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Encapsulation of Ion Pairs in Extended, Self-Assembled Structures

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Supporting Information

ABSTRACT: Encapsulation of ion pairs in small spaces that are isolated from the medium is expected to result in amplified interactions between the ions. Yet, sequestration of ion pairs in self-assembled capsules is complicated by competition of the acids and bases for binding directly to the assembly components. We describe here a hydrogen-bonded capsule $\mathbf{1.2_8.1}$ that accommodates two γ-picolines and two acids as ion pairs. The supramolecular structure of the discrete 14-component assembly is characterized by NMR spectroscopy. The structure reveals the acids in the tapered ends of the capsule and γ-picoliniums near the glycoluril spacers in the capsule's center. Similar acid−base ion pairs are also obtained with 4-ethylpyridine, γ-picoline with difluoroacetic acid, and γ-picoline with trifluoromethanesulfonic acid. The ^{1}H NMR spectrum of the γ-picoline/trifluoroacetic acid ion pair shows a signal at δ = 18.7 ppm, indicating the acidic proton is in contact with both the picoline nitrogen and the trifluoroacetate oxygen. Further details about the unusual structures of ion pairs in small spaces are reported.

Proton transfers between acids and bases are fundamental processes of chemistry. In solutions of high polarity, proton transfers are favored, leading to charged species; solvents of low polarity give complexes with varying degrees of proton transfer. For example, mixtures of trifluoroacetic acid (TFA) and pyridine derivatives in organic solvents give rise to several species.[1] The dominant components are a H-bonded pair in equilibrium with a charged molecular complex; the state of this equilibrium varies with the proton-acceptor properties of the pyridines and the solvents. In the solid state, TFA and γ-picoline form a H-bonded charged complex.[2] Because molecules confined in small spaces often show behavior quite different from that of molecules in solution, we examined the TFA/picoline system in an encapsulation complex. The isolated complexes give an unusually clear picture of the structure, and we report here details about the isolated acid−base interaction.[3]

Earlier, we described the encapsulation of γ-picoline in the cylindrical dimer **1.1** with mesitylene-d_{12} as solvent (Figure 1).[4] Two picolines were taken up as a single isomeric arrangement: the methyl groups were deep in the cavitand ends, and the N atoms were near the polar seam of hydrogen bonds of the capsule's middle. We added TFA to the encapsulated picolines and an excess of the glycoluril **2** to extend the assembly,[5] if necessary. Indeed, an extended capsule emerged through the action of TFA on the picolines. The ^{1}H NMR spectrum of the new assembly (Figure 2a) shows high symmetry and a far

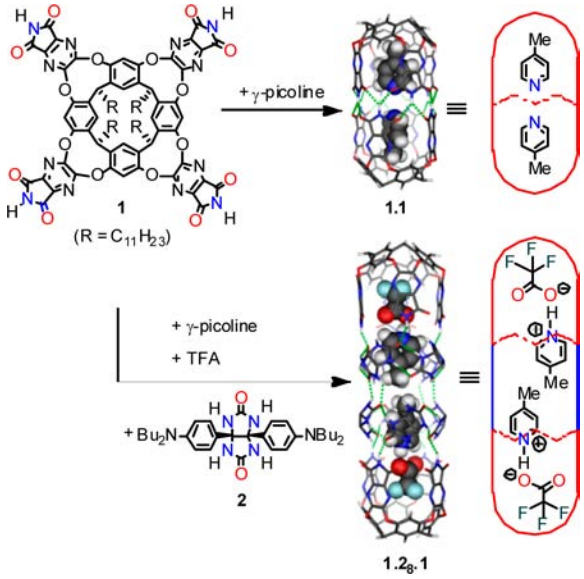

Figure 1. Chemical structures of cavitand **1** and glycoluril **2**, encapsulation complexes, and cartoons. The complexes were energy-minimized using semiempirical methods. Two γ-picoline molecules are accommodated in **1.1**, while two γ-picoline and TFA molecules occupy the complex of $\mathbf{1.2_8.1}$. Peripheral alkyl and aryl groups are omitted for clarity.

downfield signal (18.7 ppm) for the acidic proton. This region is the domain of strong hydrogen bonds, and, evidently, the acidic proton is in contact with both the picoline nitrogen and the trifluoroacetate oxygen. In fact, the proton is transferred to the nitrogen as its resonance shows coupling with the α C−H proton of picoline and shows the appropriate cross-peak in the COSY spectrum. The stoichiometry corresponds to two of each component (cavitand, picoline, and TFA) and eight glycolurils. No methyl signals appear in the upfield region (<0 ppm) as would be expected for methyl groups in the ends of the cavitand. Instead, a *downfield* shift of the CH_3 occurs (~3.8 ppm). Accordingly, the orientation of the picolines is reversed: their methyls are near the glycolurils in the assembly's center.[6] The ^{19}F NMR spectrum, on the other hand, shows a signal at −83.5 ppm, shifted *upfield* by ~6 ppm with respect to the free acid. This value, based on NICS calculations[7a] and experimental precedents,[7b] places the CF_3 groups *in the deepest ends of the cavitands*. The chemical shifts of the container assembly are likewise affected: the signals for the H-bonded N−H's of the

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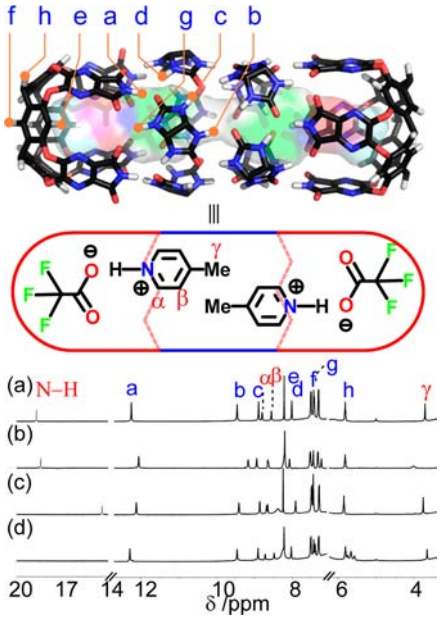

Figure 2. ^{1}H NMR spectra of **1.2$_8$.1** in the presence of (a) TFA and γ-picoline, (b) TFA and 4-ethylpyridine, (c) trifluoromethanesulfonic acid and γ-picoline, and (d) difluoroacetic acid and γ-picoline.

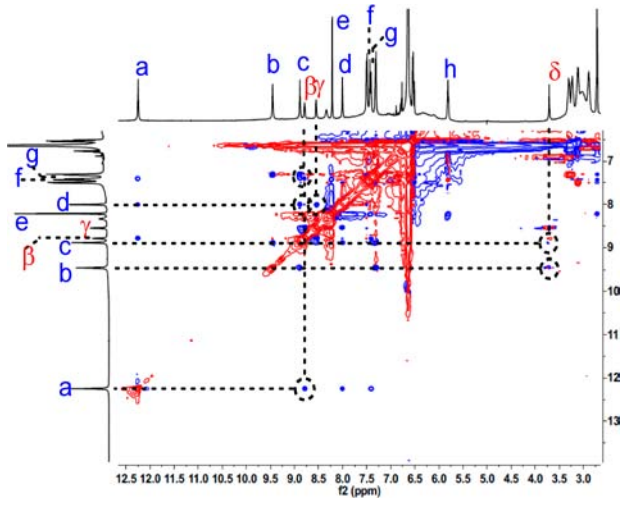

Figure 3. 2D ROESY NMR spectrum of **1.2$_8$.1** with TFA and γ-picoline (600 MHz, mesitylene-d_{12}).

imides and glycolurils are shifted *upfield* with respect to those of capsules enclosing hydrocarbons (see Supporting Information), indicating a looser network of hydrogen bonds. Under these conditions, nearly identical spectra were obtained for encapsulation of 4-ethylpyridine (Figure 2b) and for γ-picoline with CF_3SO_3H, although the acidic proton in this case was not shifted as far downfield (Figure 2c).

Additional support for the structural assignments of complexes came from diffusion ordered spectroscopy (DOSY) and rotating frame Overhauser effect spectroscopy (ROESY) experiments. In the ^{1}H DOSY NMR spectrum, the same diffusion constant was seen for the glycoluril and cavitand units of the host and for the guest γ-picoline, indicating all signals are of the same assembly. The ^{19}F DOSY experiment shows decreased diffusion coefficients for the free TFA (D = 1.54×10^{-9} m^2 s^{-1}) and guest TFA ($D = 3.25 \times 10^{-10}$ m^2 s^{-1}), as expected for the relative sizes of the molecular species. The latter value is in accord with that obtained for the assembly's imide proton at δ = 12.3 ppm ($D = 3.76 \times 10^{-10}$ m^2 s^{-1}) and clearly indicates these components are part of the same assembly. The 2D ROESY spectrum exhibits cross-peaks of γ-picoline and the container framework and indicates that the γ-picolines are located near the glycolurils (Figure 3).

The chemical shifts of the acidic protons are remarkable, inasmuch as they are positioned in a region of the capsule where nuclei are *upfield* shifted by the magnetic anisotropy of the aromatic panels. These chemical shifts approach those of strong, short hydrogen bonds between, for example, aspartates and histidines at the active sites of serine proteases.[8] The nature of the acid in contact with picoline gives rise to subtle structural details in the capsule. With TFA as the acid, a coplanar arrangement of the picoline and carboxylate allows a second hydrogen bond between the "spectator" oxygen and the α C–H hydrogen of the heterocycle. Since the cavity of the self-assembled capsule is preorganized, replacing γ-picoline with 4-ethylpyridine was expected to result in even more compressed H-bonded ion pairs. However, the signal of the acidic proton appeared at 18.4 ppm, a 0.3 ppm upfield shift. The additional methylenes in the new assembly force the acidic hydrogens deeper into the aromatic cavity, where they are more exposed to shielding caused by the anisotropy of the aromatics. The calculated value for this shielding is 1.5–2 ppm. With CF_3SO_3H, proton transfer also takes place, and a strong hydrogen bond is indicated by the chemical shift, but neither of the spectator oxygens can access the plane of the heterocycle to form the second (C–H) hydrogen bond. The complex of γ-picoline with the less acidic difluoroacetic acid (DFA) is different; the NMR signals reveal merely a H-bonded pair without coupling to the heterocycle's α C–H. The downfield signal for the acidic proton disappears, another indication of the salt-bridged character of the hydrogen bond between DFA and γ-picoline. The chiral nature of this assembly is revealed in the ^{19}F NMR spectra: diastereotopic F signals are observed. The chirality arises from the twisted arrangement of the spacer elements **2** in the middle of the capsule with respect to the long axis of the assembly. The capsular assembly racemizes on heating, and coalescence of the diastereotopic ^{19}F signals occurs at 340 K. The racemization likely involves concerted rotation of the spacers in a process that makes new hydrogen bonds as the old ones are broken.[9]

Titration of the DFA assembly **A** with TFA is shown in Figure 4. TFA completely replaces DFA to form more the stable complex **B** with the H-bonded ion pair. The equilibrium constant for the formation of **B** (K = [**B**][DFA]^2/[**A**][TFA]^2 = 1850) was determined by comparison of ^{19}F NMR peak area ratios. The ^{19}F spectra were recorded at various temperatures (299, 325, 340, and 355 K). A van't Hoff plot gave straight lines (R^2 = 0.99), which provided thermodynamic parameters: ΔH = 1.8 kcal mol^{-1}, ΔS = 2.5 cal K^{-1} mol^{-1}, and ΔG = −4.5 kcal mol^{-1}. This result indicates the favorable formation of **B** is under entropy control. A competition experiment of **B** with *n*-$C_{22}H_{46}$ was also staged. Although this alkane is an ideal guest for **1.2$_8$.1** with respect to its shape and size, addition of excess *n*-$C_{22}H_{46}$ (14 mM) to the solution of **B** (2.3 mM) led to only partial loss (10%) of **B** and corresponding encapsulation of the alkane in **1.2$_8$.1**.

What causes these arrangements inside the capsule? First, the formation of an ion pair between the weak base and strong acid is disfavored in the deuterated mesitylene solvent but takes

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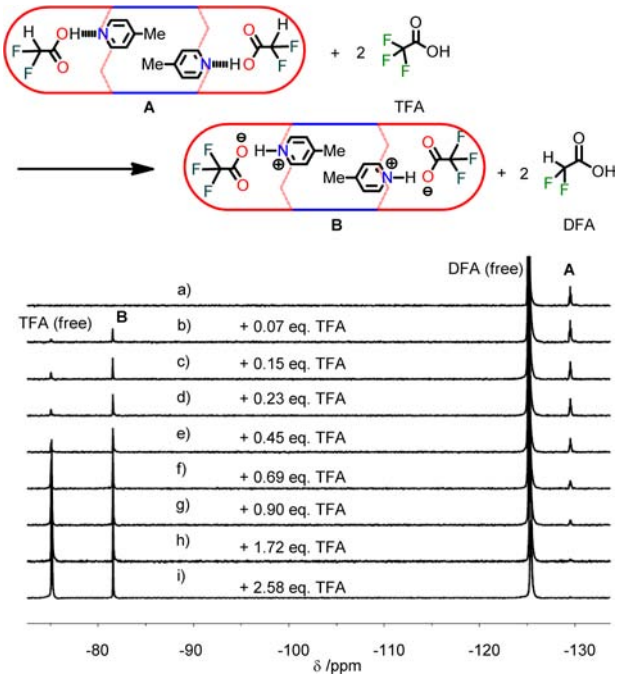

Figure 4. ^{19}F NMR titration experiment of difluoroacetic acid (DFA)/γ-picoline assembly with trifluoroacetic acid (TFA): (a) $[\mathbf{1.2}_8\mathbf{.1}]_0$ = 2.3 mM, $[DFA]_0$ = 30.4 mM, $[\gamma\text{-picoline}]_0$ = 19.8 mM; (b) add TFA (2.2 mM, 0.07 equiv); (c) add TFA (4.4 mM, 0.15 equiv); (d) add TFA (6.5 mM, 0.23 equiv); (e) add TFA (12.3 mM, 0.45 equiv); (f) add TFA (17.5 mM, 0.69 equiv); (g) add TFA (22.3 mM, 0.90 equiv); (h) add TFA (42.0 mM, 1.72 equiv); (i) add TFA (61.8 mM, 2.58 equiv).

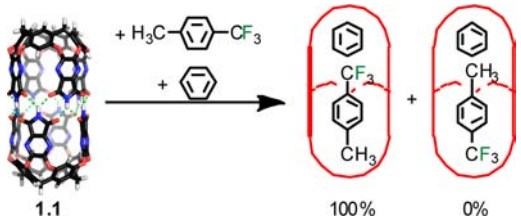

Figure 5. Selectivity for the social isomers of 4-(trifluoromethyl)-toluene with benzene in capsule **1.1**.

place in the somewhat more polar interior of the capsule. Second, cation–π interactions of the protonated picolinum with the host framework stabilize the arrangement. Third, the narrowing caused by the glycolurils favors the two methyls (rather than two TFA's) near the constricted middle of the capsule. Fourth, while one of the α-protons of γ-picoline forms hydrogen bonds with the carbonyl group of TFA, the other can form hydrogen bonds to the carbonyl groups of the glycolurils. We also considered a weak attraction between the $CF_3CO_2^-$ and the aryls at the bottom of the cavitand (CF–π interaction),[10] but a subsequent experiment indicated otherwise: direct competition of CH_3 and CF_3 was staged as shown in Figure 5, and only the social isomer[11] with the CH_3 near the bottom of the cavitand was observed.

In conclusion, acid–base pairs are difficult to sequester in hydrogen-bonded capsules as they compete for hydrogen bonds with the components of the assemblies. However, the Raymond–Bergman team[12] has observed a proton bridge between two amine guests in a capsule held together by metal–ligand interactions. We find a different arrangement in the present cases: strong proton sources and excess glycolurils convert a dimeric capsule that houses two γ-picolines—a four-component assembly—to extended 14-component assemblies that exist as discrete species. It should be possible to isolate other unlikely species with this system which appears favorably driven toward self-assembly.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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