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Molecular Recognition: Chain Length Selectivity Studies of Dicarboxylic Acids by the Cavity of a New Troger's Base Receptor

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Abstract: A new dicarboxylic acid receptor **1** having two pyridine amide motifs built on a Troger's base spacer has been designed and synthesised. The binding studies are performed with a series of dicarboxylic acids and the cavity of receptor **1** was found to be selective for suberic acid. © 1997 Published by Elsevier Science Ltd.

The design and synthesis of model receptors to recognise substrates of biochemical significance to mimic biological events is an important area in molecular recognition research.[1,2] This forms the basis of the receptor-based drug design and bioorganic models[1] towards life processes.

Recognition of dicarboxylic acids[2a-d] and their chain length selectivity by specific receptors is an interesting challenge where selectivity depends on precise complementarity between the dicarboxylic acid chain length and the receptor cavity size. However the precise selectivity is more difficult between two purely aliphatic dicarboxylic acids (close homologues) which do not differ much in lengths because these aliphatic dicarboxylic acids make a compromise between widening or closing of the two carboxyl ends at the more flexible methylene bridge to correspond to the cavity size of the rigid host. This consideration does not arise in the case of rigid aromatic dicarboxylic acids. The placement of the two pyridine amide binding moieties for carboxylic acids[3a-e] by a suitable spacer is important as shown by the specificity of the terephthaloyl spacer for adipic acid.[3a] The selective binding of glutaric acid has been reported by a resorcinol-aldehyde cyclotetramer as a multidentate host[3f] and of dibutylmalonic acid by a receptor having a benzophenone spacer[3g] between the two urea or phosphonamide type binding moieties in the cavity for the

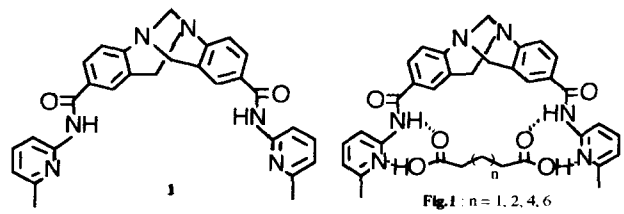

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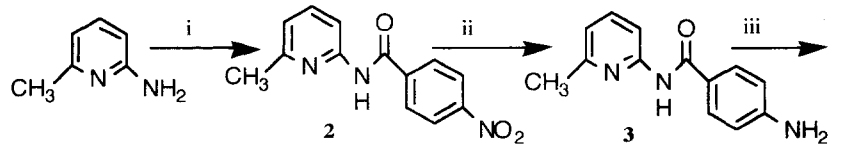
Fig.1 : n = 1, 2, 4, 6

carboxylic acid. We report here for the first time the recognition of dicarboxylic acids by a Troger's base receptor **1** in which the cavity is found to be selective for suberic acid.

More than a hundred years after of the synthesis of Troger's base,[4] an exploration of the chemistry of Troger's base analogues in recognition of adenine and other substrates was undertaken by Wilcox et. al.[5a-c] Since then considerable attention has been focussed on the synthesis of Troger's base analogues[5d-e] though only a few examples containing heterocycles have been reported.[5f-g] Molecular modeling studies reveal the relative rigidity of Troger's base analogues.[5h]

Receptor **1** was synthesised[6] (Scheme 1) from 2-(4-aminobenzoylamino)-6-methyl-pyridine **3** by reaction with hexamethylenetetramine in the presence of trifluoroacetic acid (nonaqueous medium[7a]). The amine **3** was obtained by catalytic hydrogenation of 6-methyl-2-(4-nitrobenzoylamino)pyridine **2**. Receptor **1** was isolated in 15-20% yield by careful purification (PTLC) from a difficult mixture of other uncharacterised side products. The low yield of the receptor **1** may be due to the presence of electron withdrawing amide groups on the aromatic ring.[7b,c]



Scheme 1 *Reagents and conditions* : i. p- Nitrobenzoyl chloride, CH_2Cl_2 (Dry), Et_3N, room temp (**2**, 90%); ii. H_2, Pd/C, ethanol, room temp, (**3**,90%); iii. hexamethylenetetramine, trifluoroacetic acid, 60 °C (**1**, 15-20%).

In the receptor **1**, the two pyridine units are angularly disposed by the Troger's base spacer and these hydrogen bonding groups are well arranged in a concave face to bind dicarboxylic acids. It can have three possible conformations of comparable energy values (in-in, in-out, out-out) in the solution phase. A DTMM[7d] calculation on these three conformers suggested the closeness of the two pyridine subunits (pyridine ring nitrogen distance 7.55 A^0) in the 'in-in' conformation. 'In-In' refers to the conformation where two pyridine ring nitrogens are pointed into the cavity. Titration of **1** in $CDCl_3$ with a series of dicarboxylic acids (dissolved in $CDCl_3$ containing 2% d_6-DMSO for better solubility of dicarboxylic acids and binding constants are sacrificed to some extent using DMSO as it is a competitive guest) (Table 1) shows appreciable association constants.[8] The value of the binding constant, measured in $CDCl_3$ is found to be higher than the value given in Table 1 (e. g., K_a for glutaric acid in $CDCl_3$ = 6.01x 10^3 M^{-1}). Integration of the proton signals of the 1:1 complex in the ^1H NMR spectrum as well as the break in the titration curve ($\Delta\delta$ vs C_{guest} / C_{host}) at 1.0 establishes a 1:1 stoichiometry[9] for these dicarboxylic acids with the receptor **1**. In the NMR spectrum of a 1:1 complex[6] of **1** (in $CDCl_3$) with suberic acid (dissolved in

$CDCl_3$ with 2% d_6-DMSO), the considerable downfield shift of the pyridine amide protons ($\Delta\delta$ 1.68 ppm) and of the phenyl ring as well as the methylene bridge protons of the Troger's base frame ($\Delta\delta$ 0.1-0.3 ppm) also suggests the formation of a strong complex (Fig.**1**). The self-association constant[10] of mono and dicarboxylic acids in nonpolar organic solvents is in the order of 0.01 - 5 LM^{-1}.

Table 1. Binding Constants of Receptor **1** and dicarboxylic acids

diacid	K_a M^{-1}(at 25 °C)	ΔG (at 25 °C) kcal/mole
glutaric	$1.0x10^3$	-4.09
adipic	$1.69x10^3$	-4.40
suberic	$1.5x10^4$	-5.69
sebacic	$3.10x10^3$	-4.76
benzene-1,4-diacetic	$2.88x10^2$	-3.35

The higher association constant for suberic acid compared to glutaric and adipic acids is due to the complementary cavity size with suberic but not with shorter dicarboxylic acids. Similarly sebacic acid being longer, binds less efficiently compared to suberic acid. The much lower value of K_a with benzene-1,4-diacetic acid is probably due to the presence of a rigid phenyl ring and its misfit within the Troger's cavity. The strong association of suberic acid with the receptor was suggested from the fact that dilution of the 1:1 complex with $CDCl_3$ ($\Delta\delta$ 2.0 ppm of pyridine amide protons of **1** in complex in pure $CDCl_3$) (K_a in pure $CDCl_3$ is higher than that in d_6-DMSO-$CDCl_3$) shows negligible change in the ^1H NMR spectrum. The selectivity to suberic acid is also evidenced by its exclusive extraction (>90%) in pure $CDCl_3$ from its 1:1 mixture with benzene-1,4-diacetic acid as shown by NMR.

We have thus shown that this Troger's base synthetic cavity has the chain length selectivity with suberic acid. Further studies are in progress to achieve the goal of utilising Troger's cavity in chiral recognition process either by using chiral acid guests with racemic Troger's base receptor or vice-versa.

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6. **Compound 1** (mp 110-2°C), M^+ 490.2(69.80 %), ^1H NMR (200 MH_Z, $CDCl_3$) δ: 8.38(s, 2H, NH), 8.12(d, 2H, Pyr-H, J=8 H_Z), 7.72(d, 2H, J=8 Hz), 7.61(t, 2H, Pyr-H, J= 8 H_Z), 7.57(s, 2H), 7.23(d, 2H, Pyr-H, J=8 H_Z), 6.90(d, 2H, J=8H_Z), 4.79(d, 2H, J=16 H_Z), 4.35(s, 2H), 4.30(d, 2H, J=16 H_Z), 2.45(s, 6H). $^{13}C(CDCl_3)$: 164.9, 156.8, 156.6, 151.8, 138.7, 129.9, 127.9, 126.7, 126.4, 125.3, 119.3, 110.9, 66.7, 58.7, 29.7.**Complex(1:1) with suberic acid**:^1H NMR δ: 10.06(s, 2H, NH), 8.23(d, 2H, Pyr-H, J=8 H_Z), 7.90 (d, 2H, J=8 Hz), 7.77 (s, 2H),7.65 (t, 2H, Pyr-H, J= 8 H_Z),7.21(d, 2H, Pyr-H, J=8 H_Z),6.89 (d, 2H, J=8H_Z), 4.79 (d, 2H, J=16 H_Z), 4.33(s, 2H), 4.32(d, 2H, J=16 H_Z), 2.43(s, 6H), 2.33 (t, 4H, J=6 Hz), 1.63 (m, 4H), 1.37(m, 4H).

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