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Determination of the Absolute Configuration of Alcohols by Low Temperature ^{1}H NMR of Aryl(methoxy)acetates

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Abstract: Aromatic shielding effects in esters of *(R)*- and *(S)*-aryl(methoxy)acetic acids (AMAAs) differ by a factor $\Delta\delta^{RS}$, which, due to changes in rotamer populations, was seen to increase in ^{1}H NMR spectra of esters of AMAAs **6** - **10** as NMR probe temperature (**T**) was decreased. For example, $\Delta\delta^{RS}$ for esters of **6** increased by more than 100% between T = 298 and T = 220 - 175 K (depending on the alcohol). By comparing $\Delta\delta^{RS}$ values obtained from low temperature ^{1}H NMR spectra of their esters with *(R)*- and *(S)*-AMAAs **6** - **10**, the absolute configuration of chiral alcohols can be reliably assigned.

First developed by Mislow, Dale, Mosher and Trost,[1] NMR methods for the determination of the absolute configuration of alcohols are attractive owing to the general availability of NMR spectrometers, the small sample required, and the fact that those samples are recoverable. In these methods, the chiral alcohol is esterified with the *(R)* and *(S)* enantiomers of an aryl(methoxy)acetic acid (AMAA), whose differing aromatic shielding effects are manifest by chemical shift differences ($\Delta\delta^{RS}$) in the NMR signals of certain protons of the alcohol. Fig. 1a shows how one substituent at the stereogenic centre of the alcohol (L_1) is shielded by the aryl ring in the ester of *(R)*-α-(methoxy)phenylacetic acid (*(R)*-MPA), while it is non-shielded in the *(S)*-MPA ester, in which L_2 is the shielded substituent. Comparison of the difference in the chemical shifts of corresponding L_1 (or L_2)[2] protons ($\Delta\delta^{RS}$; Fig 1a) may allow assignment of the absolute configuration of the alcohol. However, sometimes the observed value of $\Delta\delta^{RS}$ is so small that it falls within the range of experimental error, and there is thus a high risk of misassignment of configuration.[3]

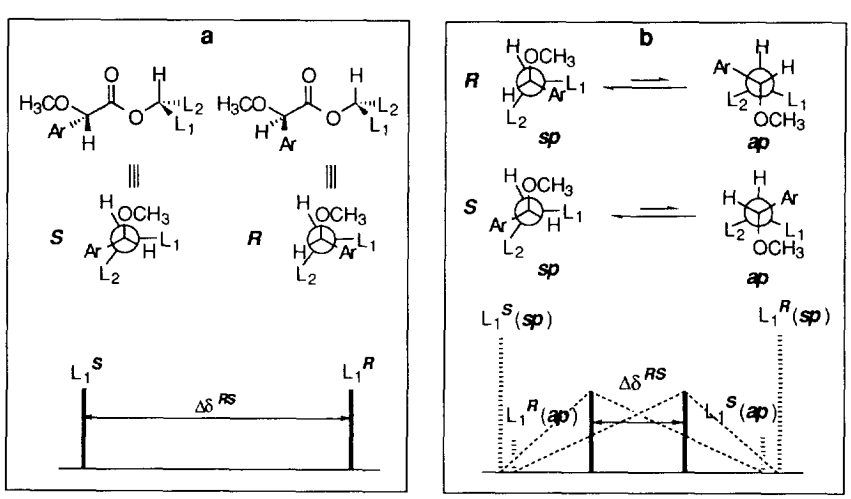

Figure 1. Differential aromatic shielding effects in the esters of *(R)* and *(S)*-arylmethoxyacetic acids (AMAAs). (a) Only one rotamer is considered in each ester. (b) Each ester is constituted by two rotamers ***sp*** and ***ap*** in equilibrium and $\Delta\delta^{RS}$ is time-averaged.

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We have recently reported[4] that AMAA esters exist in solution essentially as mixtures of two rotamers (Fig 1b): those that have the C_α-OMe and C=O bonds *syn* periplanar (***sp***), and those that have these bonds *anti* periplanar (***ap***; these are 0.4 - 0.8 kcal/mol higher in energy). In the classical representation of the theory underlying the NMR method (Fig. 1a), possible contributions to the NMR spectra from the minor, ***ap*** rotamers of ***(R)***- and ***(S)***-AMAA esters are ignored. However, owing to chemical exchange, the time-averaged chemical shift of alcohol substituent L_1 will include contributions from ***ap*** rotamers, which for ***(R)***-esters have L_1 non-shielded and thus counter the aromatic shielding experienced by L_1 in the ***sp*** conformer, increasing the chemical shifts of affected signals; while in ***(S)***-esters, in which L_1 is shielded, these contributions decrease the chemical shifts of the corresponding signals. Therefore, at room temperature, the observed $\Delta\delta^{RS}$ of the L_1 substituent ($\Delta\delta^{RS}$ in Fig. 1b) is much lower than expected,[6] and the capacity of this NMR method for differentiation between enantiomers of chiral alcohols is diminished.

One way of increasing $\Delta\delta^{RS}$ would be to bias the equilibria in Fig. 1b towards the more stable ***sp*** rotamers, thus increasing the contribution of these species to the time-averaged chemical shifts of L_1 protons, and effectively limiting upfield shifts of the L_1 signals to the ***(R)***-ester alone (and to L_2 in the ***(S)***-ester). This bias can be achieved by fine tuning of steric interactions between the aryl and carbonyl groups[4,5]. In this paper we report that, in keeping with Boltzmann's law, decreasing the temperature of the NMR probe also modifies the conformer populations leading to remarkable increases in $\Delta\delta^{RS}$.

Five enantiomerically pure alcohols having a variety of steric environments and degrees of polarity at the stereogenic centre were selected: (-)-menthol (**1**), (-)-isopulegol (**2**), ***(1S)***-(-)-borneol (**3**), ***(S)***-(+)-2-hydroxy-3-methylbutyric acid methyl ester (**4**) and ***(R)***-(-)-2-butanol (**5**) (Fig. 2). Low temperature ^{1}H NMR spectra[7] of the esters of alcohols **1** - **5** with ***(R)***- and ***(S)***-MPA were recorded and $\Delta\delta^{RS}$ for each of the groups labelled **a** - **d** in Fig. 2 were compared to the corresponding values at 298 K, which in all cases were smaller (i.e. on Fig. 3 are shown spectra of MPA esters of **5** at room and low temperatures).

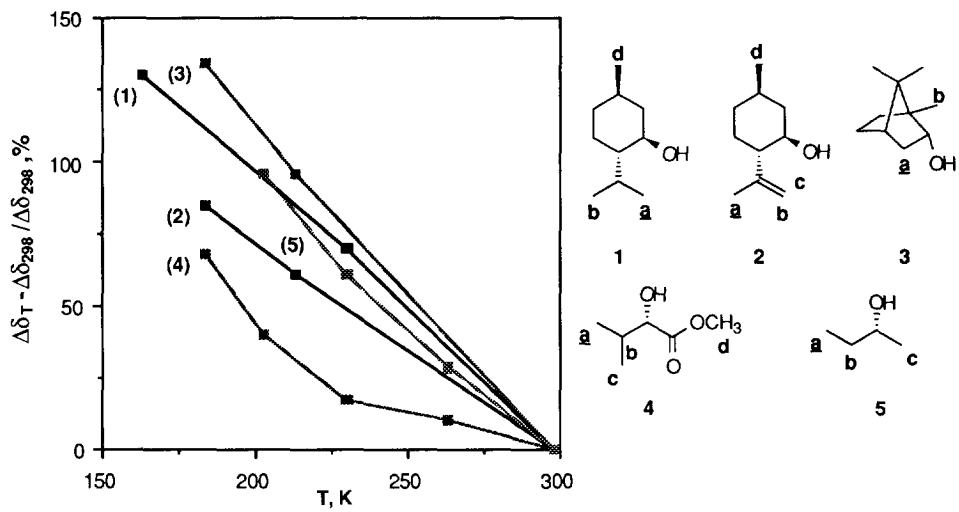

Figure 2. Plots showing the proportional increase with decreasing NMR probe temperature (**T** in K) of $\Delta\delta^{RS}$ values for the **a** protons of ***(R)*** and ***(S)***-MPA esters of chiral alcohols **1** - **5** relative to the values at 298 K.

The proportional increases in $\Delta\delta^{RS}$ (%, relative to the value at 298 K) for the protons labeled **a**, are plotted against NMR probe temperature (**T** in K) in Fig. 2, which shows that a 100 K decrease in **T** produces

an approximately 100% increase in $\Delta\delta^{RS}$ in most cases; and that even at 225 K, a T that allows to use common NMR solvents, increases close to 50% can be achieved. Moreover, within the temperature range studied (ca. 150 K), the slopes of the plots are similar for four[8] of the five alcohols, suggesting that the nature of the esterified alcohol has little influence on the conformational equilibria of the MPA moiety. Similar behaviour should therefore be attainable for any alcohol.

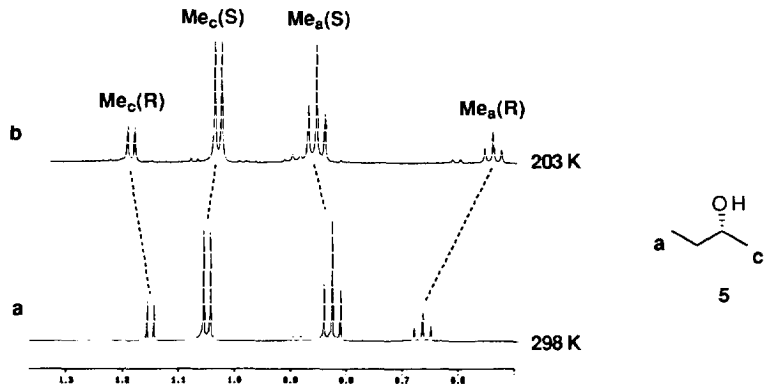

Figure 3. Partial ^{1}H NMR spectra of the ***R/S*** MPA esters (1:3 mixture) of *(R)*-(-)-butanol (**5**) in 4:1 CS_2/CD_2Cl_2 at (a) 298 K and (b) 203 K.

The variation with T of $\Delta\delta^{RS}$ was also evaluated for the esters of alcohols **1** - **5** with the recently reported new *(R)*- and *(S)*-AMAAs **7**, **8** and **9** (Fig. 4),[11] which differ from MPA **6** only in the fact that the phenyl group has been replaced by a bulkier 2-naphthyl, 1-naphthyl or 9-anthryl group, respectively.

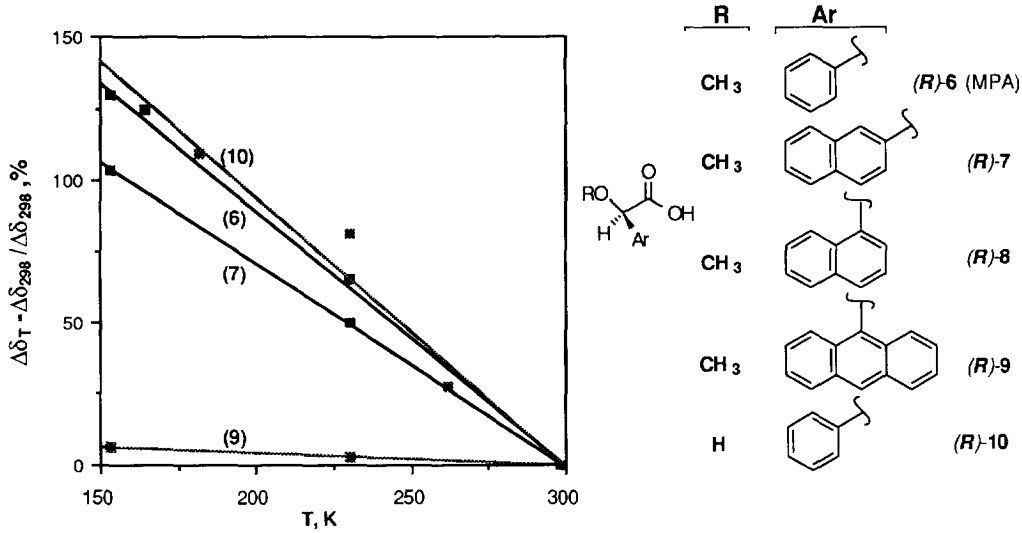

Figure 4. Plot of the proportional increase with decreasing probe temperature (T in K) of $\Delta\delta^{RS}$ for the Me(9') group of (-)-menthyl esters of arylmethoxyacetic acids **6**, **7**, **9** and **10**, relative to the values at 298 K.

Values of $\Delta\delta^{RS}$ for the protons labeled **a - d** of the corresponding esters do increase[9] at lower temperatures, but, as Fig. 4, shows for the Me(9') group of the (-)-menthyl esters, the proportional increases in $\Delta\delta^{RS}$ are less striking than for the MPA esters. This is due to the conformational equilibria already being biased towards the ***sp*** rotamers[4] and therefore it can not grow in the same proportion than in MPA.

Interestingly, increases in $\Delta\delta^{RS}$ with decreasing **T** are very similar for the esters with mandelic acid MA (**10**) and for those with the O-methylated acid, MPA (**6**). The relative conformational energies and conformational compositions of these compounds must therefore be also similar, thus contradicting the hypothesis[10] that an intramolecular hydrogen bond between the α–OH and the carboxylic ester groups is the main factor for stabilization of the ***sp*** conformation.

In summary, we have demonstrated that the difference ($\Delta\delta^{RS}$) between the aromatic shielding effects of *(**R**)*- and *(**S**)*-arylmethoxyacetic acids (AMAAs) is more marked at lower temperatures; that this temperature dependence is in keeping with a conformational model of AMAAs in solution that includes conformers having the α-methoxy and the carboxylic carbonyl groups either *syn* or *anti* periplanar, and which has interconversion of these conformers as the principal equilibrium; and that the absolute stereochemistry of a chiral alcohol can be more reliably assigned by comparing the low temperature ^{1}H NMR spectra of its *(**R**)*- and *(**S**)*-α-(methoxy)phenylacetates.

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2. $\Delta\delta^{RS}$ of L_1 (the chemical shift of the signal due to the L_1 substituent of the *(**R**)*-ester minus that of the corresponding signal of the *(**S**)*-ester) is referred to, but the situation is analogous for L_2.
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7. ^{1}H NMR spectra were measured at 500.13 MHz in a Bruker AMX-500 spectrometer and in 4:1 CS_2/CD_2Cl_2 containing TMS as internal standard.
8. In the case of the *(**R**)*- and *(**S**)*-MPA esters of (**4**), MM (CV force field; see ref. 4, 5) and AM1 calculations performed using the Insight II package indicate that the energies of the rotamers around the C(2')-CO(1) ester link are sufficiently close for temperature changes to affect rotamer populations, thus accounting for a non-linear variation.
9. In the low temperature spectra of the (-)-menthol esters of *(**R**)*- and *(**S**)*-**8**, the signals due to Me(9') were too broad and reliable values of $\Delta\delta^{RS}$ could not be obtained.
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11. Compounds **1-6** and **10** are commercially available; For compounds **7-9** see reference 4. The AMAA esters of **6 - 10** were prepared by standard methods (ref. 1c), and gave satisfactory analytical and spectroscopic data.

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