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Selective Binding of *cis*-1,3,5-Cyclohexane Tricarboxylic Acid vs Its Epimeric *trans* Isomer by a Tripodal Amidopyridine Receptor; Crystal Structures of the 1:1 Complexes

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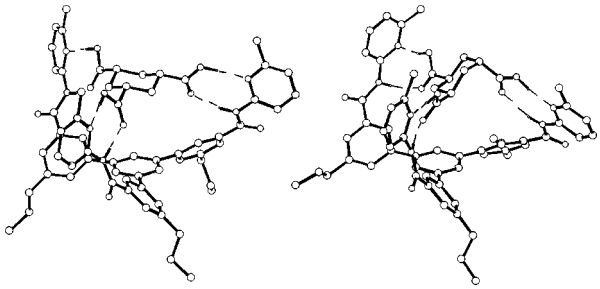
ABSTRACT



A tripodal tris-amidopyridine receptor forms a 1:1 complex with *trans*-1,3,5-cyclohexane tricarboxylic acid that is 1 order of magnitude less stable than the one formed with the corresponding *cis*-triacid epimer. The X-ray crystal structures of the complexes have been determined, confirming the binding geometry derived from NMR data in solution and force-field calculations, and its geometrical features are used to explain the observed selectivity.

The design of molecular receptors capable of selective recognition of carboxylic acids and their anions is a matter of current interest in bioorganic chemistry.[1] Recently, we have been interested in the three-dimensional recognition of tricarboxylic acids using tripodal abiotic receptors.[2] The design of our tripodal receptors is based on the spatially ordered positioning of three amidopyridine groups, which we use as complementary hydrogen-bonding partners for the carboxylic acid function.[3] If a carboxylic acid group is properly oriented with respect to an amidopyridine binding unit, up to two hydrogen bonds can be formed, one to the acidic proton and one to the *syn* lone pair of the carboxylic acid.[4] Using a 1,3,5-triarylbenzene as molecular scaffold, we

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have tailored and synthesized receptors **1a** and **1b** to study the molecular recognition of *cis*-1,3,5-cyclohexanetricarboxylic acid (*cis*-CTA) **2**.[2a] In this communication we report our findings on the selectivity of **1a** for **2** versus its epimeric isomer *trans*-1,3,5-cyclohexanetricarboxylic acid **3** (*trans*-CTA), as well as the structures of the **1a·2** and **1a·3** complexes formed in solution and in the solid state. Receptor

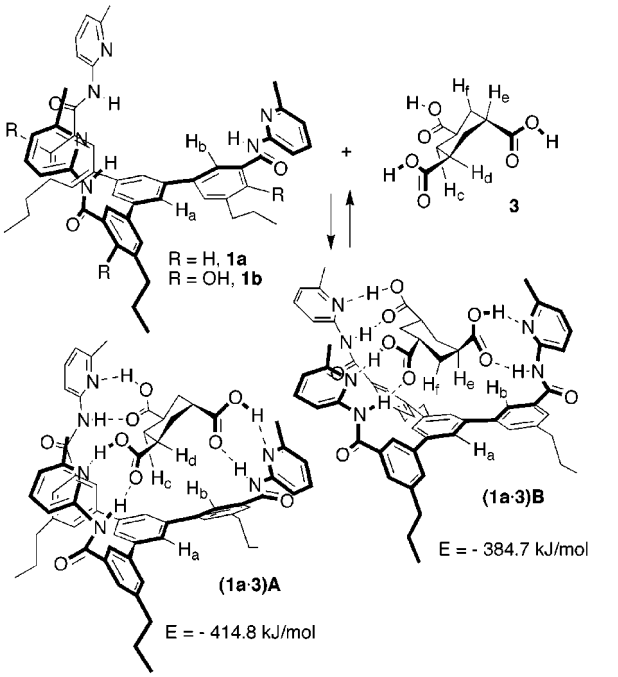

Figure 1. Possible binding geometries for the 1:1 complex of **1a** and **3**.

1a shows higher affinity for *cis*-CTA than for any other triacid assayed. For example, although 1 equiv of the normally insoluble triacids **2** or **3** is extracted in chloroform by receptor **1a**, its selectivity calculated by a liquid−liquid extraction experiment[5] and expressed as a ratio of association constants turned out to be K_a(**1a** + **2** ⇔ **1a·2**)/K_a(**1a** + **3** ⇔ **1a·3**) = 17[6] ($\Delta\Delta G \approx 1.7$ kcal/mol). The corresponding binding constants for the two guests, measured in 20% d_4-MeOD/$CDCl_3$, also differ by 1 order of magnitude K_a(**1a** + **2** ⇔ **1a·2**) = 549 ± 51 M^{-1} and K_a(**1a** + **3** ⇔ **1a·3**) = 55 ± 2 M^{-1} ($\Delta\Delta G \approx 1.4$ kcal/mol). The same difference in magnitude of K_a is obtained when the association constants are measured using isothermal titration calorimetry (ITC)[7] in 20% THF/$CHCl_3$. ITC gives ΔH_a directly as a primary parameter of measurement; ΔG_a and the host−guest stoichiometry *n* are estimated from titration curve fitting. The reaction entropy ΔS_a may then be calculated from the Gibbs−Helmholtz equation. The values obtained for systems **1a·2** and **1a·3** are summarized in Table 1.

Table 1. Isotermal Titration Calorimetry of Host **1a** with Guests **2** and **3** in 20% THF/$CHCl_3$ at 293 K

	n	ΔH_a (kcal mol^{-1})	$K_a \times 10^{-3}$ (M^{-1})	ΔG_a (kcal mol^{-1})	$T\Delta S_a$ (kcal mol^{-1})
2	0.971 ± 0.04	−8.686 ± 0.07	61.35 ± 0.8	−6.418 ± 0.07	−2.268 ± 0.07
3	0.946 ± 0.05	−6.939 ± 0.13	3.52 ± 0.6	−4.754 ± 0.10	−2.186 ± 0.12

In both cases guest complexation is highly exothermic. However, the association exothermicity for **3** is reduced by ~1.75 kcal/mol compared to that of **2**. This difference in binding enthalpy reflects a worse match of the receptor for guest **3** than for **2**.[8] The structure of the **1a·2** complex was solved in solution (ROESY)[9] and in the solid state (X-ray).[10] This structure reveals in both cases a complex geometry that is in agreement with the one previously described[2b] for the **1b·2** complex having the three axial hydrogens α to the carboxy groups pointing outside with respect to the receptor's cavity (Figure 3). In the **1a·2** complex six intermolecular hydrogen bonds are established (Table 2). One can assume

Table 2. O···N Distances (Å) for the Intermolecular Hydrogen Bonds Established in the **1a·2** and **1a·3** Complexes[a]

1a·2		**1a·3**	
OH···N	N···HO	OH···N	N···HO
2.624(0.010)	2.860(0.010)	2.673(0.010)	2.942(0.010)
2.671(0.010)	2.834(0.010)	2.678(0.010)	2.915(0.010)
2.700(0.010)	2.811(0.010)	2.750(0.010)	3.007(0.010)

[a] Each pair of distances refers to a bidentate interaction. Standard deviations are given in parenthesis.

that each hydrogen bond contributes with an average of −1.44 kcal/mol (−8.68/6) to the overall binding enthalpy.

To determine what structural features caused the reduction in binding enthalpy for the **1a·3** complex, we became interested in mapping out its 3D structure. From molecular modeling studies, two possible geometries for the **1a·3**

(5) A 10^{-2} M aqueous solution of triacid (50:50 mixture of epimers) was extracted with a $CHCl_3$ solution of the receptor. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. After treatment of the residue with excess of a diazomethane/ether solution, followed by GC analysis, a ratio of the extracted triacids **2**/**3** = 17 was obtained.

(6) The two triacids have a low solubility in cholorofom (~10^{-5} M), which can be considered identical within the experimental error. In this calculation we used this value as the free concentration in the equilibrium for both triacids.

(7) Wadsö, I. *Chem. Soc. Rev.* **1997**, *26*, 79−86. Ladbury, J. E.; Chowdry, B. Z. *Chem. Biol.* **1996**, *3*, 791.

(8) The fact that a similar difference in the free binding energy is obtained in solvents with different hydrogen bonding capabilities suggests that the observed selectivity is not related to a difference in solvation of the triacids. We assume that the initial states of the unbound guests **2** and **3** are energetically very close.

(9) Bothner-By, A. A.; Stephens, R. L.; Lee, J.-M.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811.

(10) Crystals suitable for X-ray diffraction were grown from $CDCl_3$/cyclohexane as colorless blocks.

complex were derived, each one containing six intermolecular hydrogen bonds (Figure 1). It is worth mentioning that the geometry (**1a·3**)**B** has one distorted N···HO hydrogen bond. Force field calculations carried out on both geometries (Macromodel 6.0,[11] AMBER*) resulted in a high energy difference of 30 kJ/mol (7.17 kcal/mol) in favor of binding geometry (**1a·3**)**A**. The two geometries feature a triple bidentate interaction and lack of C_3 symmetry. These characteristics are in agreement with the experimental results illustrated in Figure 2: a downfield shift for the receptor amide proton of 2.34 ppm upon complex formation[12] and NMR variable temperature experiments exhibiting, through a coalescence process, the desymmetrization of the complex, that is, the emergence of two signals (2:1 ratio) for the acid protons of the guest and for the amide protons of the host at 210 K. At room temperature, the ^{1}H NMR spectrum of the complex shows a single signal for each type of proton. The triacid is probably involved in a binding exchange process within the receptor at room temperature, rendering the three amidopyridine arms identical and the carboxylic acid protons not observable. To gain insight into the complex geometry

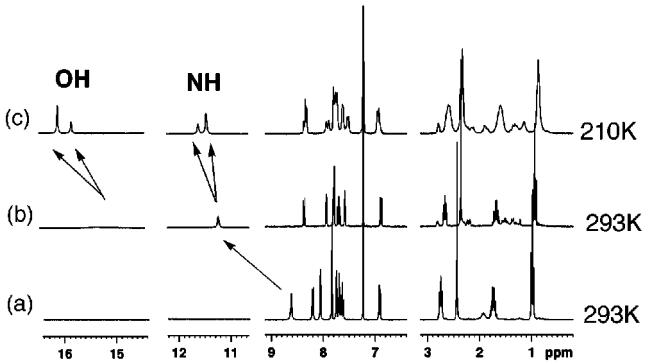

Figure 2. Selected ^{1}H NMR spectra: (a) **1a** at 293 K, (b)**1a·3** at 293 K, and (c) **1a·3** at 210 K.

in solution, a ROESY experiment was carried out at 293 K. From the cross-peaks obtained, the existence of close intermolecular contacts between protons H_a, H_b of the receptor and the H_c, H_d of the triacid were derived (see Figure 1 for proton assignment). These results, together with the absence of any other cross-peaks between the protons of the receptor and of the triacid provide strong evidence for the predominance of geometry (**1a·3**)**A** in solution. In this geometry six non-distorted hydrogen bonds are established, forcing the triacid **3** to bind in a different mode compared to the **1a·2** and **1b·2**[2b] complexes. For the (**1a·3**)**A** geometry the two axial hydrogens, α to the carboxy groups, point inside the receptor's cavity. Thus, the measured enthalpy difference cannot be accounted by distortion of a single hydrogen bond.

(11) Macromodel V6.0. Mohamadi, F.; Richards, N G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(12) This value of the downfield shift of the amide proton resonances indicates that a triple bidentate hydrogen bonding is taken place. See refs 2−4.

Host **1a** and triacid **3** crystallize from 1,2-dichloroethane/octane as a 1:1 complex (shown by ^{1}H NMR) producing colorless prisms, unstable in the absence of solvent. After several attempts, the solid-state structure of the **1a·3** complex was determined by single-crystal X-ray diffraction. The X-ray structure reveals a geometry for the **1a·3** complex (Figure 3) that is in good agreement with the proposed solution structure (**1a·3**)**A** based on calculations and NMR data. Six

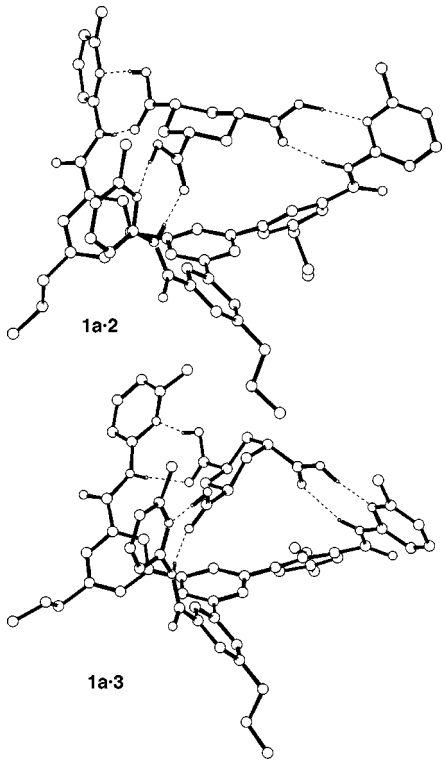

Figure 3. X-ray structures of the 1:1 complexes between tripodal host **1a** and triacids **2** and **3**. Only polar hydrogens in calculated positions are shown. Dotted lines indicate intermolecular hydrogen bonds.

different intermolecular hydrogens bonds are established (Table 2). In each bidentate interaction, the hydrogen bond established between the pyridine nitrogen and the carboxylic acid proton is shorter than the one between the amide hydrogen and the oxygen carbonyl of the carboxylic acid. In general, the distances for the intermolecular hydrogen bonds are longer than the corresponding ones found in the **1a·2** complex, reflecting weaker interactions.

Superposing the X-ray structure of **1a** in the **1a·2** and **1a·3** complexes reveals that the host conformations are not significantly different upon accommodating **3** or **2** (RMS[13] deviation 0.552 Å for all heavy atoms except the propyl chain). Moreover, the bound triacids **2** and **3** do not show any sign of conformational strain. A likely explanation for the observed selectivity is that the overall change in the

(13) Kabsch, W. *Acta Crystallogr., Sect. A* **1976**, *32*, 922; Kabsch, W. *Acta Crystallogr., Sect. A* **1978**, *34*, 827.

intermolecular interaction distances (the smaller difference for the six hydrogen bonds adds up to 0.439 Å) mainly accounts for the measured difference in binding enthalpy of ~1.75 kcal/mol.

Simple calculations using the AMBER* force field also point in this direction. The X-ray structures of the **1a·2** and **1a·3** complexes were minimized, yielding a total energy difference of 6.25 kcal/mol in favor of the **1a·2** complex. Interestingly, the major contribution to this difference comes from the electrostatic term 5.25 kcal/mol, which mainly accounts for the intermolecular hydrogen bonding.

Although the crystal packing of the two complexes is not identical the following common trends can be observed: the 1:1 complexes stack on each other involving a $\pi-\pi$ interaction between the two central aromatic rings that are rotated by 60°, in a face to face geometry separated by ca. 3.9 Å and forming a stacked dimer (Figure 4a and b);[14] the absolute stereochemistry of the complexes alternates in the stacked dimers; and adjacent dimers pack by establishing two different types of edge-on stacking interactions[15] between aromatic protons and aromatic rings of the receptor's arms (Figure 4c and d).

A close inspection of both crystal packings reveals the presence of solvent molecules assisting the dimer packing, which explains the unstability of the crystals in its absence. For the *cis* triacid an easy to observe columnar arrangement emerges from the crystal packing; the $\pi-\pi$ dimers of type b stack on top of each other in an alternating top-to-top and bottom-to-bottom fashion. The packing for the *trans* triacid complex can be described as sheets formed by the type a dimers in a "zig-zag" arrangement with reference to its central axis. The resulting sheets pack on top of each other.

In summary, the study of the complexes **1a·2** and **1a·3** and associated crystal packings provides nice examples of intermolecular interaction motifs used in solution and in the solid phase for the construction of supramolecular entities. It also reveals that when a panoply of intermolecular hydrogen bonds is established upon host−guest complexation, a small difference in the individual distances for each interaction can be responsible for considerable host selectivity. In our simple system based on only six hydrogen bonds, a subtle difference in hydrogen bonding lengths results in a binding enthalpy difference of 1.75 kcal/mol.

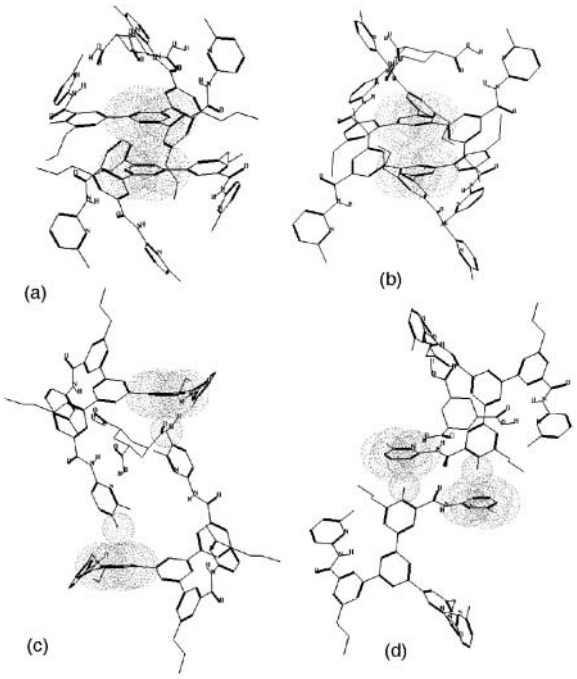

Figure 4. Common $\pi-\pi$ stacking interactions observed in the packing of the **1a·2** and **1a·3** complexes. Face to face stacking of the two 1:1 complexes (a) **1a·3** and (b) **1a·2**. Two point edge-on stacking interaction established between arms of adjacent 1:1 complexes (c) using different "arms" and (d) using the same "arm". In all cases, only polar and relevant aromatic hydrogens are shown and one guest molecule is omitted for clarity.

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Supporting Information Available: Crystal data (CIF) for complexes **1a·2** and **1a·3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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