Complexation with Barium(II) Allows the Inference of the Absolute Configuration of Primary Amines by NMR

Blanca López, Emilio Quiñoá, and Ricardo Riguera*

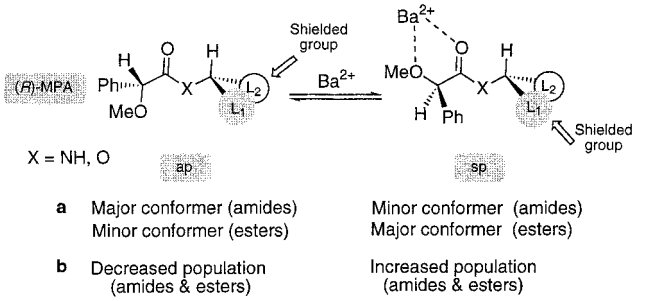
Departamento de Química Orgánica
Facultad de Química and Instituto de Acuicultura
Universidad de Santiago de Compostela
E-15706 Santiago de Compostela, Spain

Received February 25, 1999
Revised Manuscript Received August 10, 1999

One of the most useful methods for the determination of the absolute stereochemistry of a compound in solution is ^{1}H NMR spectroscopy, a technique that has been applied principally to alcohols, amines, carboxylic acids, and other substrates.[1] In its classical approach, the chiral substrate (i.e., a secondary alcohol or primary amine) is derivatized with the two enantiomers of a chiral acid, such as α-methoxyphenylacetic acid (MPA) or α-methoxytrifluoromethylphenylacetic acid (MTPA), and the ^{1}H NMR spectra of the two resulting diastereoisomers are compared. Interpretation of the chemical shift differences ($\Delta\delta^{RS}$) in light of the conformational composition of the diastereomeric esters or amides allows the spatial location of the substituents around the chiral center to be fixed and therefore the R/S configuration of the alcohol or amine to be defined.

In the case of secondary alcohols, the method has been optimized by working at low temperature[2] and, indeed, greatly simplified to require the use of only one derivative [just the ester of (*R*)- or (*S*)-MPA] instead of two.[3] Unfortunately, the determination of the absolute configuration of amines by NMR remains practically unchanged since the pionering works of Mosher and Trost with MTPA[4] and MPA[5] is limited because (a) preparation of two derivatives [the amides derived from (*R*)- or (*S*)-MPA or MTPA] is still necessary, (b) the complexity of the conformational composition of the amide prevents the application of the low-temperature strategy that proved so effective in the case of alcohols,[3] and (c) the assignment of configuration depends generally on very small $\Delta\delta^{RS}$ shifts. In addition, new or more efficient reagents have not been described to date.[6] In this communication we show that the preparation of two diastereomeric derivatives is no longer required because the absolute configuration of an amine can be determined using only one MPA amide derivative at room temperature if a complex with Ba^{2+} is formed *in situ* to fix a certain conformation.

According to conformational studies, MPA amides consist of two main forms in equilibrium: ap and sp, with the former being the most stable (Figure 1).[6a−c] The success in the use of this reagent depends on the excess population of one of these two conformers and the resulting aromatic shielding produced by the phenyl ring on L_1 or L_2. We reasoned that if a metal complex were formed between certain substituents of the MPA amide, the conformational equilibrium should shift in one direction and this should affect the shielding/deshielding of L_1/L_2 in a predictable way.



a. In the absence of the barium(II) salt. **b.** In the presence of the barium(II) salt

Figure 1. Main conformers present in the equilibrium of (*R*)-MPA amides and (*R*)-MPA esters in the absence and in the presence of a barium salt (suggested from the experimental data).

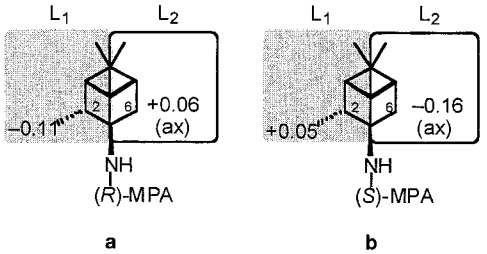


Figure 2. Selected $\Delta\delta^{Ba}$ values (ppm) obtained from the ^{1}H NMR spectra of the (*R*)-MPA amide of (−)-isopinocampheylamine (a) and the (*S*)-MPA amide (b).

In fact, when salts of Li^+, Na^+, K^+, Cs^+, Mg^{2+}, Ca^{2+}, and Ba^{2+} (progressive additions ranging from 1 up to 5 equiv of salt) were added to the NMR tubes containing the (*R*)-MPA amide of (−)-isopinocampheylamine in MeCN-d_3, useful changes in the chemical shifts of the isopinocampheylamine moiety were only observed in the cases of Mg^{2+}, Ca^{2+}, and Ba^{2+}, with the latter being the metal that gave the largest shifts (either as its perchlorate or iodide salt).[7] In particular, the signals due to substituents located under the aromatic shielding cone in the ap conformer (L_2 in Figure 1; 6-CH_2 in Figure 2a) were shifted downfield when Ba^{2+} was added ($\Delta\delta^{Ba}(L_2) > 0$),[8] while signals due to the nonshielded substituents (L_1 in Figure 1; 2-Me in Figure 2a) were shifted upfield ($\Delta\delta^{Ba}(L_1) < 0$). Shifts with opposite signs were observed when the (*S*)-MPA amide was used instead (Figure 2b).

Analogous behavior was observed when the ^{1}H NMR spectra of 26 structurally representative (*R*)- and (*S*)-MPA amides of known absolute stereochemistry (Figure 3)[9] were compared with the spectra obtained after the addition of 2 equiv[10] of $Ba(ClO_4)_2$. The highlights of this study can be summarized in two main points: (1) In all the cases studied the signs of the shifts for L_1 and L_2 show the same pattern as above, despite the different structural characteristics (presence of polar/nonpolar substituents, short/long chains, aromatic/aliphatic rings, bulky/small groups,

(1) For a review on the use of NMR for the assignment of absolute configuration and ee measurements see: Uray, G. *Houben-Weyl: Methods in Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart/New York, 1996; Vol. 1, p 253.

(2) (a) Seco, J. M.; Latypov, Sh. K.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **1995**, *6*, 107−110. (b) Seco, J. M.; Latypov, Sh. K.; Quiñoá, E.; Riguera, R. *Tetrahedron* **1997**, *53*, 8541−8564.

(3) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 877−882.

(4) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143−2147.

(5) Trost, B. M.; Bunt, R. C.; Pulley, Sh. R. *J. Org. Chem.* **1994**, *59*, 4202−4205.

(6) (a) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 1538−1545. (b) Seco, J. M.; Latypov, Sh. K.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1997**, *62*, 7569−7574. (c) Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 4669−4675. (d) Hoye, T. R.; Renner, M. K. *J. Org. Chem.* **1996**, *61*, 8489−8495. (e) García-Martínez, C.; Taguchi, Y.; Oishi, A.; Hayamizu, K. *Magn. Res. Chem.* **1998**, *36*, 429−435.

(7) Addition of salts of the monovalent cations produced no observable shifts, while that of Mg^{2+}, Ca^{2+}, and Ba^{2+} perchlorates induced downfield shifts of 0.03, 0.08, and 0.11 ppm, respectively, for 2-Me.

(8) The shifts induced by addition of the metal cation can be conveniently expressed for each substituent as $\Delta\delta^{Ba}(L_1) = [\delta\ L_1$ at (*R*)-MPA amide + $Ba^{2+}] - [\delta\ L_1$ at (*R*)-MPA amide]; *idem.* $\Delta\delta^{Ba}(L_2)$.

(9) All compounds were synthesized and purified according to standard procedures (see ref 6a for amides, ref 2b for esters) from commercial compounds of known absolute configuration. All compounds gave satisfactory analytical and spectral data.

10.1021/ja990597m CCC: $18.00
Published on Web 10/01/1999

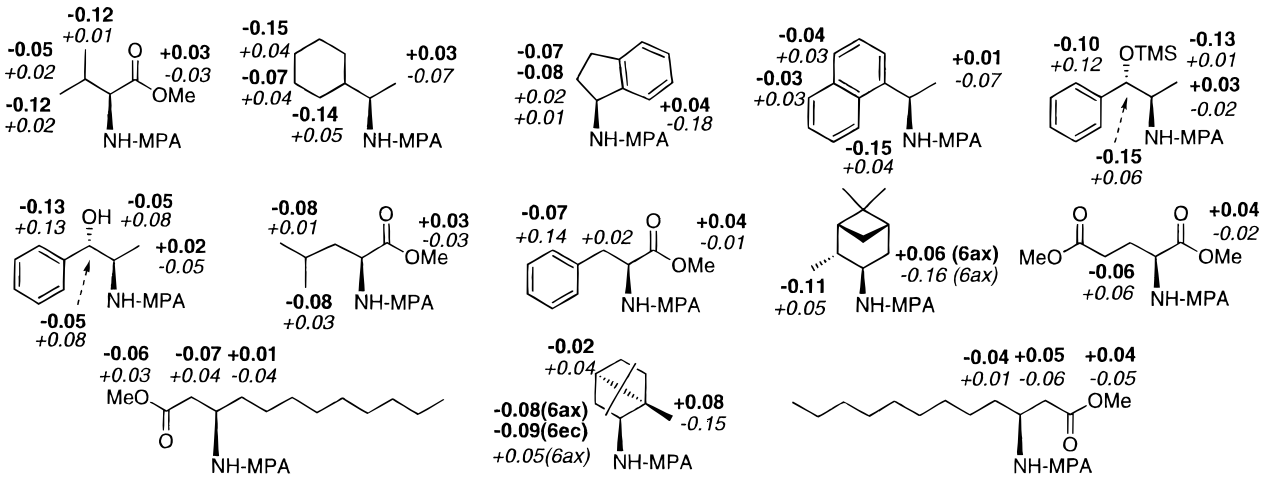


Figure 3. Selected $\Delta\delta^{Ba}$ values (ppm) obtained from the ^{1}H NMR spectra of the (*R*) (in **bold**) and (*S*) (in *italic*) MPA amides of structurally representative chiral amines.

etc.) of the chiral amines, and (2) the magnitude of the values are comparable to those obtained on using the two MPA or MTPA derivatives.[11]

From the structural point of view, these results may be explained if conformer sp becomes more populated upon addition of Ba^{2+}, suggesting a selective complexation of the metal with the C═O and MeO groups of the MPA amide that reverses the original conformational equilibrium. Experimental evidence can be found in the ^{13}C NMR spectrum of the (*R*)-MPA amide of (−)-isopinocampheylamine. In this example a 2.3 ppm downfield shift for the C═O group (from 169.3 to 171.6 ppm) is observed, which is attributed to the electron deficiency at the carbon atom generated by the complexation. In the corresponding ^{1}H NMR spectra of this derivative, the shift related to the NH proton remains practically unchanged upon addition of the salt, suggesting that this group is not involved in the complexation.

If this complexation is indeed the cause of the observed shifts, it should also operate in the case of MPA esters, where the composition of the conformational equilibrium is known to be shifted in the opposite way to that in the amides (Figure 1).[12] In this case, addition of the metal should make the population of the already dominant sp conformer even larger, and this fact should selectively increase the shielding on one substituent (L_1 in Figure 1, $\Delta\delta^{Ba}(L_1) < 0$) while decreasing it on the other (L_2 in Figure 1, $\Delta\delta^{Ba}(L_2) > 0$).[13] In fact, when the (*R*)- and (*S*)-MPA esters of (+)-isopinocampheol and (−)-menthol were treated with Ba^{2+}, the $\Delta\delta$ values were coherent with the proposed model and are shown in Figure 4. So, in both cases (esters and amides), the results strongly suggest that the metal ion shifts the equilibrium toward the sp conformer as shown in Figure 1.

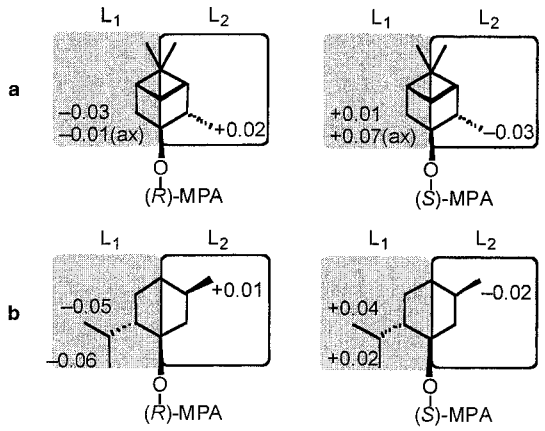


Figure 4. Selected $\Delta\delta^{Ba}$ values (ppm) obtained from the ^{1}H NMR spectra of the (*R*)- and (*S*)-MPA ester (+)-isopinocampheol (a) and (−)-menthol (b).

In conclusion, we present here a new, inexpensive way to determine the absolute stereochemistry of α-chiral primary amines, which is simpler than the existing methods. This new technique requires only half the usual amount of sample,[14] only one auxiliary reagent, and only one derivatization reaction, and is particularly suited for those areas where the quantity of the sample is a limitation.[15] A diagram to guide the user on the steps to follow can be found in the Supporting Information. Work is on progress to find out if this approach can be useful when other arylmethoxyacetic acids (AMAAs)[2b] and MTPA, which presents a more complex conformational composition than MPA,[6b] are employed as auxiliary reagents.

Acknowledgment. This work was supported by grants from CICYT (MAR95-1933-CO2-O2 and PM95-0135) and XUGA (20910B96 and 20908B97).

Supporting Information Available: Figures showing the partial ^{1}H NMR spectra of the (*R*)-MPA amide of L-valine methyl ester in the presence and absence of barium perchlorate and a diagram to deduce the absolute configuration of a chiral primary amine from the experimental $\Delta\delta^{Ba}$ signs of either its (*R*)- or (*S*)-MPA amide (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA990597M

(10) Addition of more >2 equivs of salt did not generate larger shifts. In a typical experiment, the ^{1}H NMR spectrum of 5 mg of amide dissolved in 0.5 mL of CD_3CN was recorded. 2 equiv of a 0.5 M solution of $Ba(ClO_4)_2$ in CD_3CN was added immediately to the sample in the NMR tube, and the second ^{1}H NMR spectrum was recorded. **Caution!** Although no problems were encountered during the course of this work (the barium salt is employed only in minute amounts), attention is drawn to the potentially explosive nature of perchlorates.

(11) The spectra for the (*R*)-MPA amide of L-valine methyl ester, both in the presence and in the absence of Ba^{2+}, can be found in the Supporting Information.

(12) In the case of esters, the composition of the conformational equilibrium is known to be shifted in the opposite way to amides: i.e., the sp conformer is the most populated one. For more information see: (a) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 504−515. (b) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569−8577.

(13) For a MPA ester, the population of the already dominant sp conformer becomes even larger, thus generating selective shielding/deshielding on both sides of the chiral center. The overall result implies a pattern for the $\Delta\delta$ signs that is the same as those of amides.

(14) The amide can be easily recovered by evaporation followed by solvent partition between $CHCl_3/H_2O$.

(15) Experiments carried out with 0.5 mg of substrate gave satisfactory results.