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SELECTIVE α, ω-DICARBOXYLIC ACID RECOGNITION IN A CHIRAL CLEFT SHAPED BY THE 9,9'-SPIROBIFLUORENE UNIT

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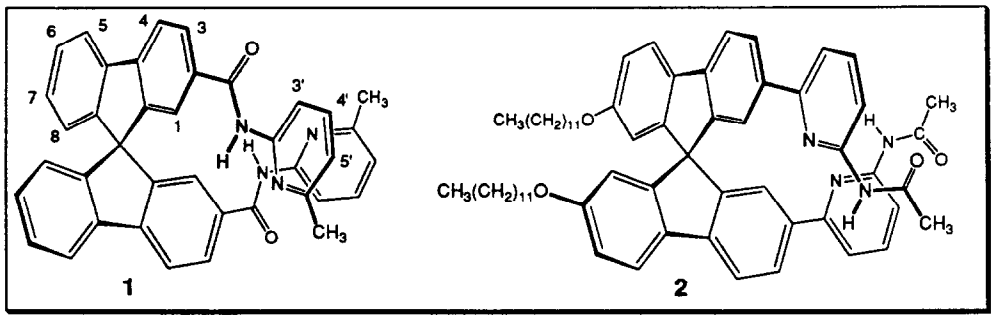
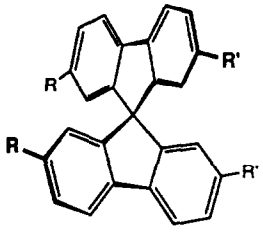
ABSTRACT *A 9,9'-spirobifluorene, functionalized in the 2,2'-positions with two 6-methyl-2-pyridinyl-aminocarbonyl residues, provides a cleft binding site for the selective 1:1 complexation of glutaric and pimelic acid in chloroform solution. Chiral recognition occurs in the complexes of the chiral cleft with N-Cbz-L-glutamic acid*

Recently, we described the efficient enantioselective complexation of cinchona alkaloids in optically active molecular clefts that are shaped by the major groove of the 1,1'-binaphthyl unit and functionalized with one or two hydroxy groups.[1] Hydrogen bonding in addition to aromatic-aromatic interactions represent the major binding forces in the diastereomeric complexes that form with quinine and quinidine in chloroform and show differential stabilities up to $\Delta\Delta G^{o} \approx 1.0$ kcal mol^{-1}. In a search for chiral building blocks that provide more rigid, organized clefts[2] than 1,1'-binaphthyls, we came across the 9,9'-spirobifluorene unit. Previously, Prelog *et al* [3] had introduced this spacer into optically active crown ethers which showed high enantiomer selectivities in the complexation of chiral ammonium ions. Here, we describe the synthesis and a preliminary assessment of the binding potential of the two 9,9'-spirobifluorene clefts **1** and **2** with amidopyridine residues attached in two different ways to their 2,2'-positions for hydrogen bonding The connectivities between the two amidopyridine rings and the spacer in **1** are similar to those in 1,4-bis(6-methyl-2-pyridinylaminocarbonyl)benzene, a remarkably simple yet efficient binder of adipic and glutaric acid recently described by Hamilton *et al.*[4] The array of hydrogen bonding centers in **2** resembles the binding site configuration in the helicopodands, chiral non-macrocyclic receptors with a helical backbone, that are currently under investigation in our laboratories.[5]

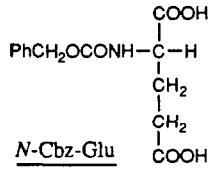


For the synthesis of **1**, 2,2'-dicarboxy-9,9'-spirobifluorene[6] was converted with $SOCl_2$ (cat. pyridine) into the bis(acyl halide). The crude material was reacted with 2-amino-6-methylpyridine in THF in the presence of Et_3N to give the colorless diamide **1** (mp > 300 °C) in 64% overall yield.[7] For the preparation of **2**, the diacetyl derivative **3**[6] was brominated (Br_2, $AlCl_3$, CH_2Cl_2, 50 °C) to give **4** in 77% yield. The subsequent Baeyer-Villiger oxidation (*m*-CPBA, $CHCl_3$, 0 °C) afforded **5** (88% yield), which was hydrolyzed to **6** (2N NaOH, MeOH; 84% yield). To ensure adequate solubility of the cleft, diol **6** was converted in a Williamson ether

synthesis into **7** (1-iodododecane, K_2CO_3, DMF, 71% yield). Finally, the boronic ester **8** was prepared from **7** (BuLi, THF, - 78 °C, then $(MeO)_3B$, 20 °C) and coupled in a Suzuki reaction with 6-acetamido-2-bromopyridine[5] ($[(C_6H_5)_3P]_4Pd$, Na_2CO_3, C_6H_6/H_2O, 80°C) to yield **2** (mp 147-148 °C) in 32% yield.

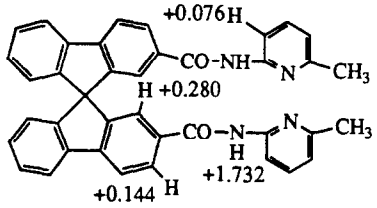


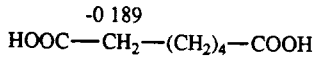
	R	R'
3	CH_3CO	H
4	CH_3CO	Br
5	CH_3COO	Br
6	HO	Br
7	$CH_3(CH_2)_{11}O$	Br
8	$CH_3(CH_2)_{11}O$	$B(OMe)_2$



Investigations into the receptor potential of the two clefts **1** and **2** in dry $CDCl_3$ at 293 K revealed major differences between the two derivatives. Host **1** forms stable solution complexes with selected aliphatic α,ω-dicarboxylic acids,[8] whereas a significant complexation of these guests by **2** was not observed. With a 1.02 x 10^{-3} M solution of **1**, approximately 0.5 equivalents of solid adipic acid, HOOC-$(CH_2)_4$-COOH, which is quite insoluble in pure $CDCl_3$, are extracted into the liquid phase. As an indication for host-guest complexation in this solution, the ^1H NMR resonance of the amide protons on **1** was shifted downfield by 1.01 ppm compared to the signal of the free host (δ 8.27 ppm). The larger solubility of glutaric acid, HOOC-$(CH_2)_3$-COOH, and pimelic acid, HOOC-$(CH_2)_5$-COOH, allowed a quantitative evaluation of the stability of their complexes with **1**. In ^1H NMR binding titrations at constant host concentration, the complexation-induced shifts of selected fluorene and pyridine protons were evaluated (Figure 1). Alternatively, the upfield complexation-induced shift of the α-CH_2 resonance was monitored in titrations at constant substrate concentration. The binding data obtained from both types of titrations were in satisfactory agreement for each guest. The 1:1 stoichiometry of the complexes was confirmed in the analysis of Job plots.[9] For the **1**·pimelic acid complex, the association constant was determined as $K_a = (1.7 \pm 0.4) \times 10^3$ L mol^{-1} ($\Delta G^o = -4.3 \pm 0.2$ kcal mol^{-1}) Having a $K_a = (7.6 \pm 1.5) \times 10^3$ L mol^{-1} ($\Delta G^o = -5.2 \pm 0.2$ kcal mol^{-1}), the complex of glutaric acid is significantly more stable. Receptor **1** is not effective in solubilizing and binding succinic acid, HOOC-$(CH_2)_2$-COOH. The spirobifluorene **2** does not form stable complexes with any of the dicarboxylic acids, independent of their size. For example, at [**2**] = 1.95 x 10^{-3} M and [pimelic acid] = 8.5 x 10^{-3} M, the amide resonance at the cleft shifts downfield by only 0.3 ppm.

Figure 1: Complexation-induced changes in ^1H NMR chemical shift at saturation binding, $\Delta\delta_{sat}$ (ppm; + = downfield), calculated for host and guest protons in the **1**·pimelic acid complex.



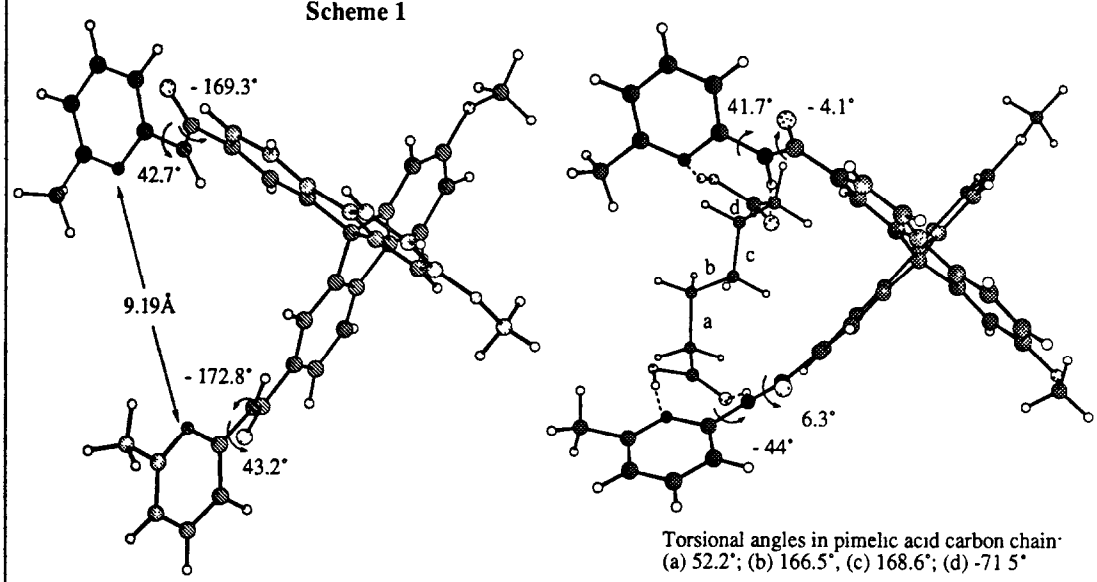


To gain more insight into the differing complexation properties of **1** and **2**, a gas phase conformational analysis of the free clefts and their 1:1 complexes with dicarboxylic acids was undertaken. All calculations in this ongoing analysis are performed with the all-atom AMBER force field as implemented in the Macromodel 3.0 program.[10] Monte Carlo multiple minimum searches are executed with the BATCHMIN routine in the same

program. This conformational analysis accurately reproduces the X-ray crystal structure of the adipic acid complex published by Hamilton *et al.*[4,11]

Scheme 1 shows the lowest energy conformations found for a cleft, which is identical to **1** except for the addition of two CH_3O groups at the remote 7,7'-positions, and its complex with pimelic acid. The differences in the geometries of free and complexed host are remarkably small.[11] The guest is bound by four non-ideal hydrogen bonds between the two carboxylates and the two amidopyridine residues. To undergo this fourfold oriented bonding, pimelic acid adopts a U-type shape with favorable anti-type torsional angles in its extended central part and two gauche-type dihedral angles at the termini (Scheme 1). According to the modeling, the complexation by **2** is much weaker since the substrates are unable to undergo fourfold hydrogen bonding while maintaining favorable torsional angles in their aliphatic chains.[12]

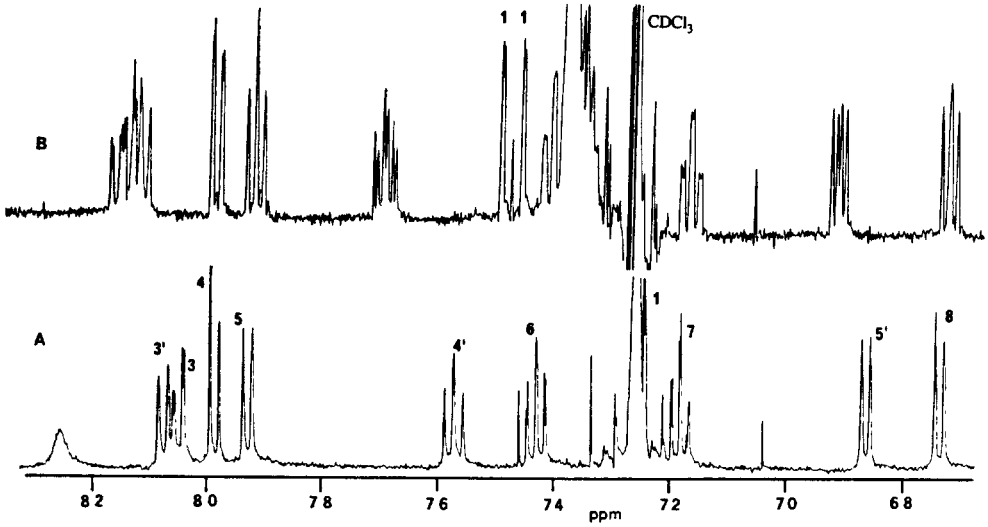
Scheme 1



Torsional angles in pimelic acid carbon chain: (a) 52.2°; (b) 166.5°, (c) 168.6°; (d) -71 5°

Chiral recognition was observed in the complexation between (*R,S*)-**1** and *N*-benzyloxycarbonyl-L-glutamic acid (*N*-Cbz-Glu). Figure 2 shows the aromatic resonances of host and guest in a solution containing [(*R,S*)-**1**] = 9.7 x 10^{-4} M and [*N*-Cbz-Glu] = 3.25 x 10^{-3} M Differential chemical shifts are clearly observed for all host resonances in the two stable diastereomeric complexes that are formed. An ^1H NMR titration with the racemic cleft ([(*R,S*)-**1**] = 9.7 x 10^{-4} M and [*N*-Cbz-Glu] = 0.6 - 6.0 x 10^{-3} M) provided preliminary evidence for different stabilities of the two diastereomeric complexes. In the two complexes, saturation binding was reached at significantly different concentrations of *N*-Cbz-Glu. At the titration endpoint, the cleft amide resonances in the two diastereomeric complexes appeared as a very broad signal around 10.83 ppm, as much as 2.54 ppm downfield from this resonance in the free receptor. Following optical resolution[6] of **1**, the chiral recognition properties of this readily available cleft will be studied in great detail.

Figure 2: ^{1}H NMR spectra (500 MHz, 293 K, $CDCl_3$) of (A) free (*R,S*)-**1** and (B) of a solution containing [(*R,S*)-**1**] = 9.7 x 10^{-4} M and [*N*-Cbz-Glu] = 3.25 x 10^{-3} M.



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[10] Macromodel 3.0, Professor W. C. Still, Columbia University, New York.

[11] For the complex published by Hamilton (ref. 4), Monte Carlo simulations (five 100-step searches) yielded 4 structures within 6 kcal mol^{-1} of the global minimum. For the pimelic acid complex shown in Scheme 1, a similar search yielded 4 low energy structures; the second being 2.3 kcal mol^{-1} higher in energy than the structure shown.

[12] Although the spirobifluorenes **1** and **2** are similar in structure, the distances between the hydrogen bonding sites in both clefts are markedly different. Characteristic distances in the lowest energy conformations of the free receptors are: Cleft **1**: 9.19 Å (N···N pyr); 7.59 Å (N···N amide); 6.53 Å (H···H amide). Cleft **2**: 7.45 Å (N···N pyr); 9.97 Å (N···N amide); 10.39 Å (H···H amide).

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