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Cross Interaction Between Auxiliaries: The Chirality of Amino Alcohols by NMR

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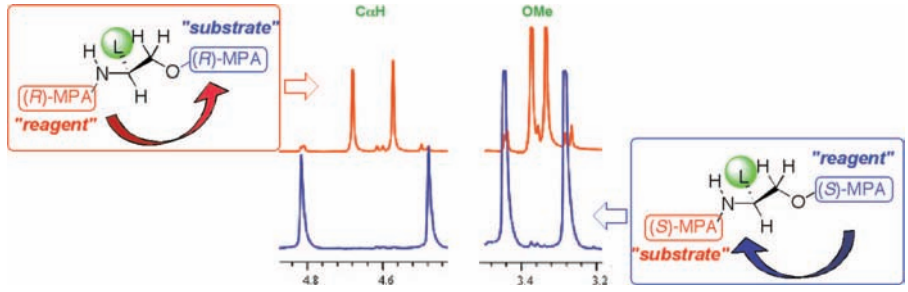
ABSTRACT



The absolute configuration of *sec/prim*- and *prim/sec*-1,2-amino alcohols is determined by comparison of the ^{1}H NMR chemical shifts of the auxiliary OMe or CαH groups at the corresponding bis-(*R*) and bis-(*S*)-MPA derivatives. This is the first NMR method that allows the assignment of absolute configuration without resorting to the shifts of hydrogens at the substrate and is based on the cross anisotropic interactions between auxiliaries.

The use of NMR for the determination of the absolute configuration of organic compounds in solution by derivatization with auxiliary reagents is well established[1] for compounds having one derivatizable group (alcohols, amines, carboxylic acids, cyanohydrins, thiols) or even two and three, such as diols,[2] triols,[3] and some amino alcohols.[4] In general, the method consists on the derivatization of the chiral substrate (unknown stereochemistry) with the two enantiomers of a chiral derivatizing agent [CDA, i.e., MPA: 2-methoxy-2-phenylacetic acid; 9-AMA: 2-(anthracen-9-yl)-2-methoxyacetic acid; 2-NTBA 2-*tert*-butoxy-2-(2-naphthyl)acetic acid...] followed by comparison of the NMR spectra of the two resulting diastereomeric derivatives. The assignment is based on the conformational composition and different shielding/deshielding effects caused on L_1/L_2 substituents around the chiral center of the substrate by the anisotropy generated by the auxiliary. The positive or negative signs of the $\Delta\delta^{RS}$ parameters on L_1/L_2 allow inferring the absolute configuration.[5]

When the substrate is a polyfunctional compound, i.e., a diol with two asymmetric carbons, the same approach works but one should have in mind two additional factors: (a) the conformational composition around each one of the derivatized groups, that may be different and (b) the final chemical shifts and $\Delta\delta^{RS}$ for L_1/L_2 result from the combination of the aromatic effects of those two auxiliary groups.[2,4]

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(5) $\Delta\delta^{RS}$ for a substituent is the difference between its chemical shift in the (*R*)-CDA derivative minus its chemical shift in the (*S*)-CDA derivative.

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In this communication, we present theoretical and experimental evidence showing that the absolute configuration of 1,2-amino alcohols with *secondary/primary* and *primary/secondary*structures,[6] (type **1** and **2** respectively, Figure 1)

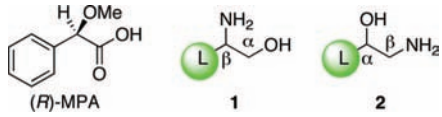

Figure 1. Structures of (*R*)-MPA, *sec/prim*-, and *prim/sec*-1,2-amino alcohols (**1** and **2**, respectively).

can be determined by comparison of the ^{1}H NMR chemical shifts of the auxiliary OMe or CαH groups at the corresponding bis-(*R*) and bis-(*S*)-MPA derivatives, easily prepared in a one-pot reaction.[7]

This constitutes the first case where the assignment of configurations by NMR can be carried out by examination of the auxiliary signals instead of those of the substrate due to the cross anisotropic interactions between auxiliaries. An additional merit is that the diagnostic signals are easily identified singlets instead of the more complex signals due to L_1/L_2 substituents.

Bis-(*R*) and bis-(*S*)-MPA derivatives of (*S*)-2-aminopropan-1-ol (**3**) were selected as model compounds to perform the conformational analysis[8] of *sec/prim*-1,2-amino alcohols with general structure **1** (Figure 1). Figure 2a shows the main processes and conformers (*sp*, *ap)* as obtained from theoretical calculations[9] (AM1, B3LYP), dynamic and low-temperature NMR, selective deuteration, and CD studies. Figure 2b−c shows the NMR significant conformers[10] and shielding effects for the bis-(*R*) and bis-(*S*)-MPA derivatives of (*S*)-2-aminopropan-1-ol (**3**). These

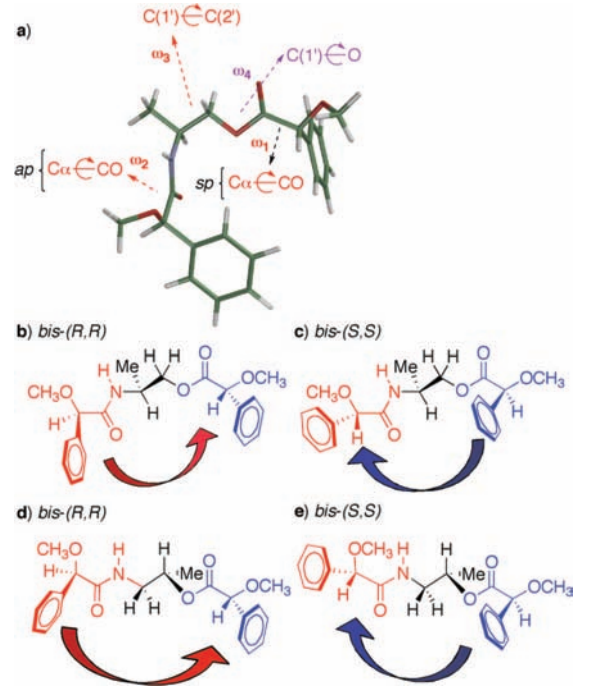

Figure 2. (a) Generation of bis-MPA main conformers. Expected shielding effect for bis-(*R*) and (*S*)-MPA derivatives of (*S*)-2-aminopropan-1-ol (**3**) (b and c, respectively) and (*S*)-1-aminopropan-2-ol (**11**) (d and e, respectively).

structures have a characteristic not present in any of the polyfunctional substrates studied so far and that makes this case special: in the bis-(*R*)-MPA derivative, the MPA amide group shields the MPA ester moiety, whereas in the bis-(*S*)-MPA derivative, the role between the two MPA units is reversed and now the MPA amide unit is shielded by the MPA ester.

A parallel situation takes place in the bis-MPA derivatives of a *prim/sec*-1,2-amino alcohol with general structure **2**[11] [i.e., (*S*)-1-aminopropan-2-ol (**11**), Figures 2d−e].

These results mean that in the bis-derivatives of 1,2-amino alcohols of type **1** and **2**, one of the MPA units is always acting as "active reagent" and projecting its aromatic shielding effect on the other MPA unit that therefore can be considered as a "substrate".

This "reagent-substrate" role of the two MPA units exchanges both with the stereochemistries of the auxiliary (the MPA unit acting as "reagent" in the bis-(*R)* is transformed into the "substrate" in the bis-(*S*)-derivative of the same amino alcohol) and with those of the amino alcohol (for the same derivative, i.e., bis-(*R*)-MPA, the role of each MPA unit is reversed with the absolute configuration of the amino alcohol: the MPA unit acting as "reagent" in the (*R*)-amino alcohol acts as "substrate" in the (*S*)-amino alcohol, Figure 2). As a consequence, the chemical shifts of the

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

(7) The bis-MPA derivatives of amino alcohols **3**−**18** were prepared (always introducing the two units of the auxiliary in a single reaction) by treatment of the amino alcohol (1.0 equiv) with the corresponding (*R*) and (*S*)-α-methoxy-α-phenylacetic acid (MPA; 2.2 equiv) in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 2.2 equiv) and DMAP (cat) in dry CH_2Cl_2, under a nitrogen atmosphere. The reactions were stirred at rt for 3−8 h, followed by the usual purification and isolation steps.

(8) See Supporting Information for conformational energy distribution and a detailed conformer description.

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(10) Only conformers generated by rotation around $\omega 1$ and $\omega 2$ bonds [Cα-CO, MPA] are of interest from the NMR point of view. They explain the shielding effects and chemical shift differences experienced by CαH and OMe MPA signals.

(11) The same conformational analysis (rotation around $\omega 1-4$ bonds, AM1, B3LYP calculations, NMR and CD) performed on the bis-(*R*) and (*S*)-MPA derivatives of (*S*)-1-aminopropan-2-ol leads to the same results. See Supporting Information for detailed information.

signals due to the two MPA units —and particularly the easily identified[12] OMe and CαH singlets —should reflect the stereochemistry of the derivatives and, hence, the absolute configuration of the aminoalcohol.

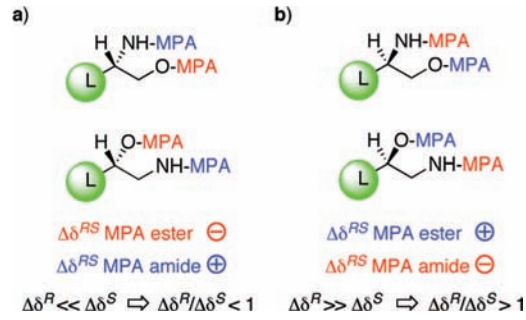

Figure 3. $\Delta\delta^{RS}$ signs and $\Delta\delta^R/\Delta\delta^S$ ratios for *sec/prim*- and *prim/sec*-1,2-amino alcohols.

Thus, the OMe and CαH protons of the MPA ester unit are more shielded in the bis-(*R*) than in the bis-(*S*)-MPA derivatives of (*S*)-2-aminopropan-1-ol (**3**) (Figure 2b), whereas

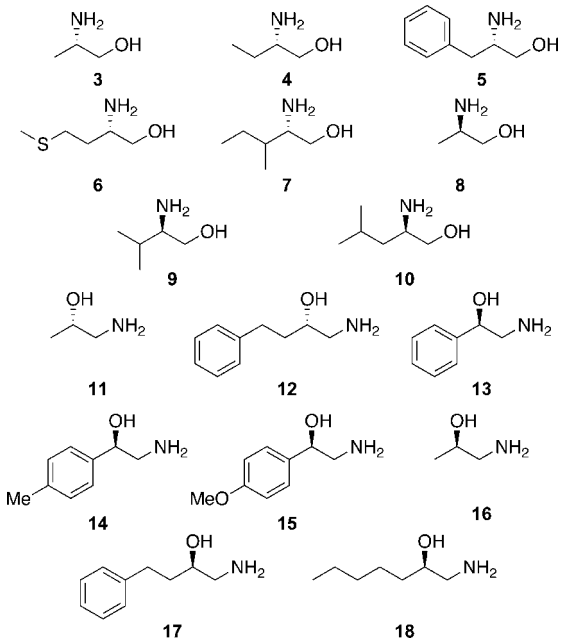

Figure 4. Amino alcohols of type **1** and **2** employed in this study.

the OMe and CαH protons of the MPA amide are more shielded in the bis-(*S*)- than in the bis-(*R*)-MPA derivatives (Figure 2c). Consequently, negative and positive $\Delta\delta^{RS}$ signs will be obtained for the OMe and CαH of the MPA ester and MPA amide, respectively, when the NMR spectra are compared (Figure 3a).

For its part, in the bis-MPA derivatives of (*S*)-1-aminopropan-2-ol (**11**) (Figures 2d−e), OMe and CαH protons of the MPA ester are more shielded in the bis-(*R*)-MPA derivative (negative $\Delta\delta^{RS}$), while those of the MPA amide are more shielded in the bis-(*S*)-MPA derivative (positive $\Delta\delta^{RS}$, Figure 3a).

Naturally, when the amino alcohols have the enantiomeric structure, the opposite set of signs will be obtained (Figure 3b).

Experimental demonstration of the rightness of these predictions was obtained by comparison of the OMe and CαH signals of the two MPA units in the bis-(*R*) and bis-(*S*)-MPA derivatives of the series of amino alcohols of known absolute configuration (**3**−**18,** Figure 4), belonging to the structural types **1** and **2** and representing the (*R*) and the (*S*) stereochemical possibilities. Table 1 shows the experimental $\Delta\delta^{RS}$ signs and values observed.

Table 1. $\Delta\delta^{RS}$, $\Delta\delta^R$, and $\Delta\delta^S$ Values (ppm) for bis-MPA Derivatives of Amino Alcohols **3**−**18**

amino	$\Delta\delta^{RS}$ CαH		$\Delta\delta^{RS}$ OMe		CαH		OMe	
alcohol	ester	amide	ester	amide	$\Delta\delta^R$	$\Delta\delta^S$	$\Delta\delta^R$	$\Delta\delta^S$
3	−0.12	+0.09	−0.06	+0.04	0.15	0.36	0.06	0.16
4	−0.13	+0.09	−0.08	+0.05	0.11	0.33	0.03	0.16
5	−0.11	+0.05	−0.05	+0.01	0.22	0.38	0.15	0.19
6	−0.11	+0.07	−0.06	+0.03	0.15	0.33	0.06	0.15
7	−0.19	+0.14	−0.09	+0.09	0.03	0.36	0.01	0.19
8	+0.12	−0.09	+0.06	−0.04	0.36	0.15	0.16	0.06
9	+0.19	−0.15	+0.08	−0.11	0.36	0.02	0.19	0.00
10	+0.15	−0.08	+0.07	−0.04	0.34	0.02	0.15	0.04
11	−0.04	+0.16	−0.02	+0.08	0.14	0.34	0.10	0.20
12	0.00	+0.18	−0.02	+0.10	0.15	0.33	0.08	0.20
13	+0.06	−0.20	−0.01	−0.11	0.44	0.18	0.20	0.10
14	+0.05	−0.20	−0.01	−0.10	0.43	0.18	0.19	0.10
15	+0.04	−0.20	−0.01	−0.11	0.41	0.17	0.19	0.09
16	+0.04	−0.16	+0.02	−0.08	0.34	0.14	0.20	0.10
17	0.00	−0.18	+0.02	−0.10	0.33	0.15	0.20	0.08
18	+0.08	−0.20	+0.03	−0.11	0.40	0.12	0.21	0.07

In this way, the absolute configuration of an amino alcohol (structures **1** and **2**), can be easily determined by preparation of the bis-(*R*) and bis-(*S*)-MPA derivatives and comparison of the $\Delta\delta^{RS}$ signs for the OMe and CαH signals with those in Figure 3.

In practice, it is not necessary to distinguish the signals for the MPA ester and MPA amide units and calculate the $\Delta\delta^{RS}$ because the direct inspection of the separation of the signals, in the bis-(*R*)-and the bis-(*S*)-MPA ($\Delta\delta^R$ and $\Delta\delta^S$, respectively) is enough to establish the correlation.[13]

(12) In all the substrates studied, the signals for the OMe and CαH of the MPA ester unit are more deshielded than those due to the MPA amide unit.

(13) The separation between the two CαH signals (MPA ester/MPA amide) in the bis-(*R*)-MPA derivatives is measured as $\Delta\delta^R$ (absolute value, ppm) and as $\Delta\delta^S$ in the bis-(*S*)-MPA derivatives. The separation between the OMe signals is calculated in the same manner.

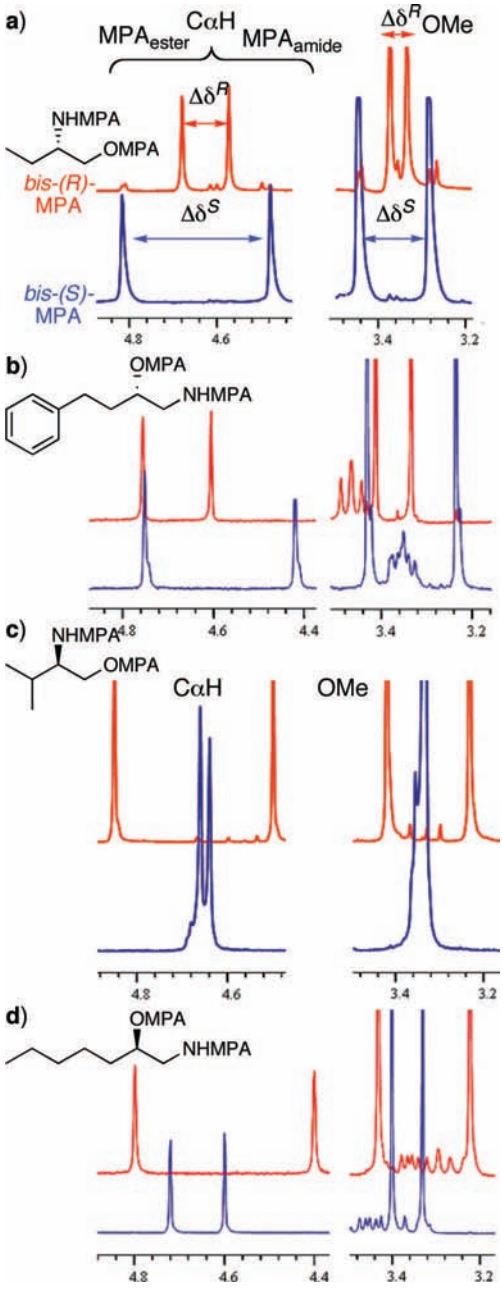

Figure 5. Partial ^{1}H NMR spectra of bis-(*R*)- and bis-(*S*)-MPA derivatives of *sec/prim*- and *prim/*sec-1,2- amino alcohols (a, c and b, d, respectively).

In the bis-(*R*)-MPA derivatives of any of the two 1,2-amino alcohols (type **1** or **2**) with the absolute stereochemistry shown in Figure 2b and d, the CαH and OMe protons of the MPA ester are more shielded than those of the MPA amide, while in the bis-(*S*)-MPA derivatives, the CαH and OMe protons of the MPA amide are more shielded than those of the MPA ester. Thus, CαH and OMe singlets are less separated in the bis-(*R*)-MPA derivative than in the bis-(*S*)-MPA derivative ($\Delta\delta^R \ll \Delta\delta^S$) as shown in Figures 5a and b.

When the separation is greater in the bis-(*R*)-MPA derivative than in the bis-(*S*)-MPA derivative ($\Delta\delta^R \gg \Delta\delta^S$), the amino alcohol has the enantiomeric spatial arrangement and its absolute configuration is like those of Figures 5c and d. Identical behavior and correlation between the separation of the OMe and the CαH signals ($\Delta\delta^R$, $\Delta\delta^S$) and the stereochemistry was observed in all the amino alcohols studied in this work (Figure 4 and Table 1).

This is the first NMR method that assigns configurations without resorting to shifts from hydrogens at the substrate. In some way, it resembles the exciton coupled CD[14] approach: both describe how the mutual interaction between auxiliaries (chromophores in CD, MPAs in NMR) allows the determination of molecular chirality.

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Supporting Information Available: Conformational Analysis; Experimental Section; Spectroscopic Data; ^{1}H and ^{13}C NMR Spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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