Metal-organic frameworks • Lanthanides • Absorption

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A new class of stable host crystals based on f-block metals allows the crystalline sponge method to be applied to a wider array of solvents and guest compounds. The new crystalline sponges can even be applied to aqueous solutions of guest molecules.

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