Absolute configuration of amino alcohols by ^{1}H-NMR

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A general NMR spectroscopy protocol for determination of absolute configuration of 1,2-amino alcohols, that allows differentiation of the four possible stereoisomers by analysis of the ^{1}H NMR spectra of their bis-MPA derivatives, is described.

The assignment of absolute configuration by NMR has experienced a remarkable development in recent years.[1] This progress has been mainly focused in: (a) the design of new and improved—more efficient—chiral derivatizing agents (CDAs); (b) new methods that make the stereochemical assignment an easier task—such as the "single derivatization" approaches and the "mix & shake" methods—and (c) the application to an increasingly larger variety of functional groups (primary and secondary alcohols, primary amines, carboxylic acids...). All these achievements were made possible by the understanding reached about the intimate (conformational) behaviour of the CDA-substrate systems through out extensive studies that comprise both spectroscopic experiments (Dynamic NMR, CD...) and theoretical calculations (semiempirical, *ab initio*).

These advances have allowed the reliable determination of the stereochemistry of a large number of monofunctional chiral compounds of natural and synthetic origin. In the reported cases, the NMR methods were successfully applied to find out the absolute configuration (*R* or *S*) of a single chiral center, usually directly attached to the functional group acting as a "handle". In the case of molecules possessing several chiral centers, tedious protocols based on selective protection/deprotection steps had to be used in order to find out the configuration of each center at the time. However, serious problems arise when all the chiral centers of these substrates (*i.e.* natural polyols) were studied simultaneously using the same protocols employed for monofunctional compounds.[2]

Therefore, the application of this NMR methodology to molecules bearing several chiral centers showed that they possess a larger degree of complexity than that of monofunctional compounds. To find an effective solution to this problem has become a major challenge in the field because it would allow the determination of the configuration of complex polyfunctionalized molecules with the same simplicity as monofunctional ones.

Recently, the assignment of configuration of *syn* and *anti* 1,*n*-diols (1,2; 1,3,...) have been systematically studied[3] by means of their bis-AMAA derivatives.†[a]The conclusion of this research is that the configuration of the carbons attached to secondary hydroxy groups can be deduced by comparison of the ^{1}H-NMR spectra of the corresponding bis-(*R*) and bis-(*S*)-AMAA esters. While in monosubstituted compounds the methodology only has to discriminate between two possible configurations (*R* or *S*), this new approach allowed configurational assignment of the diol distinguishing among four possible combinations of stereocenters (the two enantiomers of each *syn* and *anti* pair: *RR*, *SS*, *RS*, *SR*), this fact being a major achievement of the study.

The success of this approach is based in the "overall" treatment given to the bis-AMAA derivative of the difunctional compound: the anisotropic effects caused by the two AMAA units are considered acting on the substrate in a combined way and not as isolated systems. Thus, when the substrate with two chiral centers is derivatized with the (*R*)-AMAA, the substituents of the substrate experience the combined anisotropic effect of those two (*R*) auxiliaries (a 1st spectrum is recorded). The combined effect differs when the two auxiliaries are (*S*) (2nd recorded spectrum). Then, both spectra are compared and the corresponding $\Delta\delta^{RS}$ calculated.†[b] The characteristic set of $\Delta\delta^{RS}$ signs obtained confirms unambiguously the configuration of both centers.

After these findings, it became clear that it would be important to find out if this methodology, which is successful in the case of diols—where the two functional groups next to the chiral centers are identical—could be extended to more complex polyfunctional compounds of interest, such as 1,2-amino alcohols, where the two groups are different (amino and hydroxy). We now present preliminary results that confirm the validity of the "combined anisotropic effects" approximation on these structural systems. Specifically, we studied the assignment of configuration of 1,2-amino alcohols through their bis-MPA derivatives.

An analysis based on the previous knowledge of the conformational behaviour of MPA esters[4] and amides,[5] warns about the higher degree of complexity expected in amino alcohols when compared to diols.†[c] While the MPA ester moiety should exist

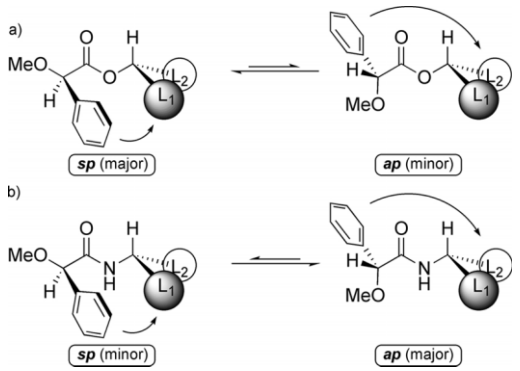

Fig. 1 (a) Main conformers in the equilibrium of a (*R*)-MPA ester. (b) *Idem.* for a (*R*)-MPA amide. Shielding effects are shown by curved arrows.

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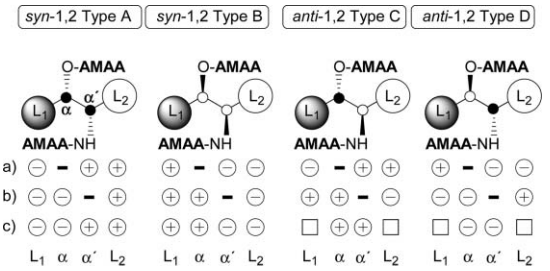

Fig. 2 $\Delta\delta^{RS}$ sign distribution for the bis-AMAA derivatives of the four possible stereoisomers of a 1,2-amino alcohol. (a) Anisotropic contribution (as $\Delta\delta^{RS}$ sign) of the AMAA ester. (b) *Idem*. of the AMAA amide. (c) Overall contribution: diagnostic pattern.

predominantly in the *sp* form (Fig. 1a),[4] the MPA amide moiety should be present mainly in the *ap* form (Fig. 1b).[5]

Fig. 3 shows the main conformational scenario expected for the bis-(*R*) (3a) and bis-(*S*)-MPA (3b) derivatives of an *anti* 1,2-amino alcohol (Type D). The spatial environments placed under the influence of the phenyl rings of the *sp* and *ap* (ester and amide) substructural moieties are clearly distinct in each case, which should also yield clearly distinct $\Delta\delta^{RS}$ values. It is necessary to point out that the rotation around the Cα–Cα′ bond does not change the spatial relationship of the phenyl rings with respect to L_1, L_2, $C_\alpha H$ and $C_\alpha{}'H$.[3b] As a result, the $\Delta\delta^{RS}$ pattern generated depends only on the absolute configuration of the chiral centers. In the example shown in Fig. 3, its corresponding enantiomer (*anti* 1,2-amino alcohol Type C) must present the opposite set of $\Delta\delta^{RS}$ signs (Fig. 2).

A similar analysis for a *syn* 1,2-amino alcohol (Type B, Fig. 3) yields a different combination of anisotropic effects, which is translated into a different $\Delta\delta^{RS}$ pattern, also opposite to that of its enantiomer (a Type A amino alcohol). Altogether, the four $\Delta\delta^{RS}$ patterns of the four possible stereoisomers are clearly distinct and should allow determination of their configuration unambiguously (Fig. 2).†[d]

Methyl 2-amino-3-hydroxybutanoate of known configuration, available both in *syn* (2*S*,3*R*; Type B; **1**) and *anti* (2*S*,3*S*; Type C; **2**)

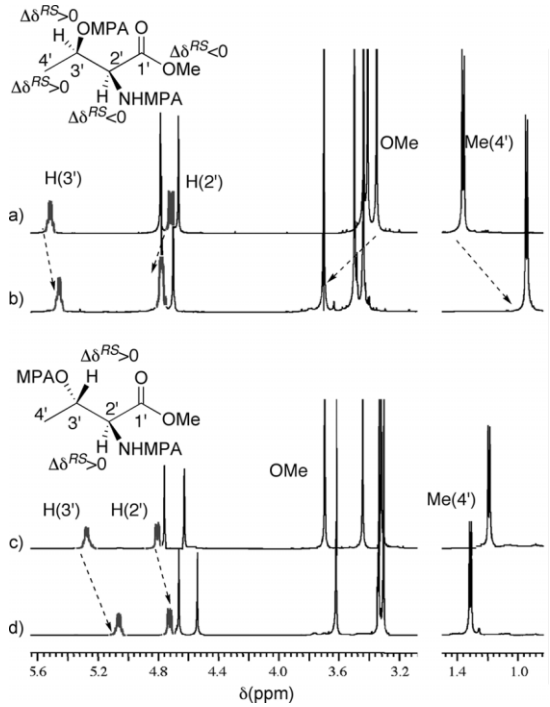

Fig. 4 (a) ^{1}H NMR spectrum of the bis-(*R*)-MPA derivative of *syn* methyl 2-amino-3hydroxybutanoate (**1**). (b) *Idem*. of the bis-(*S*)-MPA derivative. (c) *Idem*. of the bis-(*R*)-MPA derivative of *anti* methyl 2-amino-3-hydroxybutanoate (**2**). (d) *Idem*. of the bis-(*S*)-MPA derivative. The diagnostic shifts are highlighted with broken arrows.

forms, was chosen as a model compound to test the methodology. The bis-(*R*) and bis-(*S*)-MPA derivatives of the two diastereoisomers were prepared,†[e] their ^{1}H NMR spectra were recorded in $CDCl_3$ and the $\Delta\delta^{RS}$ values calculated.

In the *syn* form (**1**), the $C_\alpha H$ experienced a noticeable shielding ($\Delta\delta^{RS}$ = +0.06 ppm) when going from the bis-(*R*) to the bis-(*S*) derivative (Fig. 4a and 4b). For its part, the $C_\alpha{}'H$ moved downfield by $\Delta\delta^{RS}$ = −0.06 ppm. This shift unequivocally corresponds to a *syn*-1,2 Type B amino alcohol as predicted

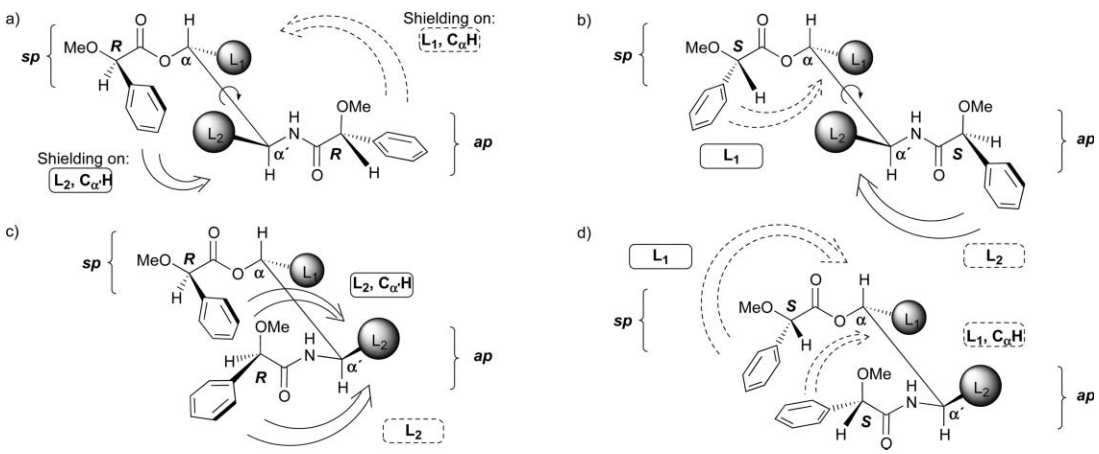

Fig. 3 (a) bis-(*R*)-MPA derivative of an *anti* 1,2-amino alcohol (Type D). (b) *Idem*. for its bis-(*S*)-MPA derivative. (c) bis-(*R*)-MPA derivative of a *syn* 1,2-amino alcohol (Type B). (d) *Idem*. for its bis-(*S*)-MPA derivative. The shielding effects are illustrated by continuous and dashed arrows. The groups shielded by the MPA ester and amide moieties are highlighted in full and broken squares, respectively. Only the NMR significant conformers (*sp* and *ap*) are shown.

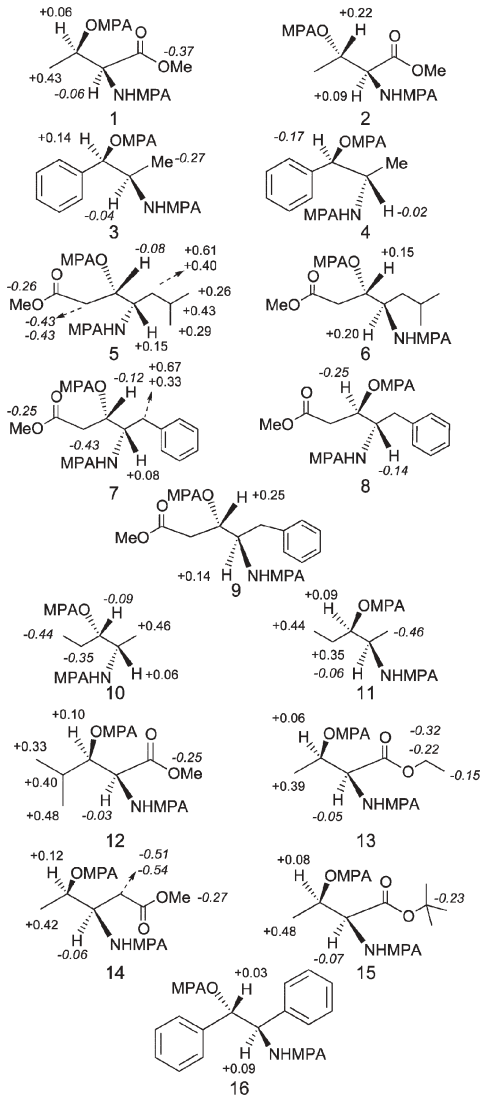

Fig. 5 *Syn* and *anti* aminoalcohols of known configuration used in this study. Diagnostic $\Delta\delta^{RS}$ signs and values are indicated.

(Fig. 2). The signals of L_1 and L_2 corroborate the assignment: The methyl group at C(4′) (L_1) undergoes a shielding effect moving upfield ($\Delta\delta^{RS}$ = +0.43 ppm) while the methoxy group (L_2) is deshielded and shifts downfield ($\Delta\delta^{RS}$ = −0.37 ppm).

In a parallel analysis, when the $\Delta\delta^{RS}$ values of C_αH and C_α′H in isomer **2** were evaluated, their positive signs (both protons experience shielding, +0.22 and +0.09, respectively) pointed correctly to an *anti*-1,2 Type C amino alcohol (Fig. 4c and 4d).†[f] In this case, the $\Delta\delta^{RS}$ values corresponding to L_1 and L_2 do not have diagnostic values, but those of the methines are enough to make a safe assignment.

Once the feasibility of the method was checked with the model compounds, other representative examples of chiral amino alcohols were employed to further reinforce it, as shown in Fig. 5. These cases include biological important molecules such as norpseudoephedrine **3** (*syn*) and norephedrine **4** (*anti*); statines **5** (*syn*) and **6** (*anti*); phenylstatines **7** (*syn*), **8** (*anti*) and **9** (*anti*); as well as other representative structures (**10–16**). In all cases, the assignment by NMR was coincident with the known stereochemistry of the test compounds.

This correlation between the absolute configuration and the NMR spectra can therefore be considered to be general for amino alcohols like those of Fig. 5 and can be used for the configurational assignment of any other amino alcohol.

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Notes and references

† (a) The arylmethoxyacetic acids (AMAAs) employed in this study include 2-methoxy-2-phenylacetic acid (MPA), 2-(anthracen-9-yl)-2-methoxyacetic acid (9-AMA) and 3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (MTPA). (b) $\Delta\delta^{RS}$ for a given substituent is the difference between its chemical shift in the bis-(*R*)-AMAA derivative and in the bis-(*S*)-AMAA derivative. (c) On generation of the diagnostic signals, a major role is played by the conformational preference of the AMAA moiety and by the kind of linkage to the substrate (*i.e.* ester, amide). It is known that two main types of conformers are present in the conformational equilibria of esters and amides: the *anti*periplanar (*ap*) and the *syn*periplanar (*sp*) forms. The former are predominant in amides and the latter are predominant in esters. The predominant forms are the NMR significant conformers, being a major cause of the combined anisotropic effects (Fig. 1). (d) The $\Delta\delta^{RS}$ values and signs resulting from the anisotropic effects can be classified in two groups: (1) those of the L_1 and L_2 substituents and (2) those of the methines linked to the hydroxy and amino groups (C_αH and C_α′H). The first ones have diagnostic values in the case of the two *syn* amino alcohols while the second ones have such values in all the four possible stereoisomers (*anti* and *syn* amino alcohols). In some situations, both auxiliaries "project" the same type of anisotropic effect on a certain group (increasing either its shielding or deshielding degree). In other cases (indicated with "blank square" in Fig. 2), when both auxiliaries "compete" projecting opposite effects on the group (shielding *versus* deshielding), the $\Delta\delta^{RS}$ signs have to be taken with caution. (e) The bis-MPA derivatives were prepared (always introducing the two units of the auxiliary in a single reaction) by treatment of the amino alcohol (1.0 equivalent) with the corresponding (*R*) and (*S*)-MPA (2.5 equivalents) in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 2.5 equivalents) and cat. DMAP in dry CH_2Cl_2, and under a nitrogen atmosphere. The reactions were stirred at r.t. for 2 h, followed by the usual purification and isolation steps. (f) Due to the fact that the ^{1}H NMR spectra of enantiomers in a non chiral solvent are identical, the $\Delta\delta^{RS}$ of the bis-MPA derivatives of the enantiomers of **1** and **2** present the same absolute values and opposite signs as their mirror images: those corresponding to *syn*-1,2 Type A and *anti*-1,2 Type D amino alcohols, respectively (Fig. 2).

1 For recent reviews see: J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Rev.*, 2004, **104**, 17; J. M. Seco, E. Quiñoá and R. Riguera, *Tetrahedron: Asymmetry*, 2001, **12**, 2915.

2 J. M. Seco, E. Quiñoá and R. Riguera, *Tetrahedron: Asymmetry*, 2000, **11**, 2781.

3 (*a*) F. Freire, J. M. Seco, E. Quiñoá and R. Riguera, *J. Org. Chem.*, 2005, **70**, 3778; (*b*) J. M. Seco, M. Martino, E. Quiñoá and R. Riguera, *Org. Lett.*, 2000, **2**, 3261.

4 Sh. K. latypov, J. M. Seco, E. Quiñoá and R. Riguera, *J. Org. Chem.*, 1995, **60**, 504.

5 Sh. K. latypov, J. M. Seco, E. Quiñoá and R. Riguera, *J. Org. Chem.*, 1995, **60**, 1538.

