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# New chiral solvating agents for carboxylic acids: discrimination of enantiotopic nuclei and binding properties

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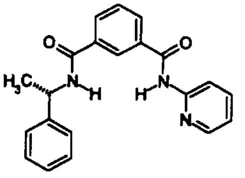
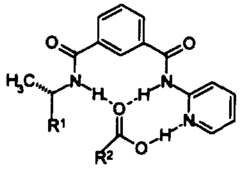
***Abstract:*** New chiral hosts for carboxylic acids have been synthesized and their capacity for discrimination of enantiotopic nuclei explored by NMR. In addition, binding properties were examined by $^1H$ NMR titration experiments and molecular mechanics calculations. © 1997 Elsevier Science Ltd. All rights reserved.

In recent years many chiral solvating agents (CSAs) have been developed[1] for the determination of enantiomeric excess by $^1H$ NMR. For carboxylic acids good results were achieved with chiral amines,[2] amino alcohols[3] and diamines[4] as reagents, i.e., by formation of diastereomeric salts. We recently developed a reagent of type **A**[5] binding its guest molecules mainly by hydrogen bonding.[6] Our previous results[5] indicated binding by three coplanar hydrogen bonds in complex **B**, leading to a marked differentiation of internally or externally diastereotopic protons by differential shielding effects of the aryl group at the stereogenic center of the bound species. However, results of molecular mechanics calculations raised doubts: the most stable structures of complex **B** with $R^1$=Ph calculated, were such that the planes of the two amide moieties were rotated out of coplanarity with the central isophthaloyl group (see Figure 1). The positioning of the guest acid in this bent host conformer did not allow the unambiguous assignment of the phenyl ring as the sole reason for diastereotopic interactions. There also could be a significant contribution by the induced chirality of the isophthaloyl group. Therefore, we decided to prepare further hosts of type **A** in which the previously used 1-(*S*)-phenylethyl group would be replaced by sterically similar, yet electronically different residues in order to understand better the interaction between $R^1$ and $R^2$.



**A**



**B**

Previously,[5] **A** was synthesized in four steps starting from monomethyl isophthalate which was first transformed into the (*S*)-1-phenylethylamide and this was then hydrolyzed. The corresponding pentafluorophenyl ester was reacted with 2-aminopyridine to give **A**. Here we present an even simpler and more general route to the hosts (*S*)-**1**, (*S*)-**2** and (*S*)-**3**, which allows the introduction of the chiral group in the very last step (Scheme 1): starting from methyl isophthalate a 2-pyridyl amide is formed which is hydrolyzed to give a carboxylic acid. The acid is transformed into the imidazolide,[8] and this is then coupled with a chiral amine.

The amides (*S*)-**1**–(*S*)-**3** were tested for their ability to induce chemical shift anisochronies of enantiotopic protons with various carboxylic acids as their guests by adding one equivalent of the reagent to a 0.25 M solution of the carboxylic acid in $CDCl_3$.[5] The results are summarized in Table 1. Generally, large shift anisochronies were observed for carboxylic acids with an aryl group in $R^2$.

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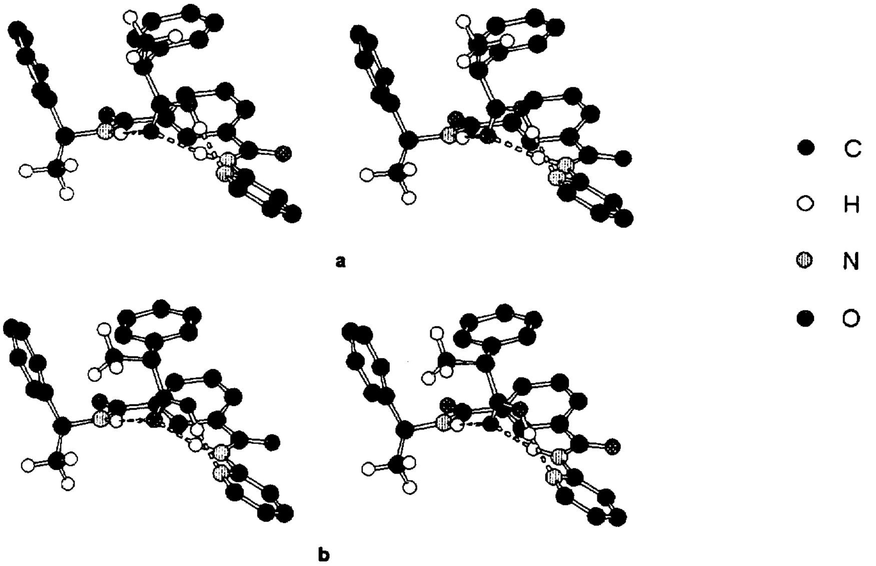
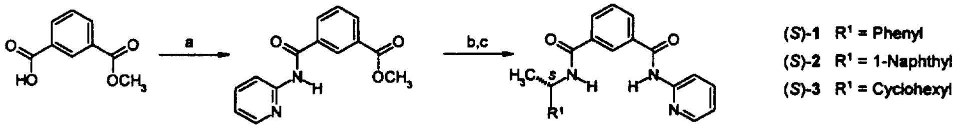


**Figure 1**. Stereo views of the calculated AMBER* minimum[7] of the complex of (*S*)-**1** with (**a**) (*S*)- and (**b**) (*R*)-hydratropic acid (**F**). Within an energy range of 10 kJ mol$^{-1}$ all other local minima showed similar structures.



[a] $(COCl)_2$ (5 equivalents), toluene; 2-aminopyridine (1.2 equivalents), $NEt_3$ (1.2 equivalents), THF, 24 h, rt, 72 %. [b] LiOH (2 equivalents), THF/MeOH/$H_2O$ = 3:1:1, rt, 4 h, 94 %. [c] $SOCl_2$ (1.2 equivalents), imidazole (4.8 equivalents), $CH_2Cl_2$, -20 °C; R*$NH_2$ (1.2 equivalents), -20 °C → rt, 24 h, 56 % for (*S*)-1, 50 % for (*S*)-**2**, 64 % for (*S*)-**3**.

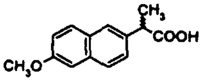
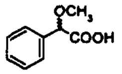
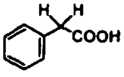
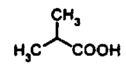
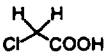
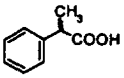
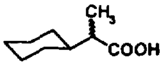
Scheme 1.

While replacement of the phenyl [(*S*)-**1**] by a naphthyl [(*S*)-**2**] group resulted in markedly increased shift anisochronies (up to 0.283 ppm for naproxene), host (*S*)-**3** [$R^1$=(*S*)-cyclohexyl] did not induce a measurable anisochrony in any of the substrates. Nevertheless, host–guest bonding in the latter case occurred as proven by the strong low field shift of the host amide protons. The data given in Table 1 strongly suggest that the substituent $R^1$ rather than the isophthaloyl group causes the observed shift anisochronies $\Delta\delta_H$. We attribute the higher $\Delta\delta_H$ for $R^1$=naphthyl than for $R^1$=phenyl to the larger magnetic anisotropic effect of the naphthyl group.

In order to further assess the importance of an aryl group for the shift differences of diastereotopic nuclei, we investigated the interaction of hosts (*S*)-**1** and (*S*)-**2** with hydratropic acid (**F**), containing an aryl group and α-cyclohexylpropionic acid (**G**), with a nonaromatic group. In addition to chemical shift differences, association constants were determined[9] (cf. Table 2). To both hosts, guest **F** was stronger bound than guest **G**; this demonstrates the importance of the aryl group. Surprisingly, homochiral guests showed different modes of association for (*S*)-**1** and (*S*)-**2**: whereas for (*S*)-**1** the (*S*)-enantiomer of both guests was stronger bound than the (*R*)-enantiomer, with (*S*)-**2** the experiment produced the opposite result for (*R*)- and (*S*)-**F**. Here, the (*R*)-enantiomer showed a stronger association than the (*S*)-enantiomer.

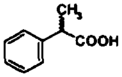
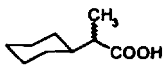
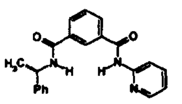
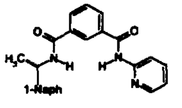
In order to understand these results better we carried out molecular mechanics calculations (MacroModel[7]) on the various host–guest complexes. In addition to locating energy minima, calculations of free energy differences were performed and the results compared with those obtained

Table 1. $^1H$ NMR shift non equivalence observed for carboxylic acids in $CDCl_3$ (293 K)[a]

| Host | Guest | | Observed resonance | $\Delta\delta_H$ [ppm][b] | Observed resonance | $\Delta\delta_H$ [ppm][b] |
|---|---|---|---|---|---|---|
| (*S*)-1 |  | A | $\alpha$-H | 0.084 (*R*) | $\alpha$-$CH_3$ | — |
| (*S*)-2 | | | | 0.283 (*R*) | | 0.038 (*R*) |
| (*S*)-3 | | | | — | | — |
| (*S*)-1 |  | B | $\alpha$-H | 0.078 (*R*) | $\alpha$-$OCH_3$ | — |
| (*S*)-2 | | | | 0.273 (*R*) | | 0.022 (*R*) |
| (*S*)-3 | | | | — | | — |
| (*S*)-1 |  | C | $\alpha$-H | 0.054 | | |
| (*S*)-2 | | | | 0.128 | | |
| (*S*)-3 | | | | — | | |
| (*S*)-1 |  | D | | | $\alpha$-$CH_3$ | 0.025 |
| (*S*)-2 | | | | | | 0.065 |
| (*S*)-3 | | | | | | — |
| (*S*)-1 |  | E | $\alpha$-H | 0.019 | | |
| (*S*)-2 | | | | 0.060 | | |
| (*S*)-3 | | | | — | | |
| (*S*)-1 |  | F | $\alpha$-H | 0.077 (*R*) | $\alpha$-$CH_3$ | 0.018 (*R*) |
| (*S*)-2 | | | | 0.279 (*R*) | | 0.020 (*R*) |
| (*S*)-3 | | | | — | | — |
| (*S*)-1 |  | G | $\alpha$-H | 0.116 (*R*) | $\alpha$-$CH_3$ | 0.033 (*R*) |
| (*S*)-2 | | | | 0.011 (*R*) | | 0.044 (*R*) |
| (*S*)-3 | | | | — | | — |

[a] Conditions: 0.25 M solution in $CDCl_3$, ratio host : guest = 1 : 1. All spectra were recorded at 300 MHz.
[b] In brackets: configuration of the enantiomer corresponding to the signal at higher field.

Table 2. Experimental association constants $K_a$ [l $mol^{-1}$] of the host–guest complexes of (*S*)-1 and (*S*)-2 with **F** and **G**

| | |  | |  | |
|---|---|---|---|---|---|
| | | (*S*)-F | (*R*)-F | (*S*)-G | (*R*)-G |
|  | (*S*)-1 | 1100 | 700 | 600 | 260 |
|  | (*S*)-2 | 860 | 1120 | 500 | 330 |

by NMR titration experiments (Table 3). With host (*S*)-**1** there is agreement: the computational results as well as the experiment indicated a stronger binding of the (*S*)-enantiomers of **F** and **G** than the (*R*)-enantiomers. However, with (*S*)-**2** as host for both guests, calculations gave higher association constants for the (*S*)- than the (*R*)-enantiomers, whereas the experiment showed stronger association for (*R*)-**F** than for (*S*)-**F**. We assume that for the combination (*S*)-**2** and **F** the MacroModel simulation only insufficiently represents the real structure of the complex. All structures of **F** and **G** and the two hosts (*S*)-**1** and (*S*)-**2** obtained by modeling are similar to those shown in Figure 1: in all cases the substituent at $C_\alpha$ (phenyl or cyclohexyl) of the guest is located on the upper side of the isophthaloylic group of the host. Presumably for (*S*)-**2** and **F** $\pi$-stacking effects, which cannot be sufficiently assessed by MacroModel calculations, lead to a stronger binding of the (*R*)- than the (*S*)-enantiomer of **F**.

**Table 3**. Experimental and calculated (*italic*) $\Delta G_S - \Delta G_R$ values [kJ mol$^{-1}$] of the complexes of the hosts (*S*)-**1** and (*S*)-**2** with both enantiomers of the guests **F** and **G**

| | F |
|---|---|
| (*S*)-1 | -1.12 (*-3.52*) |
| (*S*)-2 | +0.65 (*-0.96*) |
| | G |
| (*S*)-1 | -2.07 (*-2.43*) |
| (*S*)-2 | -1.03 (*-0.55*) |

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7. (a) W. C. Still *MacroModel v. 4.5*, Columbia University, New York, 1994. (b) The minimized host and guest structures were used as input for a conformational search by using a 1000 step Monte Carlo method conducted with the AMBER* forcefield and the GB/SA $CHCl_3$ solvation model as implemented in MacroModel v. 4.5, cf. W. C. Still, A. Tempczyk, R. C. Hawley, T. Hendrickson, *J. Am. Chem. Soc.* **1990**, *112*, 6127.
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