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The Assignment of the Absolute Configuration of 1,2-Diols by Low-Temperature NMR of a Single MPA Derivative

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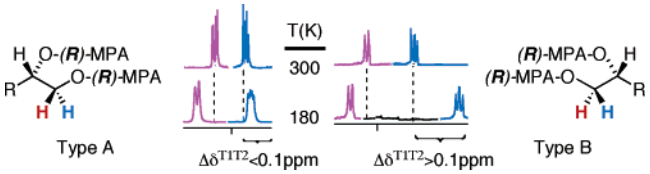
ABSTRACT



The absolute configuration of 1,2-primary/secondary diols can be easily assigned by low-temperature NMR of a bis-MPA ester derivative. The assignment requires the analysis of just the methylene protons, is not limited by the absence of signals from the R group of the diol, and requires a very small and recoverable sample.

The configurational assignment of chiral compounds by ^{1}H NMR spectroscopy has become a very useful and convenient tool for routine application. In general, this involves the derivatization of the substrate (monofunctional secondary and primary alcohols, amines, and carboxylic acids) with the two enantiomers of a chiral derivatizing reagent (9-AMA, MPA, MTPA, BPG, etc.) followed by comparison of the NMR spectra of the two resulting diastereomers.[1] More recently, procedures that require the synthesis of only one derivative[2] or simplify the preparation have emerged that allow working with very small amount of sample.

Application of this methodology to polyfunctional chiral substrates,[3] such as diols, constitutes an especial case because, in these systems, both hydroxyls are derivatized with the auxiliary agent. The combination of the anisotropic effects produced by the two auxiliary units produces chemical shifts and $\Delta\delta^{RS}$ sign distributions that cannot be correlated with the stereochemistry using the models described for monoalcohols.[4]

In this communication, we present experimental evidence showing that the absolute configuration of 1,2-primary/

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secondary diols can be assigned by analysis of the shifts that the ^{1}H NMR signals corresponding to the methylene protons of a bis-MPA (α-methoxy-α-phenylacetic acid) ester derivative [either the bis-(*R*)- or the bis-(*S*)-MPA] undergo with variations of temperature.

Theoretical calculations (AM1, HF, and B3LYP) and experimental data (dynamic and low-temperature NMR, testing deuterated derivatives, and circular dichroism studies) show that the bis-MPA ester of a 1,2-primary/secondary diol consists on two main conformers in equilibrium.[5]

Thus, in a bis-(*R*)-MPA ester of a diol with configuration of type A, the main conformers are *sp*-I and *ap*-I (Figure 1a). Conformer *sp*-I is the most populated. The dihedral angle between the carbonyl and the pro-(*S*)- and pro-(*R*)-methylene hydrogens presents values close to +44 and −74°, respectively. In this spatial arrangement, both methylene protons are inside the deshielding cone of the carbonyl, but because of the different angle, the pro-(*S*) proton should be slightly more deshielded than that of the pro-(*R*). Thus, the NMR spectrum of the bis-(*R*)-MPA ester of a type A diol should show the pro-(*S*) resonating at lower field than the pro-(*R*) proton (Figure 1c).

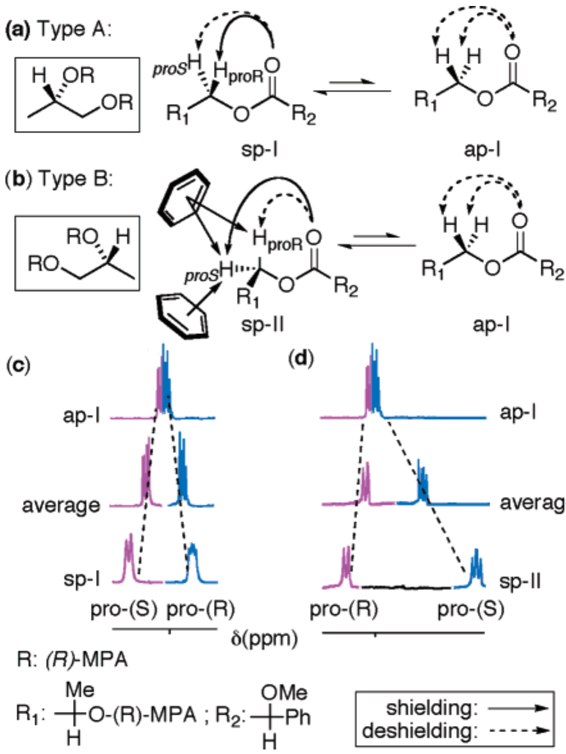

Figure 1. Main conformers and shielding effects for the bis-(*R*)-MPA esters of diol types A and B (a, b). Idealized resonances for methylene protons (c, d).

In conformer *ap*-I, the carbonyl is bisecting the methylene hydrogens (Figure 1a). These are now equally separated by about 60° and equally deshielded by the carbonyl. Therefore, both should resonate at about the same chemical shift (Figure 1c).

At lower NMR probe temperatures, the population of the most stable conformer (*sp*-I in this case) is increased, and therefore, the average resonances for the methylene protons should reflect the higher weight of the shielding/deshielding characteristics of the main conformation.

Thus, the proton resonating at room temperature at high field [pro-(*R*)] should move slightly to higher field, while the one resonating at low field [pro-(*S*)] should significantly move to lower field (Figure 1c). This prediction is experimentally observed in the NMR spectra of the bis-(*R*)-MPA ester of (*S*)-propane-1,2-diol (**1**, diol type A) taken between 300 and 183 K. In these conditions, a small shift[6] to higher field ($\Delta\delta^{T1-T2} = 0.03$ ppm) is observed for the methylene proton resonating at high field [pro-(*R*)[7]], while the proton resonating at low field shifts to lower field by $\Delta\delta^{T1-T2} = -0.11$ ppm [pro-(*S*)] (Figure 2).

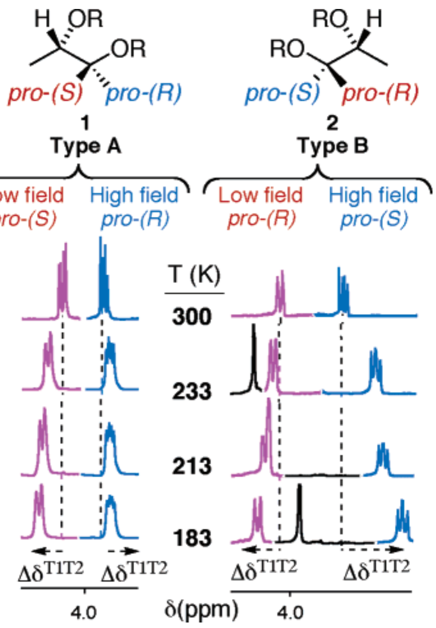

Figure 2. Evolution with the temperature of the ^{1}H NMR spectra of the bis-(*R*)-MPA esters of (*S*)-**1** and (*R*)-**2**.

In the case of the bis-(*R*)-MPA ester of a type B diol, the main conformer is the *sp*-II form (Figure 1b). It has the carbonyl group coplanar with the pro-(*R*)-methylene hydrogen. In the other conformer, *ap*-I, both methylene hydrogens are forming practically a 60° angle with the carbonyl group (Figure 1b).

In the *sp*-II conformer, one of the hydrogens of the methylene group [pro-(*S*)] is shielded by the carbonyl and

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(6) The $\Delta\delta^{T1-T2}$ values are defined as δ at the higher temperature (T_1) minus δ at the lower temperature (T_2).

(7) The pro-(*R*)- and pro-(*S*)-methylene protons have been assigned by means of deuteration experiments.

by the two phenyl groups, while the other [pro-(*R*)] is deshielded by the carbonyl and shielded by only one of the phenyl groups. This arrangement leads the pro-(*S*) proton to resonate at higher field than the pro-(*R*) proton (Figure 1d).

In the *ap*-I conformer, both methylene protons are equally deshielded by the carbonyl group and should resonate at about the same chemical shifts (Figure 1d).

At lower NMR temperatures, the population of *sp*-II increases, that of *ap*-I decreases, and the average NMR spectra should reflect those changes. As a result, we should expect that both protons move apart at lower temperature, but one [pro-(*S*)] more heavily than the other [pro-(*R*)] (Figure 1d). This is experimentally confirmed by the low-temperature NMR spectrum of the bis-(*R*)-MPA ester of (*R*)-propane-1,2-diol (**2**, diol type B). It shows the high-field proton[8] shifting to higher field in a much larger amount ($\Delta\delta^{T1-T2} = 0.25$ ppm) than the proton resonating at lower field ($\Delta\delta^{T1-T2} = -0.03$ ppm) (Figure 2).

Experimental confirmation of the general character of this correlation between the pattern of the low-temperature shifts and the absolute configuration of the diol came from the study of the 1,2-diols (**1**−**13**) shown in Figure 3.

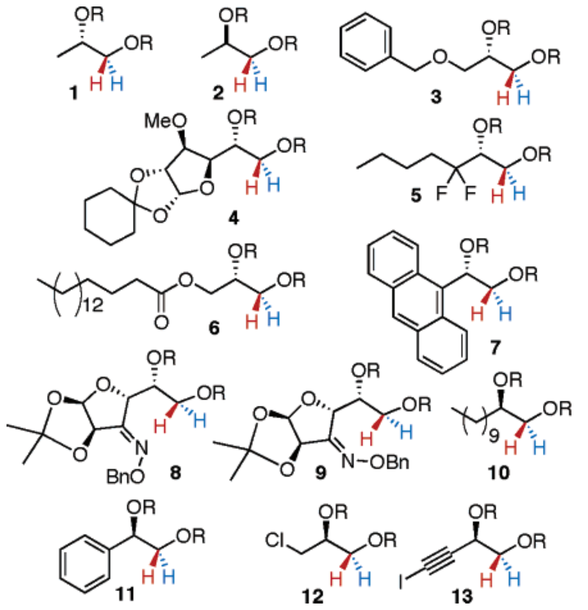

Figure 3. 1,2-Primary/secondary diols selected for this study.

Plots showing the evolution with the temperature of the methylene protons of their bis-(*R*)-MPA esters are shown in Figure 4. The data can be summarized as follows:

In all of the diols with absolute configuration type A (**3**−**9**, Figure 3), the methylene proton that resonates at room temperature at high field moves at lower temperature slightly to higher field (less than 0.1 ppm), while the methylene proton resonating at room temperature at low field moves to lower field up to 0.25 ppm (Figure 4a).

In diols with configuration type B (**10**−**13**), the methylene proton that resonates at room temperature at high field moves strongly to higher field at lower temperatures (between 0.2 and 0.3 ppm), while the methylene proton that resonates at room temperature at low field shifts to lower field very slightly (0.0−0.1 ppm, Figure 4b).

A similar study and reasoning applied to the bis-(*S*)-MPA esters leads to *sp*-II as the most representative conformation for the bis-(*S*)-MPA ester of a diol type A and to *sp*-I for the bis-(*S*)-MPA ester of a diol type B. Consequently, the low-temperature patterns of shifts obtained are opposite to the ones just described for the bis-(*R*)-MPA ester of the same diol.

Again, this has been experimentally confirmed using diols **1**−**13** as test compounds. Plots similar to those of Figure 4 are also obtained for the bis-(*S*)-MPA esters and show that the temperature dependence of the shifts is lower than that for the bis-(*R*)-MPA esters. The $\Delta\delta^{T1T2}$ values are presented in Table 1.

The data can be summarized as follows: the bis-(*S*)-MPA esters of all of the diols with configuration type A show that the methylene proton that resonates at room temperature at high field moves to higher field at lower temperatures, by 0.10−0.25 ppm, while the methylene proton that resonates at room temperature at low field just moves slightly to lower field by 0.00−0.10 ppm (Table 1). On the other hand, the bis-(*S*)-MPA esters of all the diols of type B show that the proton at high field goes to higher field by less than 0.10 ppm, while that at low field shifts by a maximum of 0.14 ppm (Table 1).

A practical application of these correlations is the assignment of the absolute configuration of a primary/secondary diol by low-temperature NMR of just one bis-MPA derivative [either the (*R*) or the (*S*)]. This method requires the following steps:

(a) Preparation of either the bis-(*R*)- or the bis-(*S*)-MPA derivative by standard methods.

(b) Comparison of its NMR spectra taken at room temperature and at lower temperature,[9] paying special attention to the signals of the methylene protons.

(c) Calculation of the $\Delta\delta^{T1T2}$ values for the methylene proton that resonates at high field and for the methylene proton that resonates at low field.

(d) If we have prepared a bis-(*R*)-MPA ester and the $\Delta\delta^{T1T2}$ for the high field proton is less than 0.10 ppm, then the diol has a type A absolute configuration, while if the $\Delta\delta^{T1T2}$ value were higher than 0.10 ppm (0.20−0.30 ppm), then the absolute configuration of the diol is represented by type B[10] (Figure 4).

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[8] Note that in a type A diol the pro-(*R*)-methylene proton resonates at high field and the pro-(*S*) resonates at low field, while in a type B diol the opposite situation applies. For simplification purposes, we will refer to them as high- and low-field protons.

[9] We found that temperatures in the range of 180−240 K are low enough to see the evolution of the signals; a 1:4 mixture of CD_2Cl_2−CS_2 is a very convenient NMR solvent for these experiments.

[10] With (*R*)-MPA, temperatures higher than 180 K can be used; that is, at 200 K, the $\Delta\delta^{T1T2}$ value to safely distinguish types A and B is 0.07 ppm and at 240 K is 0.04 ppm.

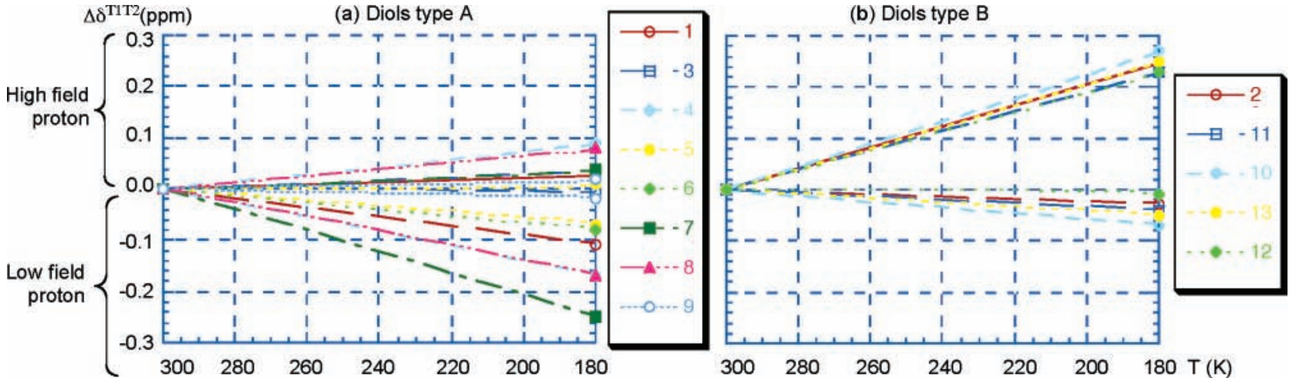

Figure 4. Evolution of the methylene protons of the bis-(*R*)-MPA esters of diols **1**−**13** [(a) type A, (b) type B] with the temperature.

Table 1. $\Delta\delta^{T1T2}$ Values (300−183 K) for the Methylene Protons of the Bis-(*S*)-MPA Esters of Diols **1**−**13**

diol		$\Delta\delta^{T1T2}$(ppm)	
type	number	low field	high field
A	1	−0.05	+0.25
	3	0.00	+0.14
	4	−0.01	+0.24
	5	−0.01	+0.19
	6	−0.02	+0.12
	7	−0.02	+0.16
	8	0.00	+0.12
	9	−0.07	+0.16
B	2	−0.14	+0.06
	10	−0.04	+0.01
	11	0.00	+0.01
	12	−0.10	+0.06
	13	−0.01	+0.02

(e) In case we have prepared a bis-(*S*)-MPA ester derivative and the $\Delta\delta^{T1T2}$ for the high field proton is greater than 0.10 ppm, then the diol has a type A absolute configuration, while if its $\Delta\delta^{T1T2}$ values were less than 0.10 ppm, then the diol has an absolute configuration represented by type B.

In conclusion, the analysis of the low-temperature shifts observed for the methylene protons of bis-MPA esters of a primary/secondary 1,2-diol allows the assignment of its absolute configuration in a very simple way because the derivatization of the two hydroxyl groups can be carried out simultaneously in a single operation and with only one enantiomer of the commercially available auxiliary reagent MPA.

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Supporting Information Available: Experimental data (α, room and low-temperature NMR, MS, etc.) of bis-MPA esters of diols **1**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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