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## Influence of Remote Intramolecular Hydrogen Bonds on the Thermodynamics of Molecular Recognition of cis-1,3,5-Cyclohexanetricarboxylic Acid.

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Abstract: Variable temperature binding studies and isothermal titration microcalorimetry were used to probe the thermodynamics of molecular recognition of cis-1,3,5-cyclohexanetricarboxylic acid by tripodal hosts. Remote intramolecular hydrogen bonds, used to restrict conformationally one of the hosts, exhibit a strong influence on the thermodynamic functions for the binding process  $\Delta H$  and  $\Delta S$ , with little effect on  $\Delta G$ . This suggests that the conformational lock imposed by the intramolecular hydrogen bonds organizes the receptor in a conformation that is not optimal for the binding of the triacid. © 1998 Elsevier Science Ltd. All rights reserved.

The complexation of organic molecules by abiotic hosts in organic solvents, where the hydrogen bond (H-bond) is the principal binding force, is characterized typically by an enthalpic benefit greater than the entropic cost.<sup>1</sup> The enthalpy change mainly arises from the energy release that accompanies the pairwise interaction of the H-bonding groups upon complexation. The entropic cost is a consequence of the formation of an ordered and fairly rigid bimolecular complex from two less ordered components, with the associated loss in degrees of freedom.<sup>2</sup> Therefore, constraining a host to a conformation close to that found in the complex (usually referred to as preorganization<sup>3</sup>) should be an important factor in reducing the entropy loss, thus improving the binding free energy.

We have reported the synthesis of tripodal host 1, its recognition of cis-1,3,5-cyclohexanetricarboxylic acid 2 (CTA) in nonpolar media,<sup>4</sup> as well as the X-ray structure of the complex.<sup>5</sup>



The receptor design incorporated an intramolecular H-bond between phenol and amide carbonyl groups on each of the three arms, restricting rotation about the three aryl-amide single bonds.<sup>6</sup> The premise was that these Hbonds would aid in preorganizing the host into an endoreceptor conformation that is optimized for triacid recognition and therefore confer an entropic advantage for the targeted complexation. However, preorganizing a receptor into a fixed geometry can be detrimental if the conformation is not perfectly complementary to the guest, which can lead to a reduced enthalpy of binding.

To probe these various preorganizational aspects of host-guest chemistry, we wish to report the synthesis and binding properties of the analogous tripodal receptors **3a-b** which are devoid of intramolecular H-bonded conformational restrictors, and to compare them with host **1** using a full complement of spectroscopic and thermodynamic binding analyses, including isothermal titration calorimetry.

Hosts **3a-b** were synthesized from the previously reported triesters **4a-b** which were obtained through SiCl<sub>4</sub> catalyzed cyclotrimerization of a suitably functionalized acetophenone derivative.<sup>3</sup> As illustrated in Scheme 1, the phenolic hydroxyls were removed by converting triesters **4a-b** to the corresponding tris aryl triflates **5a-b** followed by ring deoxygenation mediated by  $Cl_2Pd(PPh_3)_2$  to afford triesters **6a** and **6b** in 81% and 63% overall yield, respectively. Hydrolysis of triesters **6a-b** afforded the triacids **7a-b** which were converted to triacyl chlorides **8a-b** and coupled with 6-methyl-2-aminopyridine to produce tripodal receptors **3a** and **3b** in 73% and 61% overall yield, respectively, from triesters **6a-b**.<sup>7</sup>



Scheme 1. (a)  $Tf_2O$ ,  $CH_2Cl_2$ ; (b)  $Cl_2Pd(PPh_3)_2$ ,  $Ph_2P(CH_2)_3PPh_2$ ,  $Bu_3N$ ,  $HCO_2H/DMF$ , 90°; (c) NaOH,  $H_2O$ -THF; (d)  $SOCl_2/CH_2Cl_2$ ; (e) 6-methyl-2-aminopyridine,  $CH_2Cl_2$ .

As an initial assessment of the relative binding properties of hosts 1 and 3a-b, <sup>1</sup>H NMR titrations were carried out in 20% MeOH-d4/CDCl<sub>3</sub> with CTA 2. Unexpectedly, all three receptors gave similar association constants<sup>8</sup> (K<sub>a</sub>) for CTA recognition (1: 466 ± 8 M<sup>-1</sup>, 3a: 410 ± 14 M<sup>-1</sup>, 3b: 549 ± 51 M<sup>-1</sup>). The K<sub>a</sub> ratio between hosts 1 and 3a was corroborated by competitive binding experiments (CDCl<sub>3</sub>, 260K) which gave a K<sub>a</sub>1/K<sub>a</sub>3a ratio of 1.14. Apparently, the preorganization of host 1 through intramolecular H-bonding confers no clear advantage for the association of CTA.

In order to gain insight on the thermodynamic functions of the complexation process, van't Hoff analyses of the 1-CTA and **3a**-CTA pairs using variable-temperature (VT) <sup>1</sup>H NMR were carried out. In accord with the guidelines established by Wilcox<sup>1b</sup>, a full titration of the **3a**-CTA system was performed out at each temperature to determine the K<sub>a</sub> values. The K<sub>a</sub> values from 277 to 314K gave a linear van't Hoff plot and were retained for the  $\Delta$ H and  $\Delta$ S determinations.  $\Delta$ H and  $\Delta$ S values of -9.06±0.9 kcal/mol and -18.8±3.1 eu (R<sup>2</sup>=0.997) were obtained. Similar results were obtained for the same system using simpler "single-point" variable temperature van't Hoff experiments ( $\Delta$ H=-9.42±0.9 kcal/mol,  $\Delta$ S=-19.8±3 eu, R<sup>2</sup>=0.996), which is justified since the limiting chemical shifts of the aromatic hydrogens monitored during the titrations were almost temperature independent. To speed up the analyses, the same "single-point" VT method was used to study the 1-CTA system, yielding values of  $\Delta$ H=-6.95±0.3 kcal/mol and  $\Delta$ S=-10.8±1 eu (R<sup>2</sup>=0.999).<sup>9,10</sup>

These results support the view that the structural constraints imposed by the intramolecular H-bonds in host 1 have the desired effect of producing a more ordered host but, unfortunately, not in a conformation which is optimal for CTA recognition.

There is concern that  $\Delta H$  values of low accuracy may be produced from VT studies.<sup>11</sup> A versatile and accurate alternative for the determination of all thermodynamic binding data is isothermal titration calorimetry (ITC).<sup>12</sup> In our case, the host concentration was adjusted to return a "c" value of 6, high enough for a reliable calorimetric determination of K<sub>a</sub> and  $\Delta H$  while maintaining concentrations as close as possible to the NMR

titration experiments.<sup>13</sup> Accordingly, hosts 1, 3a, and 3b were titrated by ITC as  $\approx 10$  mM solutions in 20%MeOH/CHCl, with CTA. The isothermal titration calorimetry results are reported in Table 1.

Host	$K_{\bullet}(M^{-1})$	∆ <b>H</b> (kcal/mol)	Δ <b>S</b> (eu)
1	582±24	-6.90±0.1	-10.72
3a	485±33	-9.46±0.2	-19.82
3 b	563±25	-10.54±0.2	-23.18

Table 1. Isothermal titration calorimetry for hosts 1 and 3a-b with CTA 2 in 20% MeOH/CHCl<sub>3</sub> at 294 K.

The thermodynamic values  $K_a$  and  $\Delta H$ , obtained by ITC, are in general agreement with the VT NMR results. Thus, for the systems under study, the total enthalpy measured by ITC appears to be representative of the intrinsic binding enthalpy, which is not necessarily the case for other host-guest systems.<sup>11c</sup>

The collective results indicate clearly that the less preorganized hosts **3a-b** promote more optimal Hbonding interactions with CTA than host 1. The conformational changes induced in host 1 upon CTA binding reduce the exothermicity of the association by  $\approx 2.56-3.64$  kcal/mol compared to **3a-b** which must correspond to the gain in energy due to the distortion of the intra- and intermolecular H-bonds in 1-CTA. Analyzing the <sup>1</sup>H NMR signals of the H-bonded protons at 260K in CDCl<sub>3</sub> before and after CTA complexation provided experimental support for this hypothesis. Indeed, the phenol protons in free 1 appear at a concentrationinvariant value of 12.4 ppm and shift upfield to 11.8 ppm upon CTA complexation, a sign of weakened Hbonding (assuming that the binding of an acid to an amidopyridine arm has a negligible anisotropic effect on the remote H-bonded phenol proton). In addition, both the amide NH and CTA carboxyl protons in the 1-CTA complex are shifted upfield compared to those found in the **3a**-CTA complex ( $\approx 0.2$  ppm for both) a further indication of weaker H-bonded interactions.

Although the entropy of complexation, is affected by the polar nature of the solvent, there is a clear difference in the behaviour of the two systems<sup>2</sup>: the  $\Delta$ S values for hosts **3a-b** are larger than for host **1** by about 10 eu. This could be due to differences in desolvation on binding but since the hydroxyl groups are on the outside of the cavity, a more likely explanation is the difference in preorganization of the receptors.<sup>14</sup> The more flexible hosts **3a-b** can achieve better complementarity with CTA while maximizing the H-bonding interactions at the expense of an entropy loss. These systems are a beautiful abiotic example of Koshland's induced-fit hypothesis.<sup>15,16</sup>

In conclusion, we rationalize our resuls as follows: the rigidification of host 1 through intramolecular Hbonding has been achieved. Disappointingly, the improper preorganization of receptor 1 was indeed found to be detrimental to CTA binding, as the conformation was not perfectly complementary to the guest, leading to a reduced enthalpy of binding. Studies on the selectivity of receptors 1 and 3a-b towards the binding of several flexible triacids are in course and will be reported in due time.

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