Self-Assembly

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Encapsulated Carboxylic Acid Dimers with Compressed Hydrogen Bonds**

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Reversible encapsulation allows the temporary isolation and characterization of molecules in very small spaces. Self-assembled molecular capsules are generated through the formation of covalent bonds,[1] or are reversibly held together by hydrogen bonds,[2–8] metal/ligand interactions,[9,10] or hydrophobic effects.[11] Guests typically enjoy molar concentrations in capsules. When more than one guest is accommodated there is a high probability of the guests interacting, thereby generating molecular arrangements that represent a second order of supramolecular chemistry[12]—complexes within complexes—or reacting,[9b] even along pathways that are unlikely in solution.[9c] Interacting guests cannot exchange partners rapidly inside capsules (as they do in bulk solution) and they are separated from solvent molecules by mechanical barriers. Instead, the capsule is the solvent, fixed in place around the solute. Here we report a study on hydrogen-bonded carboxylic acid dimers as guests within an expanded capsule assembly. It reveals evidence of compression of the guests in the isolated environment of the host.

When cavitand **1** and glycoluril **2** (Figure 1) are dissolved in deuterated mesitylene and suitable guests are present, the racemic capsule **1·2$_4$·1** is formed. The assembly takes place on mixing, and the system reaches equilibrium in seconds at typical (mM) concentrations suitable for NMR spectroscopic analysis. The structure of the assembly, its use as a spring-loaded device,[13] its behavior toward gaseous guests,[14] and the interconversion of enantiomers[15] of coiled alkanes all point to a subtle interplay between intermolecular forces and pressure effects inside the capsules loaded with the guests. A series of guests of different sizes were encapsulated so as to examine the other side of this uneasy equilibrium—namely, the effects of the host on the guests.

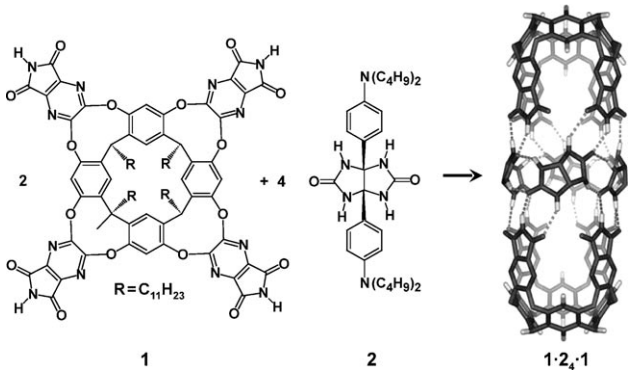

Figure 1. Chemical structures of the cavitand **1** and glycoluril **2** components, and the calculated structure of the chiral, extended capsule **1·2$_4$·1** (without the peripheral groups).

Figure 2a shows the relevant low-field regions of the ^{1}H NMR spectra of a series of partially deuterated carboxylic acids inside **1·2$_4$·1.** These guests exist as hydrogen-bonded dimers. A monotonic downfield drift of the OH signal marked "HH" (the "HD" signal will be explained shortly) is seen with increasing "effective" length of the acid—from $\delta = 14.59$ ppm

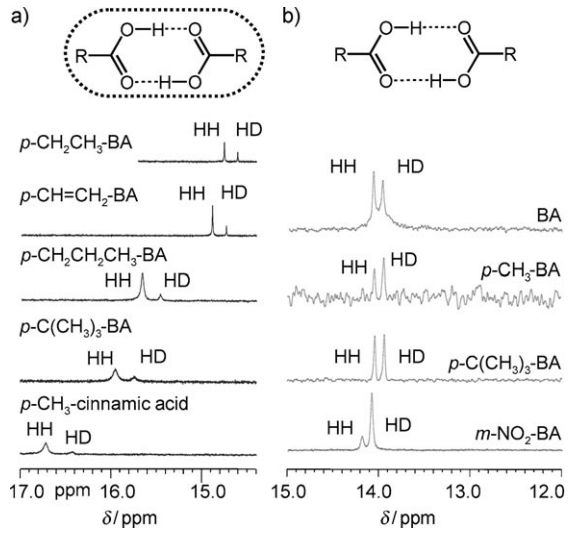

Figure 2. Partial ^{1}H NMR spectra of a) **1·2$_4$·1** with encapsulated acid dimers, partially deuterated at the OH site (600 MHz, [D$_{12}$]mesitylene 298 K) and b) sterically nonhindered, partially deuterated acid dimers (500 MHz, CDF_3/CDF_2Cl, ca. 120 K). BA: benzoic acid.

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for *p*-toluic acid to $\delta = 15.98$ ppm for *p-tert*-butylbenzoic acid. The dimer of *p*-methylcinnamic acid shows the greatest downfield shift at $\delta = 16.72$ ppm. The length of this acid is at a maximum in **1·2$_4$·1**, and it tends to be co-encapsulated with smaller guests. We use the words "effective length" since the *p*-ethyl-, *p*-isopropyl-, and *p-tert*-butylbenzoic acid guests all have the same length outside the capsule, but inside the capsule they show different positions—and apparent lengths—because of the capsule's tapered ends. The downfield shifts of the OH signals would be expected if the O···O distance decreases and the hydrogen bond gets shorter.[16] Alternatively, the downfield shifts may be due to the anisotropic effects of the capsule's walls on the acid guests.

Table 1: Geometric parameters of the OHO hydrogen bond and ^{1}H chemical shifts of carboxylic acid dimers in the liquid and in a capsule of form **1·2$_4$·1** in [D$_{12}$]mesitylene.

Compound[a]	Environment	T [K]	δ_{HH}	$\Delta\delta$[b]	r_{OH} [Å]	$r_{H\cdots O}$ [Å]	q_1 [Å][c]	q_2 [Å][c]
p-CH$_3$-BA	capsule	298	14.59	–	1.006	1.586	0.290	2.592
p-CH$_2$CH$_3$-BA	capsule	298	14.78	−0.14	1.009	1.579	0.285	2.587
p-CH=CH$_2$-BA	capsule	298	14.91	−0.16	1.010	1.570	0.280	2.580
p-CH(CH$_3$)$_2$ -BA	capsule	298	15.48	–	1.020	1.540	0.260	2.560
p-CH$_2$CH$_2$CH$_3$-BA	capsule	298	15.69	−0.20	1.021	1.529	0.254	2.550
p-C(CH$_3$)$_3$-BA	capsule	298	15.98	−0.21	1.025	1.515	0.245	2.540
p-CH$_3$-cinnamic acid	capsule	298	16.72	−0.29	1.038	1.478	0.220	2.515
acetic acid	CDF$_3$/CDF$_2$Cl	110	13.127	−0.088	0.983	1.684	0.351	2.668
chloroacetic acid	CDF$_3$/CDF$_2$Cl	110	13.250	−0.085	0.984	1.678	0.347	2.662
p-C(CH$_3$)$_3$-BA	CDF$_3$/CDF$_2$Cl	120	14.045	−0.104	0.992	1.636	0.322	2.629
p-CH$_3$-BA	CDF$_3$/CDF$_2$Cl	120	14.048	−0.104	0.992	1.636	0.322	2.629
BA	CDF$_3$/CDF$_2$Cl	130	14.071	−0.101	0.992	1.635	0.321	2.627
m-NO$_2$-BA	CDF$_3$/CDF$_2$Cl	115	14.190	−0.108	0.994	1.628	0.317	2.622

[a] BA: benzoic acid. [b] $\Delta\delta = \delta_{HD} - \delta_{HH}$ in ppm. [c] Distances estimated according to Ref. [24] by using Equation (2).

Nucleus-independent chemical shift calculations (NICS), following the protocol of Schleyer et al.,[17] show that the resorcinarenes at the ends of the capsule cause upfield shifts, and the glycolurils near the center of the assembly modest downfield shifts for nearby guest nuclei.[18] Here, we used partial deuteration to separate the contributions of hydrogen-bond contraction from those of cavity walls on the ^{1}H NMR chemical shifts. The confinement of the carboxylic acid dimers in the capsules leads to slow hydrogen-bond and proton exchange: the spectra measured at partial deuteration consist of two signals, one for the HH dimer and the second for the HD dimer. The difference, defined as $\Delta\delta = \delta_{HD} - \delta_{HH}$, serves as a sensitive probe for hydrogen-bond geometries.[19–22] The effects of the cavity walls on the chemical shift of the encapsulated acids are the same for the HH and HD isotopologues: the $\Delta\delta$ value, being a differential quantity, reflects primarily the geometric cooperativity of the two hydrogen bonds.

Usually, low temperatures down to 100 K are required to suppress hydrogen-bond and proton exchange between HH and HD dimers so as to measure $\Delta\delta$ values.[21] However, this regime is realized at room temperature for the encapsulated complexes. In this study we measured, therefore, the ^{1}H NMR spectra of various partially deuterated carboxylic acids both at low temperatures dissolved in CDF$_3$/CDF$_2$Cl as well as at room temperature in capsules dissolved in [D$_{12}$]mesitylene. The low-field regions are illustrated in Figure 2b; the values of $\Delta\delta$ and δ_{HH} are collated in Table 1 together with those measured previously for acetic and chloroacetic acids.[21]

Figure 3 shows that $\Delta\delta$ and δ_{HH} are correlated with each other. Open circles refer to encapsulated dimers at room temperature and filled circles to non-encapsulated dimers at low temperatures. $\Delta\delta = 0$ for the isolated monomer resonating around $\delta = 6$ ppm.[24] Studies on related systems indicated also that $\Delta\delta$ vanishes in the case of the strongest hydrogen bonds resonating around $\delta = 21$ ppm.[19,23] This finding implies a maximum of $|\Delta\delta|$ around $\delta = 18$ ppm, as illustrated by the dashed curve. As all the data points are located on this curve it follows that magnetic anisotropy contributions from the walls can be neglected, as these could influence δ_{HH} but not $\Delta\delta$.

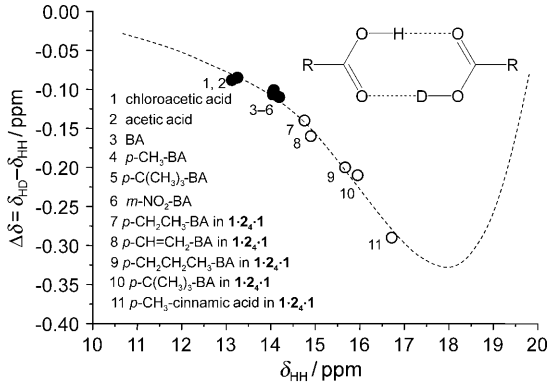

Figure 3. ^{1}H NMR H/D isotope effects, $\Delta\delta = \delta_{HD} - \delta_{HH}$, for the encapsulated *p*-toluic acid ([D$_{12}$]mesitylene, open circles) and non-encapsulated (CDF$_3$/CDF$_2$Cl; filled circles) dimers of carboxylic acids as a function of the bridging proton chemical shift δ_{HH} (Table 1). The dashed curve was obtained by optical fitting of the data. BA: benzoic acid.

We use recently established OHO hydrogen-bond correlations to establish the link between NMR parameters of the encapsulated carboxylic acid dimers and hydrogen-bond geometries.[21,24] These correlations allow us to compare the effects of encapsulation with the effect of external pressure on the hydrogen-bond geometries of carboxylic acid dimers in the solid state. Solid-state NMR spectroscopy, X-ray diffraction, and neutron scattering data gave fairly good correlations for the ^{1}H NMR chemical shifts, O···O distances, and hydrogen positions.[21,24–29] It was found that the two hydrogen-bond distances r_1 and r_2 [Eq. (1)] or their combination (in Å)

$$q_1 = {}^1/_2(r_1 - r_2) \text{ and } q_2 = r_1 + r_2 \quad (1)$$

depend on each other.[30]

For a linear OHO hydrogen bond, q_1 represents the distance of the hydrogen atom from the center of the hydrogen bond and q_2 the O···O distance. (A general correlation of the OHO hydrogen bond is depicted in the Supporting Information.) During proton transfer the hydrogen bond is first compressed but then stretched again once the proton has passed the hydrogen-bond center at $q_1 = 0$. Simultaneously, q_2 is decreased, passes through a minimum at $q_1 = 0$ and increases again. During this process the chemical shift (in ppm) of the bridging proton increases, goes through a maximum, and decreases again, as expressed by Equation (2).[24]

$$\delta_H = 6 + 15.3 \exp(-6.2\, q_1^2) \qquad (2)$$

By using Equation (2), values of q_1 were estimated from the experimental ^{1}H chemical shifts of the encapsulated carboxylic acid dimers, and the corresponding values of q_2 calculated using the q_1 versus q_2 correlation curve published previously.[24] The resulting distances are included in Table 1 and represent averages over different local environments. Assuming linear OHO hydrogen bonds, Table 1 indicates that the O···O distances decrease by about 0.08 Å, and that the bridging proton is shifted about 0.07 Å towards the hydrogen bond center when the effective length of the dimers is increased. These compression effects are of a similar order as those observed by neutron diffraction studies[33] on solid [D_5]benzoic acid when the external pressure p was increased. The values of q_2 change in a linear way with p, as illustrated in Figure 4a. By extrapolation, this graph provides an estimate that the pressure needed to compress benzoic acid dimers in the solid state to the same extent as the combined action of *para* substitution and encapsulation is between 4 and 10 kbar.

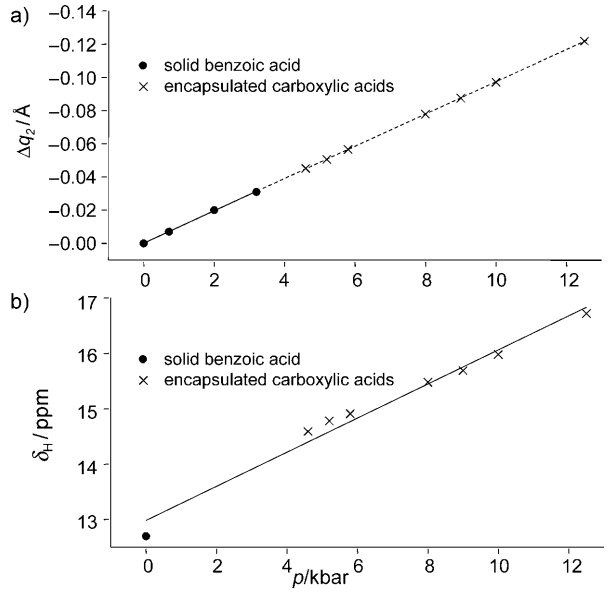

Figure 4. a) Decrease of the O···O distance $\Delta q_2 = q_2(p) - q_2(0)$ of carboxylic acids dimers with increasing external pressure p. The data for solid benzoic acid are taken from Refs. [31–33]. The data for encapsulated carboxylic acids were estimated as described in the text. b) ^{1}H chemical shifts of carboxylic acids dimers as a function of external pressure. The data for solid benzoic acid were taken from Ref. [25].

As a cross-check, we have plotted in Figure 4b the experimental ^{1}H chemical shifts as a function of the estimated pressure, and observe a good agreement between the correlation line and the value found for solid benzoic acid[25] at $p = 0$.

Thus, at first sight, the encapsulated carboxylic acid dimers behave as if they experience an external pressure from the inner walls of the capsule when it is closed. While the extrapolated pressures seem to be large, that is, 4–10 kbars, the trend is in agreement with the amplification of interactive forces, particularly equilibrium isotope effects,[34] seen during the temporary isolation of species in capsules.

One could argue that the observed effects arise from changes in the pK_a values of the carboxylic acids inside the capsules, as matrix effects can change acid–base properties.[35] However, pK_a values refer to the negative decadic equilibrium constants of a protonation/deprotonation reaction in water. Such acid–base reactions as well as water are absent in the capsules and we, therefore, do not consider such an explanation to be at the origin of the effects observed. However, double proton transfer[33] within all the dimers studied is still fast on the NMR timescale.

The pressure effects inside the capsules can, however, be rationalized in analogy to the cases of the ideal and real gases (Figure 5a). For a given temperature and an external pressure

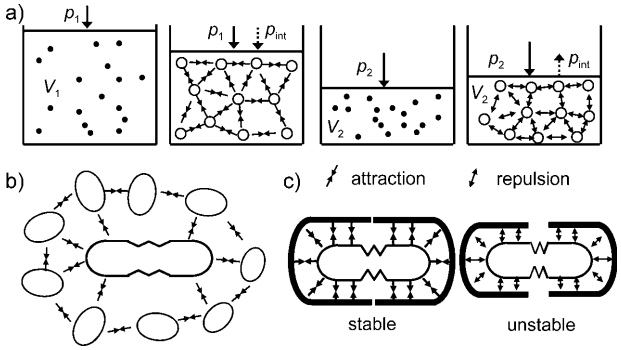

Figure 5. External and internal pressure effects of a) ideal and real gases, b) solutes in solution, and c) encapsulated solutes. The arrows indicate forces arising from cohesion. For further explanation see the text.

p_1, the molar volume V_1 of the real gas is smaller than of the ideal gas. This reduction is described by the van der Waals Equation in terms of an additional "internal" or "cohesion" pressure $p_{int} \approx a/V^2$.[36–38] This arises from the one-sided attraction forces between molecules of the surface and those inside, whereas the forces between molecules inside the capsule cancel.

By contrast, when the external pressure p_2 is very large the eigenvolume of the real gas molecules leads to repulsion between the molecules and hence to a larger molar volume compared to that of the ideal gas. In a similar way, a solute also experiences an internal cohesion pressure because of the attractive forces with and between the solvent molecules (Figure 5b). Optimization of the solute–solvent interactions can then lead to a compression of the solute. For example, the

O···O distance of acetic acid dimers in the gas phase is 2.68 Å, whereas it is reduced in solution to a value of about 2.63 Å.[21] This reduction is of the same order as that observed for benzoic acid dimers on applying a pressure of several kilobars to the bulk solid (Figure 4a). However, the entropy-driven disorder of the solvent molecules does not allow for perfect solvation at room temperature.

Let us now consider a guest inside a capsule. If the guest fits well inside, attractive van der Waals interactions between the guest and the internal walls are operative. As a result, the inner walls exert an internal pressure on the guest. The attractive interactions may be maximized by compression of the guest, even if some energy is needed for this purpose (Figure 5c). On the other hand, when the guest or the energy needed to compress the guest is too large, the intermolecular forces between the solute and the internal walls become repulsive. In this case, the encapsulated solute exerts a pressure on the walls and will leave the capsule.

In conclusion, reversible encapsulation is a unique tool for physical organic chemistry which operates at equilibrium under ambient conditions and in solution; it reveals molecular behavior that has been accessible only under extreme conditions.

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