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Preliminary Communications

A New Chiral Solvating Agent for Carboxylic Acids Based on Directed Hydrogen Bonding

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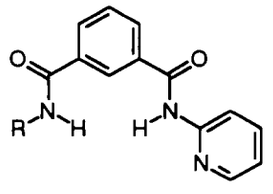
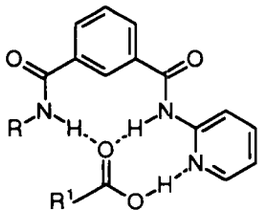
Abstract. Readily available structural modules were combined to a new chiral receptor for carboxylic acids which shows triple hydrogen-bonding to various substrates. Large chemical shift anisochronies were observed with chiral and prochiral carboxylic acids.

Many years ago it was demonstrated[1] that mixtures of enantiomeric carboxylic acids can be readily analyzed by formation of diastereomeric amides followed by NMR analysis (external diastereotopicity) or LC separation. Chiral recognition *via* covalent derivatives has the advantage of high predictive power by models based on conformational analysis, but the disadvantage of additional preparative steps and dependence of an enantiomeric excess (ee) determination on the enantiomeric purity of the reagent. Furthermore, the differentiation of enantiotopic H's in α-position to the COOH group was unsatisfactory (although good results were obtained with esters of chiral alcohols). In the meantime, advances in host-guest chemistry have led to a number of chiral solvating agents[2] (CSA's), which allow the rapid determination of ee's by ^{1}H NMR. The best results for carboxylic acids were achieved with chiral amines[3], amino alcohols[4] and diamines[5] as reagents. As the success in these cases is based on the formation of diastereoisomeric salt complexes, we wondered whether a reagent might be found which would bind its guest molecules mainly by hydrogen bonding, thus leading to a type of associate that is easily prepared and allows clear correlation of structural and spectroscopic properties.



A

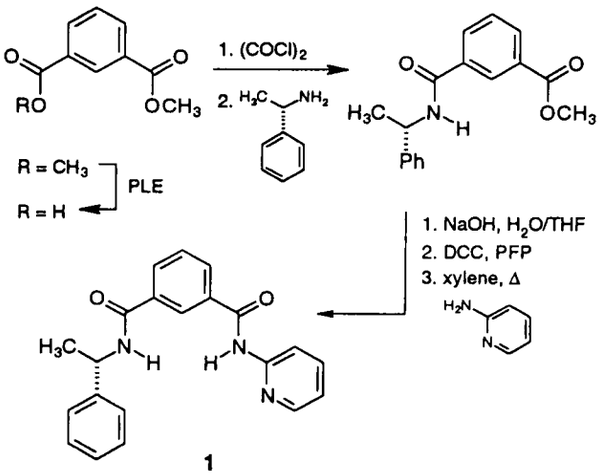


B

Our analysis suggested a system of type **A**. These host molecules show triple hydrogen bonding to carboxylic acids as depicted in **B**[6]. With a chiral group R, these receptors should lead to external or internal chiral recognition.

As first compound of this type we prepared the diamide **1** (Scheme 1), starting from dimethyl isophthalate which was selectively hydrolyzed to monomethyl isophthalate (catalysis by pig liver esterase, yield: 94 %); this was transformed into the corresponding (*S*)-1-phenylethylamide (88 %) *via* the acyl choride. The ester amide was hydrolyzed (72 %) and transformed to the pentafluorophenyl ester[7] (87 %). Heating this ester with an excess of 2-aminopyridine in boiling xylene produced the target compound **1** in 92 % yield.

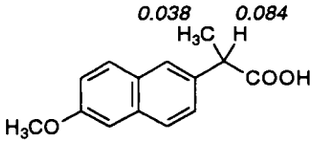
Scheme 1



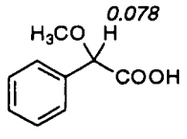
1

External Diastereotopicity. - Host **1** was tested under standard conditions in combination with various chiral and prochiral carboxylic acids: ca. 25 mM solutions[8] of the respective carboxylic acid and 1 eq. of **1** in $CDCl_3$ were used in ^{1}H NMR experiments which invariably showed large chemical shift anisochronies. These ranged from 0.009 to 0.2 ppm, depending on the type of carboxylic acid and the signal observed. For the α-H typically a chemical shift nonequivalence of ca. 0.075 ppm (**2a**, **2b**) is found; α-halo-carboxylic acids (**2c**) display a particularly large difference of 0.2 ppm[9]. Steric bulk in the substrate acid leads to a value of

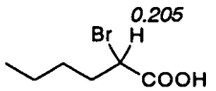
ca. 0.046 ppm (**2d**). A slightly lower value of ca. 0.038 is found for the CH_3 signal in α-methyl-carboxylic acids.



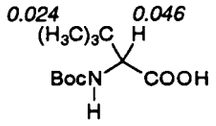
2a



2b



2c



2d

Because of the ready availability of either enantiomer of α-methoxyphenylacetic acid, we examined its interaction with host **1** more closely. The determination of the affinity of **1** for (-)-(*R*)- and (+)-(*S*)-α-methoxyphenylacetic acid in $CDCl_3$ gave K_{Ass}-values of 860 [$lmol^{-1}$] and 630 [$lmol^{-1}$], respectively[10]. The corresponding ΔG values of 16.5 and 15.7 [$kJmol^{-1}$] indicate triple hydrogen bonding[11]. In addition, a Job plot[12] of (±)-α-methoxyphenylacetic acid with **1** showed a maximum at the 1:1 complex, supporting the assumed mode of binding.

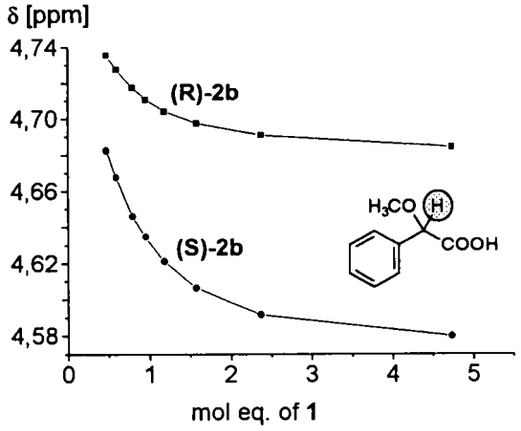
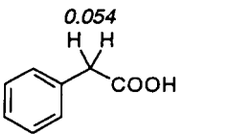


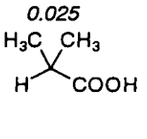
Fig. 1: Variation of the α-H-resonance of (±)-α-methoxyphenylacetic with increasing amount of added **1**

Another valuable feature of this new CSA is the dependence of the observed anisochrony on the ratio of **1**:acid. As shown in Figure 1 the addition of incremental amounts of **1** to a $CDCl_3$-solution of (±)-α-methoxyphenylacetic leads to a constant increase in the chemical shift non-equivalence of the α-H-resonance reaching saturation after addition of ca. 3 eq. Thus, in principle, the chemical shift non-equivalence can be tuned to allow for optimum baseline separation.

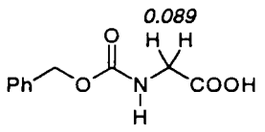
Internal Diastereotopicity. - Using experimental conditions as given above, we also tested prochiral carboxylic acids. Significant chemical shift differences were found both for internally enantiotopic methylene hydrogens of acids **3a** and **3c** and for internally enantiotopic CH_3 groups of isobutyric acid (**3b**).



3a



3b



3c

In conclusion, we have shown that host **1** is capable of forming multiple hydrogen bonds to carboxylic acids. The complexes formed with (pro-)chiral acids show large chemical shift anisochronies and can be employed for the convenient determination of enantiomeric excess of chiral carboxylic acids. We are currently examining other hosts of type **A** in order to obtain information on the origin of chemical shift non-equivalencies. Further work is directed at standardization of ee-determination and possibly the correct prediction of absolute configuration.

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8 Self aggregation of **1** was found to be negligible under our standard conditions.

9 The unusually high anisochrony of α-halo-carboxylic acids has been noticed before, see ref. 5.

10 Association constants were determined by non-linear regression analysis of the shift of the amide and various aromatic protons of **1** upon addition of acid according to *C. S. Wilcox*, "Frontiers in supramolecular organic chemistry and photochemistry", *H. J. Schneider* and *H. Dürr*, eds., VCH, Weinheim, 1991, p. 123.

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