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Molecular Recognition of cis-1,3,5-Cyclohexane Tricarboxylic Acid

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Abstract: The design and synthesis of a new receptor designed to bind tricarboxylic acids in organic solvents is described. The properties of the complex formed between the new receptor and cis-1,3,5-cyclohexanetricarboxylic acid are studied.

Molecular recognition of carboxylic acids in organic solvents has been traditionally achieved by the use of neutral receptors with complementary hydrogen bonding groups[1-3]. For example, Hamilton[2] and Diederich[3] have both synthesized several neutral receptors for the selective binding of dicarboxylic acids in organic solvents by separating two amidopyridine residues with a suitable spacer. The 2-amidopyridine group can form two hydrogen bonds, one to the acidic proton and one to the syn lone pair of the carboxylic acid carbonyl[4]. We rationalized that if a relatively large and rigid molecular component was used to adequately position three 2-amidopyridines groups, then a potential receptor for the formation of stable host-guest complexes with tricarboxylic acids in organic solvents would be at hand.

Our recent experience[5] in the use of the tetrachlorosilane-ethanol induced self condensation of ketones[6] for preparing 1,3,5-tris(3-bromo-5-carboxyphenyl-4-hydroxy-)benzene, prompted us to consider the use of compound **2a** (m.p. 222-225°C) as a rigid molecular component for positioning three hydrogen bonding arrays within a receptor. Molecular modeling studies[7] on the newly designed receptor **3a** suggested that the syn conformation of the molecule was very well suited for the complexation of cis-1,3,5-cyclohexanetricarboxylic acid **4** (Figure 1). In this conformation the hydrogen bonding groups converge and can act simultaneously in "grasping" the guest molecule in the induced cleft of the receptor.

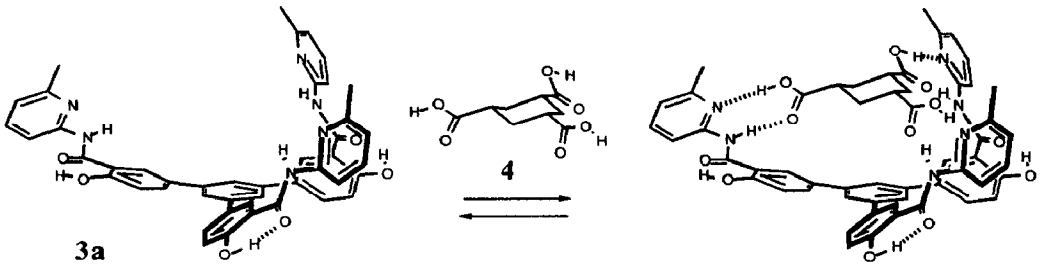
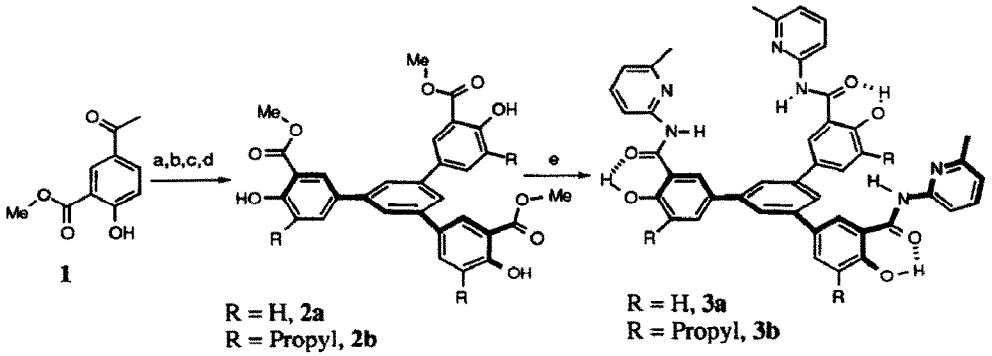


Figure 1

It is worth mentioning that we made use of intramolecular hydrogen bonding between the amide carbonyls and the phenolic protons for controlling receptor preorganization.[8] The other possible conformer in which the

amide protons are hydrogen-bonded to the phenolic oxygens is expected to be largely disfavored[9]. Thus, the favored intramolecular hydrogen bonds restrict the rotation of the C_{aryl}-C_{amide} bonds forcing the amide hydrogens to be directed towards the interior of the cavity and locking each amidopyridine subunit in an almost planar configuration with respect to their aryl ring. Receptor **3a** (m.p. > 310°C) was synthesized uneventfully in five steps from 4-acetylmethylsalicylate **1** in 31% overall yield[10].

Unfortunately, host **3a** was insoluble in $CHCl_3$ or other organic solvents which do not considerably disrupt hydrogen bonding. In order to increase the solubility of the receptor in $CHCl_3$, a more lipophilic version of the spacer was prepared which involved etherification of the phenols of **2a** with allyl bromide[11], followed by a triple Claisen[12] rearrangement and catalytic hydrogenation of the double bonds to afford the propylated triaryl benzene triester **2b** (m.p. 202-205°C, 61% overall yield). Triamide **3b** (m.p. 281-284°C) was prepared from **2b** by a slight modification of the Weinreb[13] procedure in 26% yield (Scheme)[14]. Chloroform solutions of receptor **3b** of up to 10^{-2} M could now be prepared.



Scheme. (a) Cl_4Si/EtOH, r.t., 24h; (b) Cs_2CO_3, DMF/acetone, Br-CH_2-CH=CH_2, reflux, 24h; (c) N,N-dimethylaniline, reflux, 12h; (d) H_2, Pd/C 10%, ethyl acetate, 10 psig, 5h; (e) 3 equiv Me_3Al, then Me_3Al/2-amino-6-methylpyridine complex, benzene reflux, 48h.

The ^{1}H-NMR spectrum of **3b** in $CDCl_3$ showed that the phenolic protons are shifted downfield to 12.4 ppm indicating that they are strongly hydrogen bonded while the amide protons appears at 8.8 ppm, a reasonable position for free aromatic amide protons. These observations strongly support the conformational preference aforementioned. At room temperature, C_{aryl}-C_{aryl} bond rotations are fast in the NMR time scale and the signals are sharp and well resolved. At low temperature, broadened signals are observed for **3b** since interconversions between different conformers become slower.

Addition of solid cis-1,3,5-cyclohexanetricarboxylic acid **4** to a $CDCl_3$ solution of **3b** led to a rapid dissolution of the normally insoluble substrate. Large downfield shifts (2.8 ppm) of the NH resonances in the ^{1}H-NMR spectrum indicated the formation of a hydrogen-bonded complex, which integration established as a 1:1 stoichiometry. The spectrum of the 1:1 complex formed by solid-liquid extraction was no longer temperature dependent. Thus, the binding of the triacid **4** restricts the conformation of **3b** to the one featuring convergent hydrogen bonding. Only this conformation can involve all three acylamidopyridine groups of the receptor, thus freezing the three C_{aryl}-C_{aryl} bond rotations. Host **3b** and triacid **4** crystallize out of a chloroform/cyclohexane solution as a 1:1 complex, as shown by ^{1}H-NMR. Attempts to obtain an x-ray crystal structure have not yet been successful, although single crystals have been obtained.[15]

Molecular modeling studies suggest two c3-symmetric geometries for a complex between **3b** and **4** in which six intermolecular hydrogen bonds between the three COOH residues of **4** and the three CONH(py)N groups of **3b** are possible (Figure 2). In geometry **A**, the acids and H_c hydrogens of the guest are endo to the receptor cavity, while in geometry **B**, the acids are exo and the H_d hydrogens are endo. Both geometries were

optimized with MacroModel 3.5X using the OPLS*[16] force field and the GB/SA-$CHCl_3$ solvation model[17], which resulted in an energy difference of ΔE = 8 kcal/mol in favor of binding geometry A. The calculated energy difference could be attributed to the fact that intermolecular hydrogen bonding in complex geometry B may not be optimal. In fact, modeling suggests that the three (py)N····H—OOC hydrogen bonds in geometry B are longer (3.01Å *vs.* 2.91Å) and less collinear (150° *vs.* 174°) than in geometry A, which may account for the calculated energy difference.

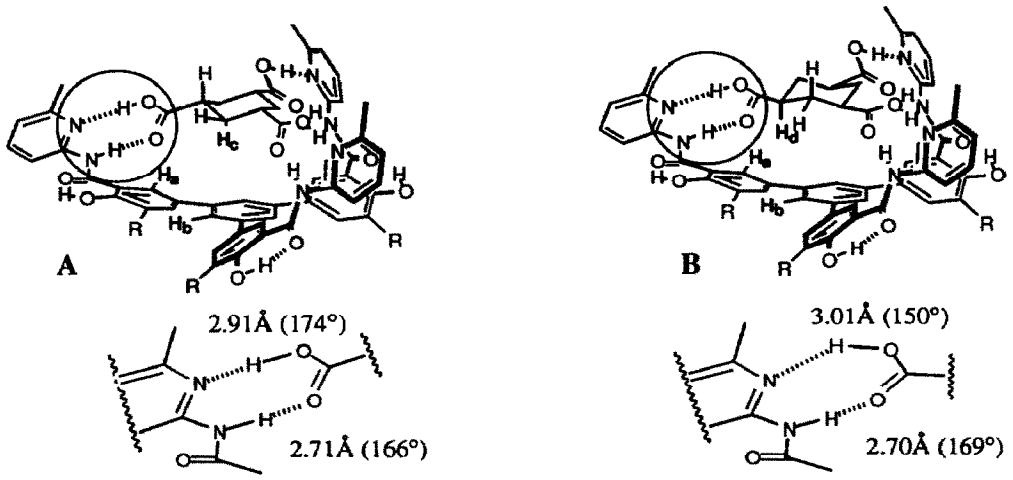


Figure 2. Above, two different geometries of the convergent complex between triacid **4** and receptor **3b**. Below, schematic representations of the selected areas highlighting bond lenghts and bond angles for the hydrogen bonds in the complexes. R = propyl.

The A type binding geometry was confirmed experimentally by 2D ^{1}H-NMR studies of the 1:1 complex in $CDCl_3$ solution. A ROESY experiment on the 1:1 complex (mixing time=0.75 s., spinlock=2KHz) revealed close intermolecular contacts between the H_a and H_b hydrogens of the receptor and the H_c hydrogens of the triacid. This observation, together with the absence of rOe's between the receptor and the triacid's H_d hydrogens, provides strong evidence for the predominance of the type A complex geometry in chloroform solution.

The association constant between triacid **4** and triamide **3b** was estimated by the solubility titration method[18]. By plotting the insoluble component **4** *vs.* soluble component **3b** and by simple analysis of the slope and intercept, we determined the association constant for the complex $K_a > 10^5$ L mol^{-1}. Furthermore, a standard solution NMR titration experiment,[19] made possible by using 20%d^8-THF/$CDCl_3$ as solvent, gave also an association constant $K_a > 10^5$ L mol^{-1}.

To the best of our knowledge, this is the first report of an organic soluble receptor for a triacid. The binding geometry of the complex between **3b** and **4** has been probed by molecular modeling and 2D nOe experiments. The high association constants observed for the complex reflect a precise match between receptor and guest in establishing a panoply of intermolecular interactions. Studies on the binding selectivity of receptor **3b** to several other triacids are in progress and will be reported in due time.

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