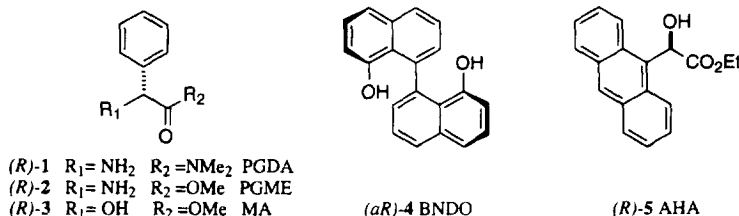# The use of ethyl 2-(9-anthryl)-2-hydroxyacetate for assignment of the absolute configuration of carboxylic acids by ^{1}H NMR

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Abstract: Both theoretical and experimental evidences prove that the absolute configuration of an α-chiral carboxylic acid can be safely assigned by comparison of the ^{1}H NMR spectra of its esters with *(R)*- and *(S)*-ethyl 2-(9-anthryl)-2-hydroxyacetate (**5**, AHA). A simplified conformational model, based on the dominance of the *ap* over the *sp* conformer and the selective effect of the anthryl group, allows the *(R/S)* assignment directly from the NMR chemical shifts. © 1997 Elsevier Science Ltd

The determination of the absolute stereochemistry of organic compounds by NMR of selected derivatives constitutes one of the most useful stereochemical techniques. In spite of its wide use, this methodology has been applied to very few organic functional groups and, in fact, only secondary alcohols and α-substituted primary amines have been fully investigated. In a recent publication[1] we showed preliminary results on the application of this method to primary alcohols and we now focus our attention on carboxylic acids because there are a large number of optically active organic compounds that present this functionality.

(R)-**1** R_1= NH$_2$ R_2 =NMe$_2$ PGDA
(R)-**2** R_1= NH$_2$ R_2 =OMe PGME
(R)-**3** R_1= OH R_2 =OMe MA

(aR)-**4** BNDO

(R)-**5** AHA

A few reports that correlate the absolute configuration of carboxylic acids with the NMR spectra of certain esters and amides have been recently published.[2] In those papers, auxiliary reagents *(R)*- and *(S)*-(**1–4**) are used and the configuration is derived in the usual way by comparison of the NMR spectra of the corresponding derivatives. Although the results of those studies are apparently good, the absence of reliable information about the conformational composition (structure, populations), the real influence of the aryl group on the substituents at the carboxylic acid part in each conformer and the sensitivity of the chemical shifts to the structure of the acids, limit the consideration of **1–4** as reagents for general application. Moreover, the models proposed are surprisingly identical for esters and amides, without conformational support and in conflict with former studies.[3]

In this communication we present theoretical[4] (Molecular Mechanics, semiempirical AM1 and aromatic shielding effect calculations) and experimental data (DNMR and testing with acids of known configuration) to support the conformational composition of the esters of carboxylic acids with *(R)*- and *(S)*-arylhydroxyacetates (i.e. **3**) and demonstrate that the absolute configuration of an α-chiral

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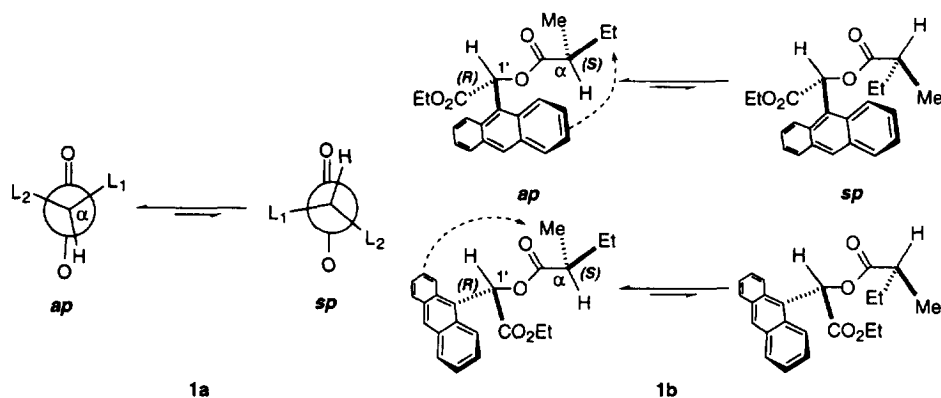
Figure 1.

carboxylic acid can be safely and better assigned by use of the new reagents (R)- and (S)-ethyl 2-(9-anthryl)-2-hydroxy-acetate (5, AHA) that are general for carboxylic acids.

It has already been shown that the alcohol part of an ester adopts a preferred conformation where $C_{1'}$–O–C=O are in a plane[5] and H–$C_{1'}$ is *syn (sp)* to the C=O.[3a] Therefore, to complete the conformational characteristics of the esters of a chiral carboxylic acid with auxiliary alcohols such as 3 or 5, only the behavior of the acid moiety remains to be studied. To this end, MM and semiempirical calculations were carried out on the structures of more than 20 different carboxylic acids — and their esters — comprising open chain and cyclic compounds with different substitutions (a selection is shown in Figure 2). MM calculations showed two main orientations around the C_α–CO bond, with either the H–C_α *antiperiplanar (ap)* or *synperiplanar (sp)* to the C=O (Figure 1a). Semiempirical calculations (AM1) predicted a preference of the *anti* over the *syn* conformer for all the acids searched by approximately 1.0 Kcal/mol. Thus, the corresponding esters are essentially constituted[6] by two conformers in equilibrium as represented in Figure 1b for the esters of (S)-2-methylbutyric acid with auxiliary alcohols (R)- and (S)-5.

In accordance with the structures shown and the steric position of the aromatic ring, different shieldings (and consequently, different chemical shifts) are expected in each conformer for the methyl and ethyl substituents at the acid part. Due to the conformational exchange, the observed NMR spectrum is averaged between the two conformers but dominated by the *ap* (the most populated one) and as a result, the signals of the ethyl group resonate at higher field (more shielded) in the ester with the (R)- than with the (S)-auxiliary reagent, while those corresponding to the methyl group resonate the opposite way: at higher field in the (S)- than in the (R)-ester. This outcome is usually expressed[7] in the form of $\Delta\delta^{RS}$, that has to be positive for the methyl protons and negative for the ethyl ones in the example shown.

Experimental support to those findings was obtained from low temperature NMR experiments on the esters of (S)-2-methylbutyric acid with auxiliary alcohols (R)- and (S)-5, selected on the basis of our previous experience.[8]

Thus, the NMR spectrum of the (R)-ester showed that the signal for the CH_2 group was shifted to higher field ($\Delta\delta^{T1,T2}$=0.022 ppm)[9] when the probe temperature was decreased from 300 to 203 K, while the methyl group was the one shifted to higher field ($\Delta\delta^{T1,T2}$=0.026 ppm) in the (S)-ester when the temperature was decreased to 193 K. These shifts are due to the increase of aromatic shielding associated with the increment of population of the most stable conformer (ap) at lower temperatures in both the (R)- and the (S)-esters (Figure 1b).

Additional experimental demonstration of the generality of the above results was obtained by comparison of the ^{1}H NMR spectra[10] of the esters of auxiliary reagents (R)- and (S)-5 with a series of
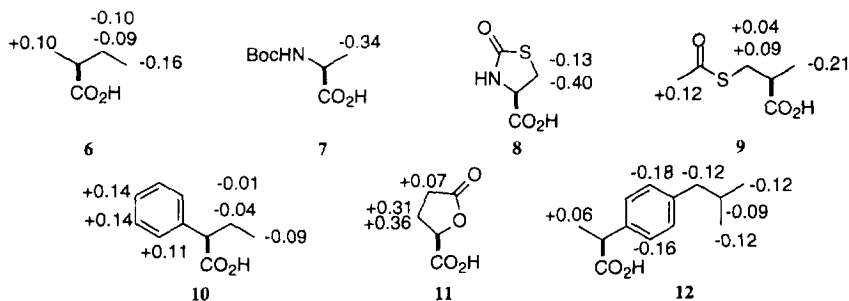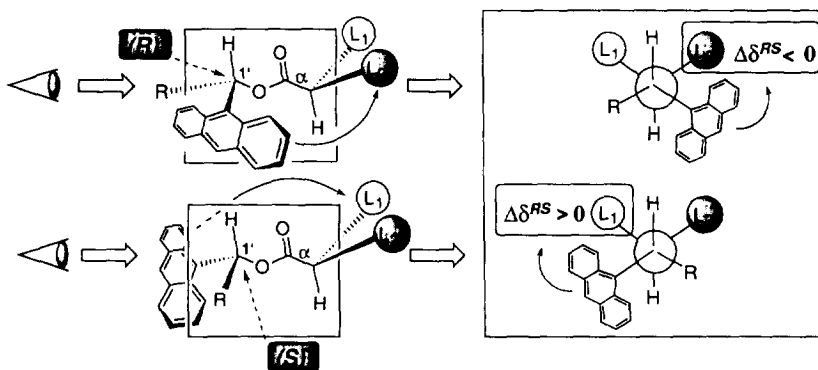
Figure 2.

Figure 3.

α-chiral carboxylic acids of known absolute configuration and miscellaneous structural characteristics. The structures of a selection (6–12) and the corresponding $\Delta\delta^{RS}$ values are shown in Figure 2.

As predicted, the signs of $\Delta\delta^{RS}$ are homogeneously distributed in all the compounds tested: they are positive for the substituent located at one side of the molecule and negative for those at the other side. The absolute configurations deduced by interpretation of those signs (considering the *ap* conformer as the most representative one in the average chemical shifts) are coincident in all cases with the real ones.

The magnitude of the $\Delta\delta^{RS}$ values are much higher than those obtained when the anthryl system is replaced by a phenyl group.[11] Moreover, 5 allows the use of protons several bonds away from the asymmetric center for the comparison of $\Delta\delta^{RS}$ (i.e. ibuprofen, 12).

In conclusion, the absolute configuration of a α-chiral carboxylic acid can be reliably determined by application of the conformational model indicated in Figure 3. The procedure consists on the identification of substituent L_2 as the one more shielded in the *(R)*- than in the *(S)*-ester (that is to say, it presents a negative $\Delta\delta^{RS}$), and substituent L_1 as the one more shielded in the *(S)*- than in the *(R)*-ester (positive $\Delta\delta^{RS}$). The absolute configuration at C_α is then deduced straightforward from the spatial location of L_1/L_2.

Further studies on other arylhydroxyacetates and aminoarylacetates are underway.

Acknowledgements

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4. MM, semiempirical and aromatic shielding effect calculations, were carried out as indicated in Ref. 3a.

5. To keep coherence with previous works (Ref. 3), $C_{1'}$ refers to the carbon bearing the hydroxyl group in the alcohol moiety, although it is carbon 2 in the systematic name.

6. Comparison of the aromatic shielding calculated for each conformer with the experimental value reveals an energy difference between conformers in good agreement with the AM1 calculated one.

7. $\Delta\delta^{RS}$ represents the difference between δ (ppm) in the *(R)*- and in the *(S)*-ester [$\Delta\delta^{RS}=\delta(R)-\delta(S)$].

8. Reagent **5** was chosen on the basis of the superior effectivity of the anthryl system over the phenyl (i.e. **3**) to obtain greater $\Delta\delta^{RS}$ values (see Ref. 3). *(R)*- and *(S)*-ethyl 2-(9-anthryl)-2- hydroxyacetate (**5**) were prepared by treatment of ethyl (9-anthryl)glyoxylate (Ref. 3a) with *(R)*- and *(S)*-alpine-borane® respectively and further purification by chiral HPLC. The absolute stereochemistries were confirmed by CD. *(R)*-**5**, $[\alpha]_D=-84$; *(S)*-**5**, $[\alpha]_D=+83.5$. For spectroscopic data of **5** (NMR, MS, UV, IR, CD), see Ref.3a.

9. $\Delta\delta^{T1,T2}$ represents the difference between δ (ppm) at the higher temperature (T_1) and at the lower temperature (T_2) [$\Delta\delta^{T1,T2}=\delta(T_1)-\delta(T_2)$].

10. ^{1}H NMR spectra were measured at 500.13 MHz in a Bruker AMX-500 spectrometer in CDCl$_3$ containing TMS as internal standard. The esters were prepared by the standard method (see Ref. 3a) without racemization and purified by HPLC. All compounds gave satisfactory elemental analysis and spectroscopic data.

11. For $\Delta\delta^{RS}$ values of the esters of acids **6** and **10** with alcohol **3**, see Ref. 2b.