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Encapsulating Organic Crystals (EnOCs)

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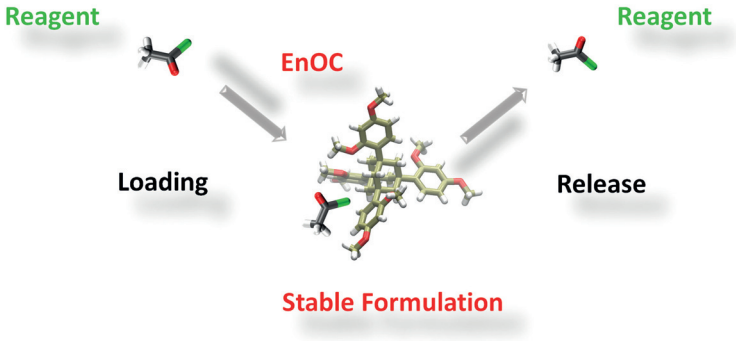

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Abstract Achieving efficient capture, storage and release of small molecules is a challenge. Most materials that can harbor small molecules have been studied in the context of gas storage or separation. Formulations for hazardous reagents have only recently attracted attention, when organic compounds were discovered that encapsulate a broad range of guest molecules in crystals. Such encapsulating organic crystals (EnOCs) can suppress problematic properties of reagents and allow for controlled release in reaction mixtures. Unlike materials used for gas storage, which possess permanent porosity, their cavities are not held together by covalent or strong noncovalent interactions. Instead, EnOCs crystallize with the help of weaker packing forces. Substituted tetraaryladamantane octaethers can form high-loading inclusion compounds with reagents as guests, but they can also transition into tightly packed, solvate-free forms. Here we highlight the differences between EnOCs and known porous materials and discuss the potential of EnOCs as formulations in organic synthesis.

Key words functional materials, inclusion complexes, reagents, uptake and release, X-ray crystal structure

There is a special fascination with organic matter that can take up and release molecules. Perhaps this is because the phenomenon is intimately linked to life. Breathing is a process that leads to the uptake of oxygen and the release of carbon dioxide from the body. Likewise, the uptake of water and nutrients by organisms is linked to life as we know it. Efficient storage for times of need, as in potatoes that accumulate starch in the amyloplasts of their tubers during summer, is also important for the survival of the plant and those who cultivate and consume it. Being able to emulate nature's approaches to take up, store, and release for chemicals, perhaps as part of sustainable processes, could provide a solution to energy problems but may also lead to safer synthesis procedures because of proper formulation of reactive compounds.

There is active research on new ways to store molecules in solids. Different materials are being proposed for achieving this task. Perhaps the best known solids that can capture and release small molecules are zeolites,[1] that is, inorganic polymers with covalent bonds setting up a rigid structure that reversibly binds water and small organic molecules (Figure 1). But, other porous materials are rapidly gaining ground. Among them are metal-organic frameworks (MOFs) and covalent organic frameworks (COFs) that are partially or entirely based on stiff organic building blocks assembling with crystalline or partially crystalline order.[2] Another exciting new class of compounds are organic cage compounds that posses a cavity large enough to host other molecules.[3] As materials, the organic cages can be porous in amorphous or in crystalline states. Like calixarenes they can engage in supramolecular host–guest interactions even when they are found as individual molecules in solution.[4] A different class of organic compounds that can act as hosts for small molecules are compounds that require crystallization to form the cavities that bind the guests. When they are porous, such organic materials are said to exhibit 'extrinsic' porosity, as opposed to an intrinsic porosity that is inherent in the molecular structure.[5]

The better known organic materials with extrinsic porosity posses hydrogen-bond donor and acceptor functionalities and form their crystal lattice via strong hydrogen bonds.[6] Recent advances in computational structure prediction have led to impressive advances in the design and experimental realization of highly porous organic crystals that are held together by directional intermolecular interactions between molecules with shapes that hinder close packing.[7] Some examples of such molecules 'designed not to pack tightly' form inclusion compounds or solvates with

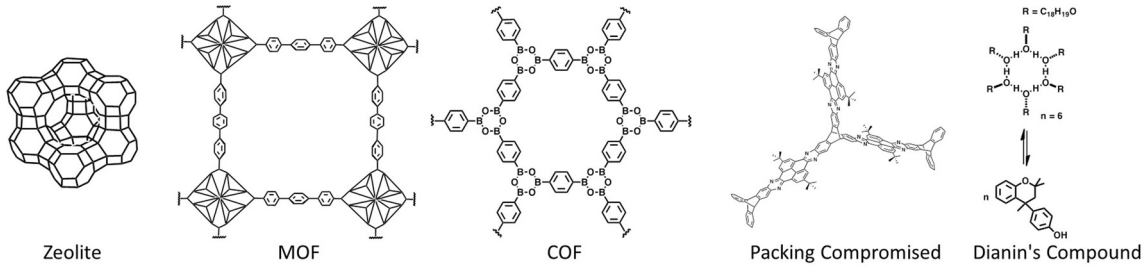

Figure 1 Structural components of materials for the uptake and release of small molecules. Besides a zeolite, substructures of a metal-organic framework (MOF), a covalent organic framework (COF), a compound designed not to pack tightly (packing compromised), and Dianin's compound are shown.

guest molecules, even if they lack hydrogen-bond donor groups,[8] but no tightly packed, solvate-free forms have been reported.

Organic crystals with extrinsic porosity are a special case of the significant number of compounds that include solvent upon crystallization when tight packing is geometrically difficult or when hydrogen-bond acceptor/donor groups cannot be 'satisfied'.[9] Perhaps the best known example of such inclusion-forming compounds that shows 'zeolite-like' behavior is 'Dianin's compound' (Figure 1). It is long known to take up (and release) a range of small molecular guests in cavities lined by a hydrogen-bonding network.[10,11]

There are molecules, though, that readily form inclusion compounds even though solvate-free, tightly packed crystalline forms are also accessible to them. So the conventional wisdom that solvate formation is a consequence of remaining intermolecular cavities that cannot be readily filled during crystallization does not seem to apply. Many of us have recrystallized a new compound, hoping that we obtain a solvate-free form that matches the theoretical values in the elemental analysis. A new solvent often solved the problem. But there are also compounds for which guest molecules as different as *n*-hexane, trimethylphosphate, and nitrobenzene are being incorporated efficiently. The first such compound found in our laboratory is tetraaryladamantane octaether 1,3,5,7-tetrakis(2,4-dimethoxyphenyl)adamantane (TDA). The second such compound is the related ethyl ether 1,3,5,7-tetrakis(2,4-diethoxyphenyl)adamantane (TEO). For these compounds, we feel the term 'encapsulating organic crystals' (EnOCs) is particularly fitting.

The tetraaryladamantanes shown in Figure 2 exhibit significant diversity in their crystal structures. This is probably because the structural arrangements in their crystals are not fixed in place by strong, directional interactions or covalent bonds. As shown in Figure 2, both TDA and TEO crystallize in solvate-free forms and in encapsulating forms with similar density. For TDA, monoclinic, triclinic, and hexagonal crystal systems have been published.[12,13] For TEO, both a monoclinic and a tetragonal tightly packed solvate-free form were found. But, another monoclinic form was found to encapsulate more than three molar equivalents of *p*-xylene as guest molecule, and many other inclusion compounds were of a triclinic crystal system.

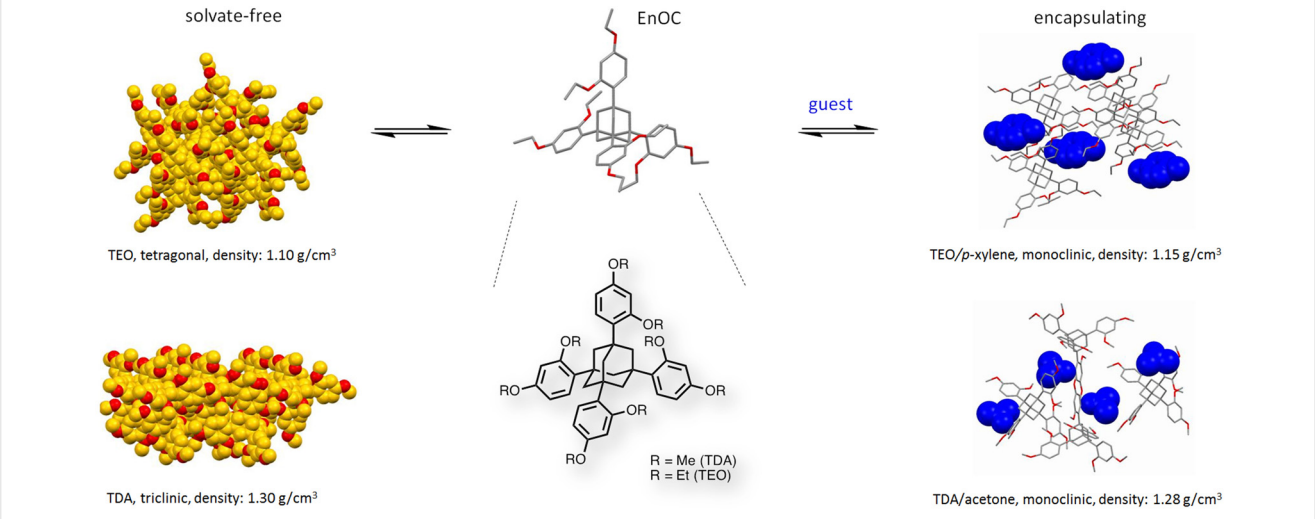

Figure 2 Structures and representative crystal forms of tetraaryladamantane EnOCs, as described in the recent literature[12,14]

How are these EnOCs useful as tools in synthesis? After encapsulating and stabilizing fairly reactive molecules, like acid chlorides, the octaether-based EnOCs can shed their guest molecules, either upon dissolving in a solvent or upon warming. So, after formulation by crystallization, captured guests can be released.[12]

The two EnOC-forming compounds shown in Figure 2 are accessible in a three-step synthesis from inexpensive starting materials.[13,14] They crystallize readily, often within minutes. Their loading capacity for small molecules is up to 35% of the dry weight of the material. Overall, more than 100 crystal structures with encapsulated small molecules have been solved for these two compounds thus far in our laboratories. Most importantly, as mentioned above, the ability to form inclusion compounds with liquids is not limited to solvents. Encapsulation upon crystallization can be used to formulate toxic, malodorous, or highly reactive compounds. In the encapsulated form, the undesirable properties of the guests are masked, so that encapsulated acid chlorides or isocyanides are odorless. Some reagent formulations of water-sensitive compounds are stable to air, or, as in the case of benzoyl chloride encapsulated in TEO, stable to immersion in water.[14]

All encapsulated reagents studied thus far by us can be handled outside a fume hood and are easy to dispense. The most common way to induce the release of the reagent is to dissolve the material in the reaction solvent. Because the crystalline formulation unleashes the reagent more slowly than addition in neat form, some transformations are cleaner with the encapsulated reagent.[13] Slight increases in yield were also traced back to a smaller extent of hydrolysis, probably because the encapsulated form is a solid that does not get in contact with as much surface water as a liquid that is being dispensed with the help of glass pipettes. In solvents such as DMSO or acetone, TDA that had acted as crystalline coat for an acid chloride or an isocyanide was found to precipitate upon shedding its molecular cargo, so that up to 99% could be recycled by filtration at the end of the synthetic transformation (Figure 3).[13]

Recently, the vacuum-dried form of TEO that had been crystallized as a high-loading solvate was found to adsorb xylene vapors reversibly from the gas phase, with 15 uptake and release cycles over the course of 17 days.[14] This suggests that the loading of liquid guest molecules can occur not only through gentle thermal crystallization, as performed with reagents such as benzoyl chloride, trimethylsilyl chloride, cyclohexyl isocyanide, or pyrrolidine, but may also be performed by absorbing vapors. This, again, may be useful for synthetic procedures where problematic compounds must be captured to avoid contamination or side reactions.

It is not clear to us how many substance classes other than tetraaryladamantane octaethers show attractive features as crystalline coats for reagents. The ability to encapsulate such a broad range of small molecules in crystals was found serendipitously. Structurally, the EnOC-forming tetraaryladamantanes are made up of aliphatic and aromatic rings and eight ether functionalities. Neither of these structural elements is unusual in the context of crystal engineering.[15] So, to predict new EnOCs, there is a need for a better molecular understanding of their properties, and a quantitative description of the kinetic and thermodynamic processes that govern their crystallization. Even without such deeper theoretical insights, TDA and TEO can be tested as coats for other problematic reagents, so that safe formulations are found, with little remaining vapour pressure of the reagent and the option to perform synthetic transformations without a fume hood. The use of EnOCs thus complements Buchwald's method for glovebox-free syntheses involving single-use capsules.[16]

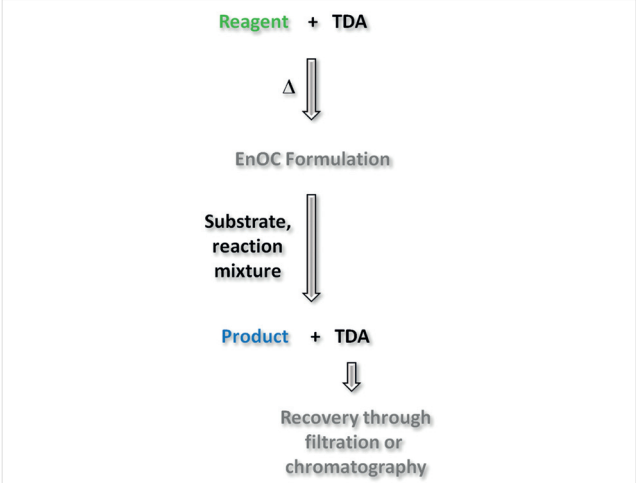

Figure 3 Flow-chart for a synthetic procedure involving encapsulation of a reagent in TDA

In summary, while zeolites, MOFs, COFs, organic cages, and organic materials assembling via hydrogen bonds or with compromised packing are well-established matrices for uptake and release of gases, EnOCs appear to be particularly well suited for liquids. They are distinct from the porous matrices in that they form cavities without covalent bonds or hydrogen bonds between host molecules, and despite the accessibility of tightly-packed, solvate-free crystal forms. Not one specific cavity is formed when EnOCs assemble, as with Dianin's compound, but many different structural arrangements lead to encapsulation, many of them with high crystalline order. This opens up a broad structure space of potential guest molecules, making EnOCs attractive for the formulation of labile compounds. Experiments aimed at formulating even more reactive reagents than those studied thus far[12–14] are currently under way in our laboratories.

Independent of what the final breadth of the method will be, EnOCs are interesting for practical applications and academic exploration alike. Their capability to take up and

release small molecules as if they were 'breathing', sometimes without macroscopic loss of crystallinity, provides a fascination to us as strong as if they were involved in processes of life.

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