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Assigning the Configuration of Amino Alcohols by NMR: A Single Derivatization Method

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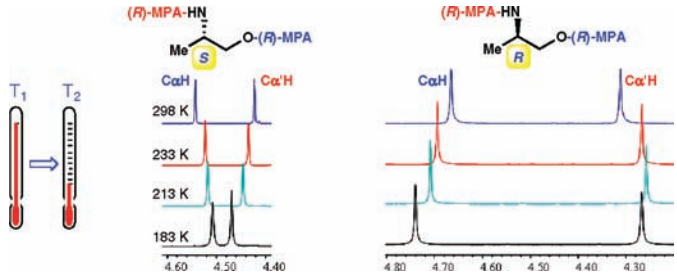
ABSTRACT



The chirality of *sec/prim*- and *prim/sec*-1,2-amino alcohols can be determined by ^{1}H NMR of just one MPA derivative —either (*R*) or (*S*)— by comparison of two spectra at different temperatures and analysis of the evolution of the easily observable singles of the CαH signals.

The most usual method for the assignment of configurations by NMR resort to the comparison between the spectra of two diastereomeric derivatives prepared from the chiral substrate of unknown configuration and the two enantiomers of an adequate chiral derivatizing agent (CDA).[1]

In recent years, the knowledge of the processes that justify this method has allowed the development of single derivatization procedures: only one enantiomer of the CDA —either (*R*) or (*S*)— is necessary.

These approaches present obvious advantages to the researchers —timesaving, reduction of the amount of sample necessary for analysis, only one reaction needed— and are based on the controlled manipulation of the equilibria among the main conformational species present in the NMR solutions. Temperature variation of the NMR probe and in situ formation of Ba^{2+} complexes have been successfully applied to secondary alcohols,[2] primary amines,[3] and diols.[4]

The configuration of *secondary/primary* and *primary/secondary* 1,2-amino alcohols[5] can be assigned by a double derivatization method, that is the comparison of the ^{1}H NMR spectra of the bis-(*R*) and bis-(*S*)-MPA (methoxyphenylacetic acid) diastereomeric derivatives.[6] In this case, the correlation structure-NMR is based on the mutual interaction between the two auxiliary MPA units, and the NMR signals for stereochemical diagnosis are the singlets for the CαH and

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(5) The terms *secondary/primary* and *primary/secondary* refer only to the carbons to which the amino/hydroxy groups are linked.

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OMe of the MPA units. The signals are easy to locate in the spectra, and there is no need to analyze the signals from the substrate (L_1/L_2 in the amino alcohol part).

We now present a single derivatization procedure for the assignment of configuration of *secondary/primary* and *primary/secondary* 1,2-amino alcohols (**1** and **2**, respectively; Figure 1) based on the cross interaction between auxiliaries mentioned above and on the conformational changes introduced by lowering the NMR probe temperature. It consists of the preparation of just one bis-MPA derivative of the amino alcohol —either (*R*) or (*S*)— and the recording of two ^{1}H NMR spectra at two different temperatures. The evolution of the singlet signals of the two CαH of the MPA auxiliaries allows inference of the absolute configuration of the amino alcohol.

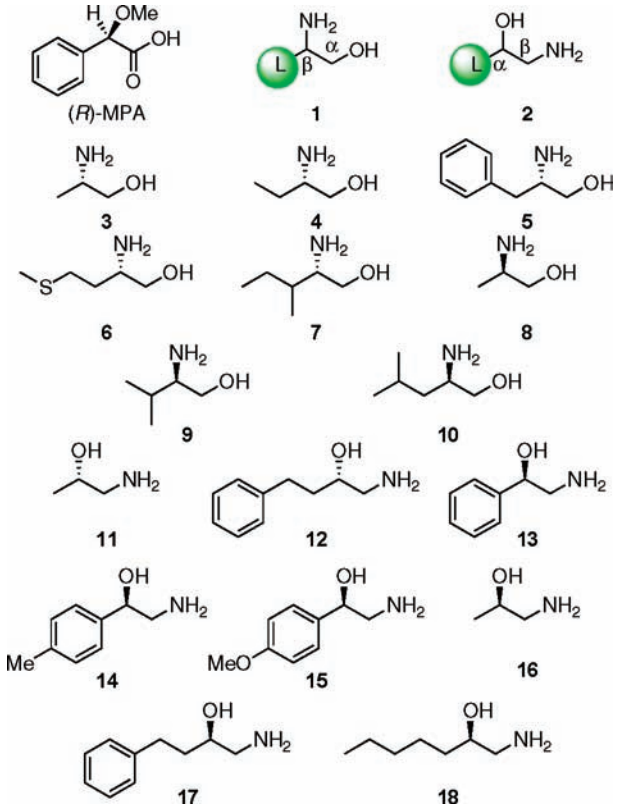

Figure 1. Structures of (*R*)-MPA and *sec/prim*- and *prim/sec*-1,2-amino alcohols (**1** and **2**) and amino alcohols (**3**−**18**) employed in this study.

The conformational analysis of the bis-MPA derivatives of *sec/prim*-amino alcohols shows that the MPA ester unit is composed of two main conformers *sp* (*synperiplanar*, major) and *ap* (*antiperiplanar*, minor) in equilibrium,[7] while in the MPA amide moiety, the major conformer is *ap* and the minor one is *sp* (Figure 2). Thus, at lower temperatures, the equilibrium should shift increasing the number of molecules having the MPA ester unit in the *sp* and the MPA amide in the *ap* conformation (with the corresponding reduction of the those in the *ap* and *sp*, respectively). From the NMR point of view, this means that the CαH group[8] that is shielded in the major conformer will be more heavily shielded at lower temperatures, while the signals due to the CαH that is shielded in the minor conformer, will be deshielded at lower temperature.

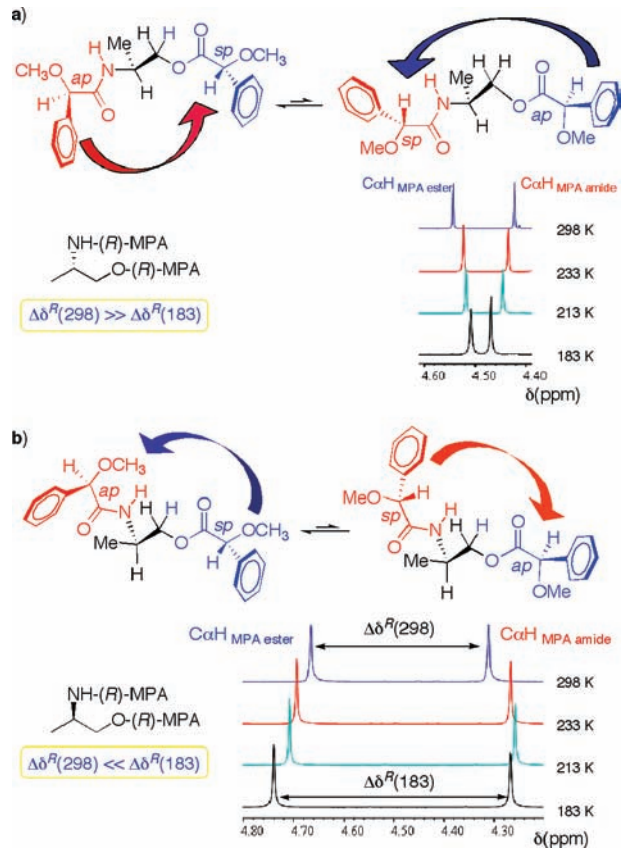

Figure 2. Conformational equilibrium for the bis-(*R*)-MPA derivatives of *sec/prim*-amino alcohols [(*S*)- and (*R*)-2-aminopropan-1-ol (**3** and **8**), **a** and **b**, respectively] and evolution of their ^{1}H NMR spectra with temperature.

Therefore, the assignment of the absolute configuration of the amino alcohol can be performed in a simple way, if two NMR spectra of only one derivative, taken at room and lower temperatures, are compared and the chemical shifts are analyzed in accordance with the above reasoning.

This is illustrated in Figure 2 with the low temperature NMR spectra of the bis-(*R*)-MPA derivatives of (*S*)- and (*R*)-2-aminopropan-1-ol (*sec/prim*-1,2-aminoalcohols **3** and **8**, Figures 2a and 2b, respectively).

In the bis-(*R*)-MPA derivative of **3**, the CαH of the MPA ester is shielded in the major conformer while the CαH of

(7) The *sp* conformer presents the methoxy and carbonyl groups in a synperiplanar disposition, while in the *ap* conformer those groups are antiperiplanar.

(8) In both types of vicinal amino alcohols, the evolution of the OMe signals with the temperature depends not only on the rotation around the Cα-CO bond (*sp/ap*) but also on the rotation around the Cα−OMe bond, and therefore, their chemical shifts reflect the shielding/deshielding effects of the phenyl and carbonyl groups, making it difficult to predict their evolution in many cases. For this reason, only CαH is used as a diagnostic signal.

the MPA amide is shielded in the minor conformer. As the NMR probe temperature is decreased, the signal corresponding to the MPA ester gets more shielded and that of the MPA amide gets more deshielded. Therefore, the two CαH signals are more separated at room than at lower temperature [$\Delta\delta^R(298) \gg \Delta\delta^R(213)$, Figure 2a].

The evolution with the temperature of the ^{1}H NMR spectra of the bis-(*R*)-MPA derivatives of the enantiomeric amino alcohol **8** shows the opposite behavior (Figure 2b): the CαH of the MPA amide (shielded in the major conformer) gets more shielded as temperature decreases, while the CαH of the MPA ester (shielded in the minor conformer) gets more deshielded. Thus, the signals of these protons are less apart at room temperature than at lower temperature [$\Delta\delta^R(298) \ll \Delta\delta^R(213)$, Figure 2b].

Analogous reasoning applies for the *prim/sec*-amino alcohols. Figure 3a shows that in the bis-(*R*)-MPA derivative

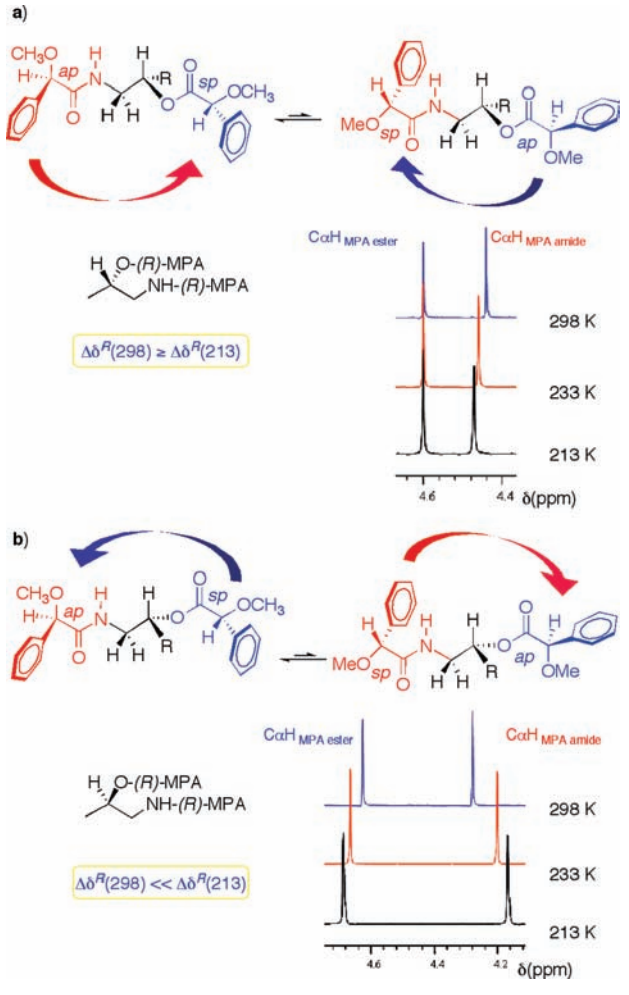

Figure 3. Conformational equilibrium for the bis-(*R*)-MPA derivatives of *prim/sec*-amino alcohols [(*S*)- and (*R*)-1-aminopropan-2-ol (**11** and **16**), **a** and **b**, respectively] and evolution of their ^{1}H NMR spectra with temperature.

of (*S*)-1-aminopropan-2-ol (**11**), where the MPA ester part is shielded in the main conformer and the MPA amide part is shielded in the minor conformer, only the groups of the MPA amide are effectively deshielded when the temperature goes down and therefore their signals are equally or slightly less separated[9] at lower temperature [$\Delta\delta^R(298) \ll \Delta\delta^R(213)$].

As expected, in the bis-(*R*)-MPA derivatives of the enantiomeric aminoalcohol [(*R*)-1-aminopropan-2-ol, **16**] the CαH protons are less separated at room temperature than at lower temperature [$\Delta\delta^R(298) \ll \Delta\delta^R(213)$, Figure 3b].

If instead of the bis-(*R*)-MPA we choose the bis-(*S*)-MPA derivatives of the amino alcohols (*sec/prim* or *prim/sec*), the evolution of the ^{1}H NMR spectra and the separation of signals shows an opposite effect.

Experimental proof of the generality of this correlation between evolution with temperature and stereochemistry was obtained by the study of low-temperature NMR of the complete series of amino alcohols shown in Figure 1. The experimental data ($\Delta\delta^R$ and $\Delta\delta^S$) are shown in Table 1.

Table 1. $\Delta\delta^R$ and $\Delta\delta^S$ Values (ppm) for bis-MPA Derivatives of Amino Alcohols **3**−**18** at Room and Low Temperatures

	$\Delta\delta^R$CαH		$\Delta\delta^S$CαH	
amino alcohol	298 K	213 K	298 K	213 K
3	0.17	0.12	0.37	0.47
4	0.12	0.04	0.36	0.47
5	0.25	0.21	0.41	0.48
6	0.16	0.08	0.35	0.47
7	0.05	0.02	0.38	0.51
8	0.37	0.47	0.17	0.12
9	0.38	0.52	0.09	0.04
10	0.34	0.51	0.12	0.02
11	0.16	0.13	0.34	0.51
12	0.18	0.18	0.35	0.52
13	0.41	0.55	0.21	0.19
14	0.40	0.52	0.21	0.19
15	0.40	0.53	0.20	0.17
16	0.34	0.51	0.16	0.13
17	0.35	0.52	0.18	0.18
18	0.40	0.59	0.16	0.13

Consequently, the analysis of the evolution with the temperature of the CαH of both MPA of only one bis-MPA derivative [bis-(*R*) or bis-(*S*)] allows the assignment of the absolute configuration of amino alcohols of types **1** and **2**.

A protocol for the assignment of the absolute configuration using only one derivative based on the unambiguous correlation between the low-temperature NMR and the stereochemistry follows: (a) Preparation of either the bis-(*R*)- or the bis-(*S*)-MPA derivative. (b) Comparison of the NMR spectra taken at room and at lower temperature.[10] Only the

(9) In the MPA amide of a *prim/sec*-1,2-amino alcohol, the phenyl ring cannot transmit its shielding effect very efficiently due to the conformational flexibility around the C(1)−NH bond, and therefore, the CαH of the MPA ester is known to be affected by the anisotropy (deshielding) of its carbonyl group. Thus, the shifts observed in this signal result from the combination of those two effects.

(10) Temperatures in the range of 180−220 K are low enough to see the evolution of the signals; a mixture of CD_2Cl_2/CS_2 (1:4) is a very convenient NMR solvent for those experiments.

CαH singlet signals have to be examined. (c) If we have prepared the bis-(*R*)-MPA derivative and the signals of the CαH protons are more separated at room than at lower

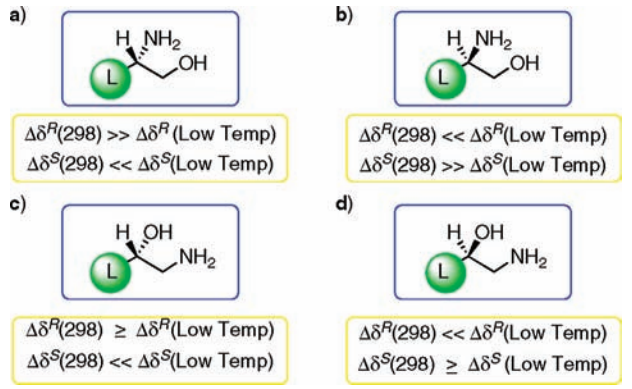

Figure 4. Diagram to assign the absolute configuration of 1,2-amino alcohols using only one derivative.

temperature, the absolute configuration of the amino alcohol corresponds to that represented in parts a and c of Figure 4. If the protons are less separated at room than at lower temperature, then the absolute configuration of the amino alcohol is the one represented in parts b and d of Figure 4. (d) If for the same amino alcohol we prepare the bis-(*S*)-MPA derivative, the evolution of the CαH singlets with temperature is the opposite (Figure 4). This low-temperature method represents an alternative to the one based on double derivatization and is especially useful in those cases where the amount of sample available is scarce.

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Supporting Information Available: Selected NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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