Host–Guest Systems

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Gas Hosting in Enantiopure Self-Assembled Oximes**

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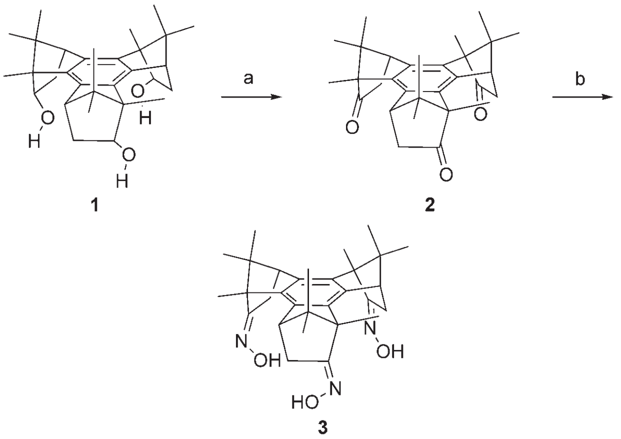
Dedicated to Professor Leo A. Paquette

Molecular self-assembled capsules are supramolecular objects held together by means of metal–ligand interactions[1] or weak intermolecular forces such as hydrogen bonding[2] or ion pairing.[3] In recent years, these nanosized containers have gained increasing interest because of the unique properties experienced by the bound guest within the cavity, and molecular encapsulation is emerging as a particularly useful tool to investigate weak intermolecular forces.[4] The trapped guest, in fact, is physically isolated from the bulk solution and its behavior in terms of conformation,[5] stability,[6] and reactivity[7] is atypical.

Metal–ligand-bonded molecular capsules can reach the size of a few nanometers,[1] and thus hydrogen-bonded capsules are generally smaller,[8] with the pioneering "tennis ball" reported by Rebek and co-workers a few years ago being the smallest.[9] As a general rule, complementarity between the cavities of the host and the volume of the guest, as well as their reciprocal shapes, are key prerequisites for encapsulation to be clearly observed. Analogously, a second important issue is the presence of a sufficient activation energy barrier for the in–out exchange of the guest through complete or partial dissociation of the self-assembled host.[10]

Among the suitable guests, gases are emerging as targets for host–guest chemistry, as well as for storage and catalysis, aspects of which have been outlined elsewere.[11] Herein we report the behavior of a recently synthesized C_3-symmetric enantiopure cyclotrimer bearing three oxime moieties which dimerizes in solution to form a reversible molecular capsule that entraps gaseous guests within the cavity.

The trioxime scaffold **3** was readily prepared in two steps from the previously reported (+)-*syn*-benzotriborneol (**1**),[12] with the first step being an oxidization following the standard Swern protocol.[13] Scaffold **2** was then condensed with hydroxylamine according to a well-known procedure,[14] which led to the formation of the expected *syn*-benzotri(camphor oxime) (**3**, Scheme 1). The *E* configuration of the oximes in the solid state was established by X-ray crystallography;[15] NOE correlations between C=N−O−H moieties and the rest of the scaffold were ambiguous.



Scheme 1. Synthesis of trioxime **3**. Reagents and conditions: a) DMSO, oxalyl chloride, Et_3N, CH_2Cl_2, −78 °C to RT (75 %); b) $HONH_2 \cdot HCl$, NaOH, H_2O/EtOH (conversion 65 %, 98 % yield).

Trioxime **3** displays proton resonances which are noticeably broad in $CDCl_3$ and C_6D_6, in particular for the methyne, methylene, and bridgehead methyl groups (Figure 1 a). Similar behavior is observed in the ^{13}C spectrum for the aromatic and methylenic carbon atoms (Figure 1 c). Bubbling inert gas (nitrogen or argon) into the NMR tube containing the solution of **3** causes a sharpening of the signals in the ^1H and ^{13}C spectra (Figure 1 b,d). The broadening effect is again observed when oxygen or air is bubbled into the same solution, thus showing that complete reversibility is exhibited. This behavior is not observed in solutions of triol **1** or triketone **2** in $CDCl_3$, or in solutions of camphor oxime,[16] which is formally one third of the cyclotrimer **3**.

This effect can be ascribed to the paramagnetic nature of triplet oxygen, which affects the relaxation of nuclei positioned in proximity, and thus acts as a probe for determining

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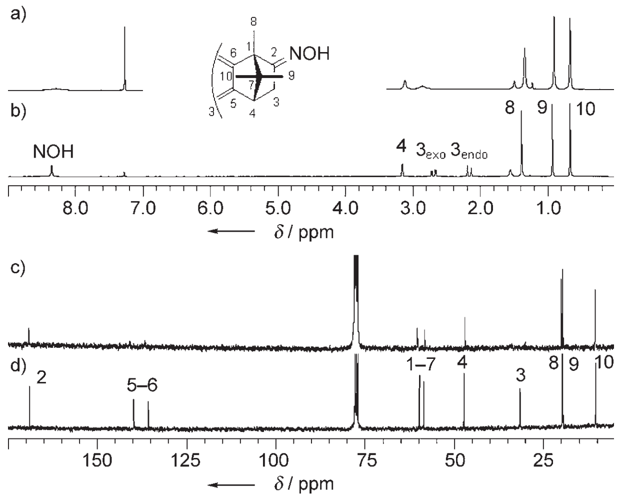

Figure 1. Effect of solvated gas on the ^{1}H and ^{13}C NMR spectra (300 and 75 MHz, respectively, RT) of trioxime **3**. a) and c) ^{1}H and ^{13}C NMR spectra, respectively, of a solution of **3** in $CDCl_3$ saturated with oxygen, b) and d) ^{1}H and ^{13}C NMR spectra, respectively, of the same sample after bubbling nitrogen into it.

the position of the gas molecule with respect to the host structure. In detail, the broadening of the methyne, methylene, and bridgehead methyl protonic signals and the two nearly unaffected apical methyl signals suggest that the oxygen molecule resides in the concave portion of the host molecule. Portionwise addition of [D$_6$]DMSO to a solution of **3** in $CDCl_3$ saturated with oxygen results in a simultaneous downfield shift of the proton resonances of the oxime moieties and a sharpening of the signals. These observations indicate that the event of encapsulation is related to the formation of hydrogen bonds between the oxime moieties (see the Supporting Information).

Bubbling methane into a solution of **3** in $CDCl_3$ saturated with O_2 once again causes sharpening of the signals in the NMR spectra of the cyclotrimer, while methane appears as a broad resonance at $\delta = 0.13$ ppm. These observations are indicative of the replacement of the oxygen molecule by methane and of an ongoing dynamic process, as confirmed by lower temperature experiments (see the Supporting Information). The rate of the dynamic process at 223 K is lowered to such an extent that two sharp singlets resonanting at $\delta = 0.21$ and -2.64 ppm are observed (Figure 2), which correspond respectively to methane dissolved in the solvent and encapsulated in **3**. The 4:6 ratio between the integrals of the upfield signal and the methyne proton of the cyclotrimer confirms the formation of a 2:1 host–guest adduct. The remarkable $\Delta\delta$ value (2.85 ppm) between the encapsulated and free methane is caused by the strong shielding effect exerted by the aromatic rings of the two host molecules, which sandwich the methane molecule.

Encapsulation of methane was unambiguously demonstrated by a ROESY experiment performed at 223 K, which clearly displays correlations between the methane signals resonating at higher fields with the signals of the methyne, methylene, and oxime moieties. Furthermore, integration of the exchange cross-peak between the two methane species

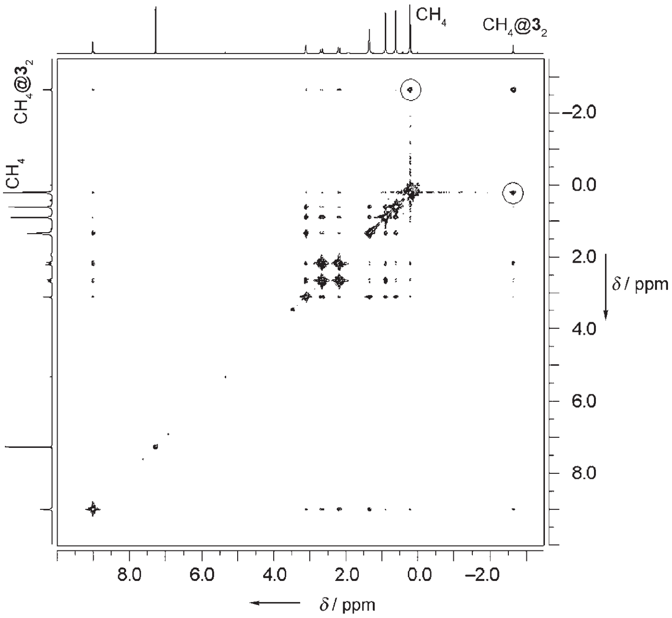

Figure 2. ROESY spectrum (300 MHz) of **3** in methane-saturated $CDCl_3$ at 223 K.

allows the value of the activation energy for the in–out switch equilibrium to be calculated as 13.2 kcal mol^{-1} at 218 K by using the Eyring equation.[17]

The oxime residue is characterized by both a hydrogen-bond donor and an acceptor, similar to a carboxylic acid group—which is a well-studied functional group in the construction of host systems. Indeed, to the best of our knowledge, while the ability of oximes to self-assemble in the solid state was described recently,[18] no examples of a supramolecular assembly based on an oxime have been reported so far. The seam of six hydrogen bonds, which are responsible for the dimerization of the host and formation of a chiral enantiopure capsule, is depicted in Figure 3.

Monoatomic, diatomic, and triatomic gases, auch as Ar, CO, and CO_2, respectively, were bubbled into a solution of **3** in $CDCl_3$. In the latter case, precipitation of **3** occurred, while

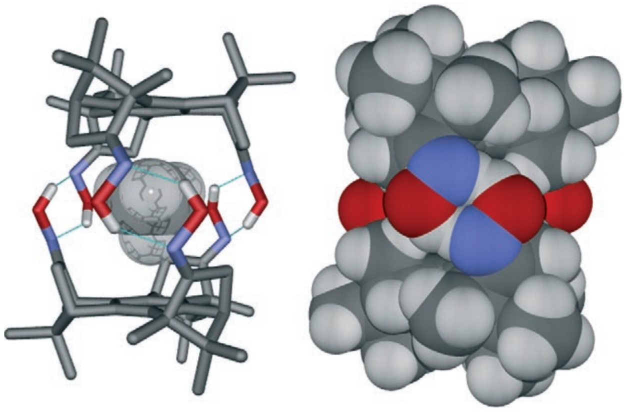

Figure 3. Proposed molecular structure of the self-assembled host 3_2 with encapsulated methane (left: a mixed sticks/CPK representation, with hydrogen bonds highlighted; right: a full CPK representation, including all the hydrogen atoms).

in the other cases sharpening of the original NMR spectrum was observed as a result of replacement of the O_2-filled capsule with the incoming gaseous guest.

The volume of the cavity in the capsule, calculated from molecular modeling studies, is about 46 Å^3 and it allows the accommodation of guests with a maximum volume of about 55 % of the available space.[19] Large molecules that cannot be accommodated within the cavity leave the NMR spectrum of O_2@$\mathbf{3}_2$ unchanged. In fact, addition of cyclohexane to a solution of **3** saturated with oxygen did not show any changes in the position or a sharpening of the peaks in the ^{1}H NMR spectrum.

To compare the binding affinity with the different gases we studied the effect of temperature on the chemical shift of the OH protons. Temperature-dependent chemical shifts are suitable tools for the investigation of the relative stability and complementarity of hydrogen-bonded networks.[20] Table 1 lists the values for the different guests, as well as the molecular volumes of the gases and the packing coefficients of the guests within $\mathbf{3}_2$.

Table 1: Temperature and packing coefficients for different gases@$\mathbf{3}_2$ in $CDCl_3$.

Gas	$\Delta\delta/AT\times10^2$ [ppm K^{-1}]	Mol. volume[a] [Å^3]	Packing coefficient[b]
Ar	−2.01	28	0.61
CH_4	−2.06	26	0.57
O_2	−1.90	21	0.46
N_2	−1.97	18	0.39
CO	−1.79	18	0.39

[a] Molecular volume were calculated with the program MacSpartan.[22] [b] Packing coefficients were calculated by following a procedure reported in the literature.[18] The volume of the cavity (46 Å^3) was calculated with the program DeepView/Swiss PdbViewer 3.7 by using a 1-Å molecular probe on the dimeric structure $\mathbf{3}_2$ minimized with the program MacSpartan.[22]

As observed, both very small guests such as monoatomic Ar, as well as large guests such as methane, lead to weaker hydrogen-bonded networks between the oxime residues, as observed by the higher values of the corresponding temperature coefficients. In contrast, diatomic guests such as N_2, O_2, and CO are hosted more readily by $\mathbf{3}_2$. It is worth noting that the values of the packing coefficients observed for the best gaseous guest are in the range 0.40–0.55, which is generally lower than that commonly observed for liquid guests[18] and in agreement with former examples with gaseous guests.[21]

The strength of the oxime hydrogen bonds and the distance between the N-OH moieties of the two subunits of the capsule are not sufficient to observe slow exchange of the guest on the NMR timescale at room temperature. Gas solubility data[23] and dilution experiments performed on N_2@$\mathbf{3}_2$ at 298 K allowed the determination of the association constant for the self-assembled host capsule N_2@$\mathbf{3}_2$ to be approximately $1\times10^4\,\text{M}^{-2}$.

While gas binding in monomolecular hosts is a field of supramolecular chemistry that boasts several examples,[11,24,25] soluble nonmetal-containing self-assembled hosts with the ability to reversibly bind gaseous guests, in particular atmospheric ones, are rare.[26] Herein we have described the peculiar properties of a chiral cyclotrimeric structure **3**, which spontaneously binds atmospheric gases with the generation of a chiral enantiopure self-assembled dimeric capsule. The small volume of the cavity, compared with that of the $CDCl_3$ employed as solvent in these studies, as well as those of many other dimeric hosts,[27] is one of the driving forces that promotes the binding, which at room temperature is a fast phenomenon on the NMR timescale, but is slow and complete at lower temperature.

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