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# An azamacrocyclic receptor as efficient polytopic chiral solvating agent for carboxylic acids

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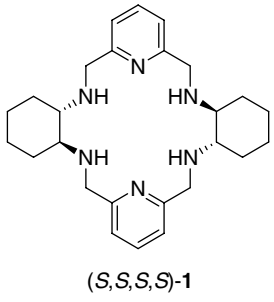
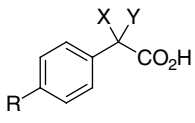
**Abstract**—The efficient use of a polyazamacrocycle as chiral solvating agent (CSA) for the determination of the enantiomeric excess of different carboxylic acids has been studied. All the data agree with the formation of multimolecular diastereomeric complexes in solution, which render good splitting of the NMR signals for the enantiomers of the acids (up to $\Delta\Delta\delta = 0.20$ ppm) using a small amount (even 0.125 equiv) of the receptor.


Considering the importance of chiral species in biological and pharmaceutical chemistry,[1] there is a need for the easy and fast measurement of the enantiomeric excess (ee) of chiral organic molecules.[2] Among others, methods based on NMR spectroscopy have the advantages of easy performance and accessibility.[3] Thus, very usually, there is no need for special equipment, apart from the commonly used NMR spectrometers, or complicated methodology for their accurate application. As enantiomers cannot be distinguished in an achiral environment, these techniques require the modification of the chiral analyte by the reaction or simple non-covalent interaction with a chiral shift agent (CSA) that would convert the mixture of enantiomers into a mixture of diastereomeric molecular or supramolecular species. Ideally, these diastereomeric species will show anisochrony in some of their NMR signals. Then, the integration of these bands can be directly related to the enantiomeric composition of the analyte.[4] The advantage of using non-covalent CSAs relies on the possibility of carrying out the experiment in situ, with no further purification steps.[5] Besides, the starting chiral materials, analyte and CSA, could be recovered after the measurement. In contrast to the large number of non-covalent CSAs described for amines,[6] alcohols,[7] ammonium salts,[8] and aromatic compounds,[9] there are relatively few reports on efficient examples for carboxylic acids,[10] in spite of the presence of this function in many biologically and economically important compounds.[11]

Previous studies showed that macrocycle **1**[12] (Scheme 1) displayed unprecedented enantioselectivity for the

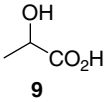



(*S*,*S*,*S*,*S*)-**1**

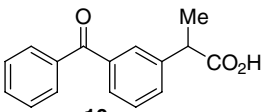



**2-8**

**2** (R=H, X=OH, Y=H)
**3** (R=Cl, X=OH, Y=H)
**4** (R=OMe, X=OH, Y=H)
**5** (R=H, X=OMe, Y=H)
**6** (R=H, X=NHBoc, Y=H)
**7** (R=H, X=Me, Y=H)
**8** (R=H, X=OMe, Y=$CF_3$)




**9**




**10**

**Scheme 1.** Chemical structures of the receptor (*S*,*S*,*S*,*S*)-**1** and the carboxylic acids (**2**–**10**) studied herein.

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molecular recognition of malate dianion in aqueous solution.[13] The $D_2$ symmetrical chiral structure of this receptor provides a highly asymmetric environment. The presence of four protonable amino groups[13] would lead to the formation of the corresponding diastereomeric salts with chiral carboxylic acids. Besides, the two pyridine moieties could display additional interactions (H-bonding, solvophobic or π–π interactions) and highly anisotropic environments due to the electronic π-cloud of the aromatic rings. Taking all this into account, we envisioned the possibility of using (*S*,*S*,*S*,*S*)-**1** as a CSA for the fast measurement of the ee of carboxylic acids.

The structures of different chiral carboxylic acids (**2**–**10** in Scheme 1) were selected in order to map different possible residues attached to the chiral center (aromatic, aliphatic, polar, non-polar, H-bonding acceptor or donor). Thus, we could demonstrate the scope and limitations of the practical applicability of **1** as CSA. The experiments were carried out by adding increasing amounts of (*S*,*S*,*S*,*S*)-**1** to a solution of the racemic acid (**2**–**10**) in $CDCl_3$ (20 mM). Immediately after each addition, $^1$H NMR spectrum was acquired in a 300 MHz spectrometer at room temperature (Supplementary data for experimental details). Different acid to receptor molar ratios were analyzed. Table 1 shows selected values for the induced chemical shifts ($\Delta\delta$) and the splitting between signals corresponding to each enantiomer of the acids ($\Delta\Delta\delta$) after addition of **1**. For all the tested examples, the signals for the protons attached to the asymmetric carbon of the substrate were split. However, only the acids possessing a heteroatom in the α position presented baseline resolution that was good enough for an accurate integration (Fig. 1 for a selected example, the rest is given in the Supplementary data). For the other cases (**7** and **10**), signal de-convolution was necessary for the integration of the peaks.[14] Therefore, for the best splitting, the presence of an electronegative group attached to the stereogenic center should be advisable.

It is interesting to note that chiral discrimination was also observed for OMe signals of **4**, **5**, and **8**, which are further from the stereocenter. On the other hand, the splitting for lactic (**9**) acid demonstrates that the presence of an aromatic ring in the substrate is not necessary for the diastereomeric signal separation as, for **9**, the $C^{\alpha}H$ $^1$H NMR signal was also successfully resolved (see Supplementary data).

Some other remarkable facts should be commented from the data gathered in Table 1. First of all, the signals from the acids move upfield ($\Delta\delta < 0$), suggesting a deprotonation of the carboxylic group. Only NH proton from *N*-Boc-phenylglycine (**6**) resonates at lower field ($\Delta\delta = 0.49$) upon the addition of the receptor, which can be interpreted as the establishment of a stronger intramolecular hydrogen bond with the carboxylate anion thus formed.[15] Concomitantly, signals from the receptor move downfield, which clearly indicated the proton transfer from the acid to the receptor, leading to the corresponding diastereomeric salts. These salts are expected to form intimate ionic pairs in $CDCl_3$, rendering the observed anisochronic nuclei in NMR for the corresponding enantiomers of the acids. Besides, a simple analysis of the protonation state of **1** can be performed by monitoring the chemical shift of the signal of protons attached to the chiral center of the receptor (H1). Since this macrocycle is able to accept four protons, it is expected that the chemical shift of the compound with an excess of trifluoroacetic acid (TFA) corresponds to the tetraprotonated species (Fig. 2). This H1 chemical shift value is similar to those of the examples exhibiting larger splitting in the CSA experiments (see Supplementary data). Thus, the tetraprotonated species of **1** seemed to be the actual CSA in most of the cases. This proposal also correlates with the fact that the best splitting corresponded to the acids bearing an electronegative atom in the α position, which increases the acidity of the carboxylic group, favoring the above-mentioned proton transfer from the acid to the receptor.

**Table 1.** Selected induced shift ($\Delta\delta$) and splitting ($\Delta\Delta\delta$) for the formation of diastereomeric complexes between (*S*,*S*,*S*,*S*)-**1** and different carboxylic acids (**2**–**10**) measured by NMR (300 MHz, 20 mM in $CDCl_3$)

| Acid | Molar ratio[a] (*S*,*S*,*S*,*S*)-**1**:acid | Signal | $\Delta\delta$[b] (ppm) | $\Delta\Delta\delta$ (ppm) | $\Delta\Delta\delta$ (Hz) |
|---|---|---|---|---|---|
| **2** | 1:8 | $C^{\alpha}H$ | −0.51 | 0.18 | 55 |
| **3** | 1:4 | $C^{\alpha}H$ | −0.60 | 0.15 | 45 |
| **4** | 1:4 | $C^{\alpha}H$ | −0.57 | 0.19 | 57 |
| **4** | 1:4 | OMe | −0.06 | 0.02 | 5 |
| **5** | 1:1 | $C^{\alpha}H$ | −0.30 | 0.05 | 14 |
| **5** | 1:1 | OMe | −0.13 | 0.04 | 11 |
| **6** | 1:8 | $C^{\alpha}H$ | −0.35 | 0.07 | 20 |
| **6** | 1:8 | N*H* | 0.49 | 0.20 | 59 |
| **7** | 1:1 | $C^{\alpha}H$ | −0.29 | 0.02 | 7 |
| **7** | 1:1 | Me | −0.15 | — | — |
| **8** | 1:1 | OMe | −0.09 | 0.09 | 27 |
| **8** | 1:1 | $CF_3$[c] | −0.54 | 0.07 | 22 |
| **9** | 1:4 | $C^{\alpha}H$ | −0.47 | 0.20 | 60 |
| **9** | 1:4 | Me | −0.33 | 0.08 | 25 |
| **10** | 1:1 | $C^{\alpha}H$ | −0.32 | 0.02 | 4 |
| **10** | 1:1 | Me | −0.17 | 0.01 | 3 |

[a] Values showing maximum splitting.
[b] Averaged between signals from both enantiomers.
[c] Measured in the $^{19}$F NMR spectra.

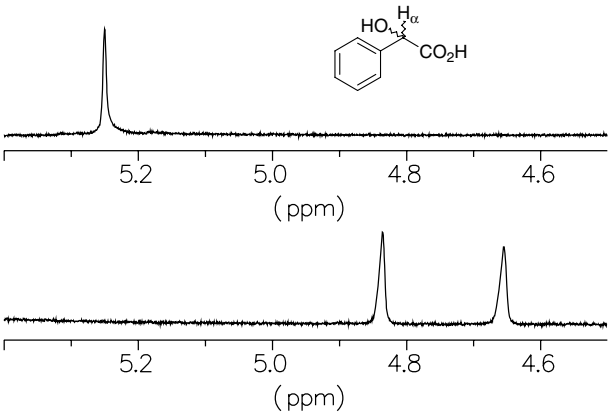


**Figure 1.** Partial $^1$H NMR spectra showing C$^\alpha$H signal for racemic **2** (20 mM, $CDCl_3$, 300 MHz, 25 °C) in the absence (upper trace) and in the presence (lower trace) of 0.125 equiv of (*S*,*S*,*S*,*S*)-**1**.

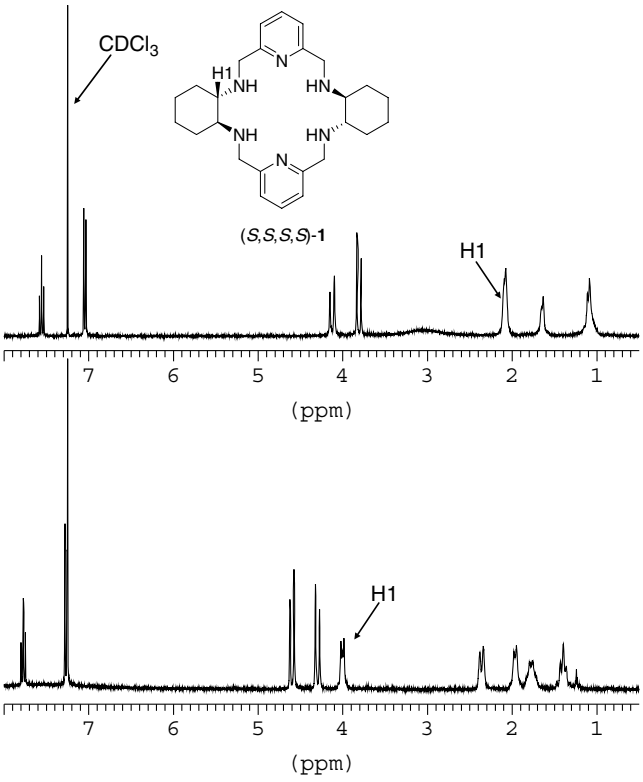


**Figure 2.** $^1$H NMR spectra of (*S*,*S*,*S*,*S*)-**1** (20 mM, $CDCl_3$, 300 MHz, 25 °C) alone (upper trace) and in the presence of a 8-fold excess of trifluoroacetic acid (lower trace).

On the other hand, for most of the tested examples, the amount of CSA necessary for splitting of the signals was lower than the amount of acid. For instance, the very low proportion (0.125 equiv with respect to the acid, Table 1) needed with mandelic acid (**2**) was particularly welcome. Interestingly, the splitting was eliminated when an excess of receptor was added. These data suggest the formation of multimolecular complexes. Accordingly, Job's plot analysis was performed for each enantiomer of **5** (Fig. 3) in separate experiments, showing a clear 1:4 receptor:acid stoichiometry for both enantiomers of the acid. These experiments also agree with a tetra-protonation state of the macrocycle in the optimal supramolecular complexes. Unfortunately, the complicated pattern of interconnected equilibria between different species and chiral configurations makes the unambiguous measurement of binding constants and the proposal of models for the interaction very difficult tasks.[16]

Finally, we attempted to demonstrate the practical applicability of our method for the measurement of the enantiomeric excess of carboxylic acids. With this aim, samples containing different proportions of both enantiomers of **5** were prepared and analyzed with our methodology (Fig. 4). Integration of the corresponding C$^\alpha$H $^1$H NMR signals rendered measured ee's showing an excellent linear correlation with the prepared ones ($R^2 = 0.996$). Besides, the experiments were carried out using a 1:6 receptor:substrate molar ratio, highlighting the polytopic nature of the CSA receptor.

In summary, macrocyclic receptor **1** has shown to be an efficient CSA for the fast and easy determination of the ee of carboxylic acids. Our study of the system shows that this compound acts as a polytopic receptor, binding

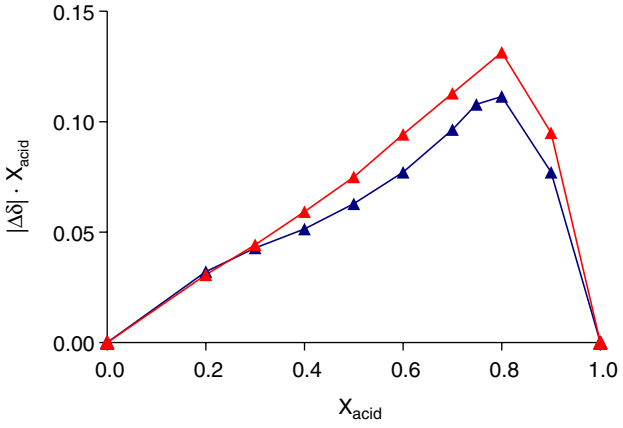


**Figure 3.** Job's plot obtained for (*S*,*S*,*S*,*S*)-**1** and either (*S*)-**5** (red) or (*R*)-**5** (blue). The signal corresponding to the OMe group was used in both cases.

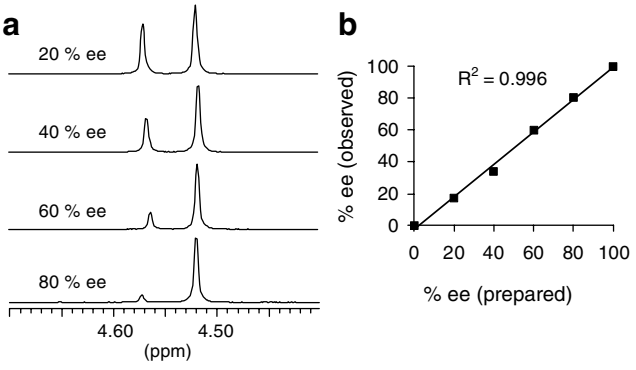


**Figure 4.** (a) Selected region of the 300 MHz $^1$H NMR spectra of (*S*)-**5** with various enantiomeric purities (20 mM) in the presence of 0.167 equiv of (*S*,*S*,*S*,*S*)-**1**. (b) Correlation between theoretical and observed % ee values.

up to four molecules of the substrate. Despite the complicated equilibrium pattern present in solution, very good splitting of the signals was obtained after addition of a very small amount of the CSA. The high symmetry and very simple $^1$H NMR spectrum of our CSA decrease the possibility of large overlapping with signals of the substrate. The formation of the diastereomeric complexes is fast and quantitative, being possible its in situ analysis in an easily accessible 300 MHz NMR spectrometer at room temperature and without previous purification. Moreover, as the interaction between receptor and substrate is non-covalent and pH dependent, both compounds can be separated and recovered by a simple acid–base extraction procedure. The synthesis of **1** has been carried out from commercially available materials in a high yield one-pot two-step process, with no need for chromatographic purification.[12] Thus, all these advantages make our methodology very attractive for the practical application of **1** as a CSA for carboxylic acids.

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## Supplementary data

Experimental details and full spectra of racemic **2**–**10** in the presence of different proportions of (*S*,*S*,*S*,*S*)-**1**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.154.

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15. Interestingly, the presence of the macrocycle also affects the proportion of rotamers in the carbamate bond of **6**.
16. We also tried NOESY and ROESY experiments with the complex [*rac*-**5** + (*S*,*S*,*S*,*S*)-**1**] using different mixing times but, unfortunately, we did not observe unambiguous intermolecular NOE effects between receptor and substrate.