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Assignment of Absolute Configuration on the Basis of the Conformational Effects Induced by Chiral Derivatizing Agents: The 2-Arylpyrrolidine Case

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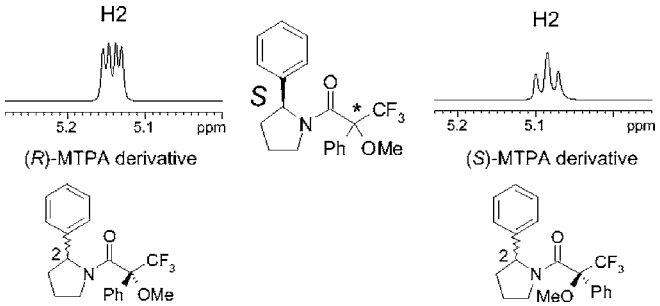
ABSTRACT



A novel approach for determining the absolute configuration of a chiral compound is proposed. The methodology is based on the distinct conformational effects imposed on a chiral substrate by each enantiomer of a chiral derivatizing agent. As a proof of concept, it is shown that the absolute configuration of 2-arylpyrrolidines can easily be determined by inspection of the multiplicity of the NMR signal of the methine proton of the pyrrolidine ring in the corresponding Mosher's amides.

Since its description more than 30 years ago, the so-called "Mosher's method" has been successfully applied to a great variety of chiral alcohols and amines.[1] The method involves derivatization of the chiral substrate with the two enantiomers of the chiral reagent α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), followed by the comparative analysis of the ^{1}H NMR spectra of the resulting diastereoisomers. The sign of the chemical shift differences of the substituents attached to the asymmetric carbon can then be correlated with the absolute configuration by using an empirical model. It is well-known that such chemical shift differences are a consequence of the different anisotropic effect experienced by the substituents from the phenyl group of the chiral auxiliary in each diastereoisomer.

Although the conformational aspects of the MTPA derivatives have been studied in great detail,[2] such studies have focused more on the conformational composition of the MTPA moiety—mainly on the rotation around the Cα−CO and Cα−Ph bonds—than on the conformational properties of the substrate upon ester or amide formation. In general, it is assumed that the conformation of the substrate moiety is similar in both diastereomers and it is generally treated as a rigid unit in the conformational correlation models. Nevertheless, one can envisage that each enantiomer of the chiral auxiliary may induce the chiral substrate to adopt different conformations in the resulting diastereomers. If this

(1) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2453. (c) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(2) Seco, J. M.; Latypov, S. K.; Quiñoa, E.; Riguera, R. *J. Org. Chem.* **1997**, *62*, 7569.

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is the case, we propose that such conformational differences can be exploited for the assignment of the absolute configuration of the chiral compound, provided the conformational preferences are interpreted in terms of a structural model. This approach differs from, and complements, current NMR methodologies that are based on the assessment of the chemical shift differences between the protons of the Mosher's derivatives.[3]

This novel concept has been explored with chiral 2-phenylpyrrolidine **1** of known (*S*)-configuration[4] (Figure 1). This

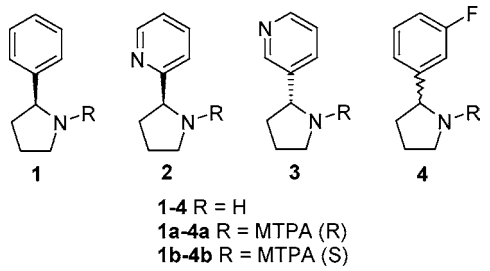

Figure 1. Structure of the 2-arylpyrrolidines and their corresponding MTPA amides.

substrate has been selected because (i) the conformational behavior of five-membered rings is usually highly influenced by the nature of the substituents[5] so that each enantiomer of the chiral auxiliary may have a distinct effect on the conformational preferences of the pyrrolidine ring, (ii) the application of standard Mosher's technology to these compounds is complicated by the coexistence of two unequally populated *syn* and *anti* rotamers around the C−N amide bond,[6] and (iii) 2-arylpyrrolidines are important compounds in organic and medicinal chemistry and the development of a rapid procedure for the determination of their absolute configuration would be highly beneficial.

To investigate the conformational properties of the pyrrolidine ring in the two diastereomeric Mosher's amides, we resorted to molecular mechanics calculations using the MMX force field within PCModel program.[7] A conformational search was performed for the diastereomeric amides *SR* and *SS* of amine **1**, where the first character refers to the configuration of the pyrrolidine carbon and the second to the configuration of the MTPA auxiliary. Rotation around the amide bond was allowed to take into account *syn* and *anti* orientations. The calculations predict that the *syn* rotamer is higher in energy than the corresponding *anti* form, in which steric interactions between the MTPA α-carbon substituents and the aryl ring are largely avoided. The MTPA moiety arranges the amide carbonyl synperiplanar to the trifluomethyl group, in agreement with previous studies of MTPA amides that showed that the synperiplanar arrangement is predominant over the antiperiplanar disposition.[2] Regarding the pyrrolidine moiety, the ring adopts a slightly distorted envelope conformation that places N1, C2, C3, and C5 on the plane and C4 at the flap of the envelope. Two conformational families, represented by conformers **A** and **B**, coexist in solution (Figure 2). The conformers differ in the

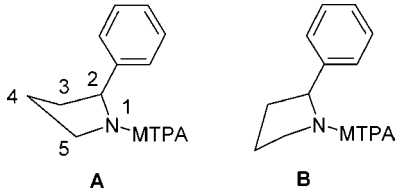

Figure 2. Representation of conformers **A** and **B**. The atom numbering is shown in conformer **A**.

orientation of the flap of the envelope relative to the phenyl substituent (located on the same side in conformer **A** and on opposite sides in conformer **B**). Remarkably, the calculations predict that **A** is the most abundant conformer in the *SR* isomer, whereas **B** is the preferred conformer in *SS* (Figure 3), indicating that the configuration of the derivatizing agent has an influence on the conformational behavior of the pyrrolidine ring as desired.

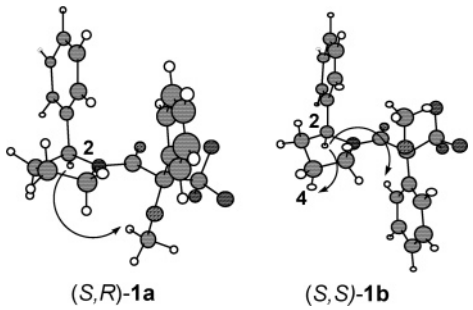

Figure 3. Conformational preference of diastereoisomers **1a** and **1b** according to the MMX force field.

The computational results were evaluated by NMR studies of amides **1a** (*SR*) and **1b** (*SS*). The ^{1}H spectra of both amides showed two sets of signals in 90:10 (**1a**) and 96:4 (**1b**) ratios as a consequence of slow rotation around the amide bond, as reported for other cyclic amides.[6] The major peaks were attributed to the most stable *anti* rotamer and assigned with the assistance of a HSQC experiment. The ^{1}H spectra of both amides showed an isolated signal at about 5.1 ppm corresponding to the methine proton (H2) of the pyrrolidine ring. In both amides, selective excitation of H2 in a 1D-NOESY

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(4) Matteson, D. S.; Youn, Kim, G. *Org. Lett.* **2002**, *4*, 2153.
(5) Eliel, E. E.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Eliel, E. E., Wilen, S. H., Eds.; Wiley-Interscience: New York, 1994; Chapter 11, p 758.
(6) (a) Hoye, T. R.; Rener, M. K. *J. Org. Chem.* **1996**, *61*, 2056. (b) Hoye, T. R.; Rener, M. K. *J. Org. Chem.* **1996**, *61*, 8489.
(7) PCModel for Windows, Version 8.5; Serena Software: Bloomington, IN, 2003.

experiment[8] produced NOEs to the vicinal protons (H3 and H3′) and to the *ortho* protons of the phenyl substituent on the pyrrolidine ring. Interestingly, a NOE between H2 and one of the protons at C4 is clearly observed in **1b**, whereas this NOE is weaker in **1a** (Figure 4), indicating a distinct

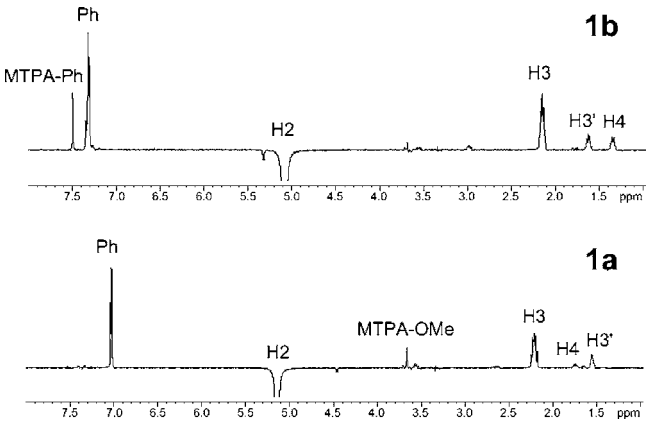

Figure 4. 1D-DPFGSE NOESY spectra of Mosher's amides **1a** and **1b** in DMSO-d_6. H2 resonance was inverted by using a Gaussian-shaped pulse.

conformational behavior of the pyrrolidine ring in each diastereomeric amide.

The intensity of the H2−H4 NOE is sensitive to the population of conformer **B** because in this conformer H2 is close to H4, whereas in conformer **A** these protons are too far away from each other to give rise to a NOE (Figure 3). Therefore, the fact that the H2−H4 NOE is stronger in **1b** than in **1a** agrees with the predominance of conformer **B** in the former, and of conformer **A** in the latter, as predicted by the molecular mechanics calculations. In addition, the orientation of the MTPA moiety relative to the pyrrolidine ring can also be inferred from the NOEs between the H2 and the protons of the chiral auxiliary (Figure 4). While a NOE between H2 and the methoxy protons was observed in **1a**, this NOE was absent in **1b**, where a NOE between H2 and the *ortho* protons of the MTPA phenyl ring was detected. This NOE pattern is consistent with the calculated structures that show that H2 is located on the same side as the methoxy group of the MTPA with respect to the plane of the envelope in **1a** and on the same side as the phenyl group of MTPA in **1b** (Figure 3).

The differences in the conformational behavior of the pyrrolidine ring in each diastereomeric amide are also reflected in the vicinal ^{1}H−^{1}H coupling constants between the pyrrolidine protons. Specifically, in comparing the ^{1}H spectrum of **1a** with that of **1b** (Figure 5), we noticed a significant difference in the multiplicity of the H2 signal. In **1a**, H2 is coupled to the vicinal protons at C3 with different coupling constants (7.9 and 3.7 Hz), resulting in a doublet

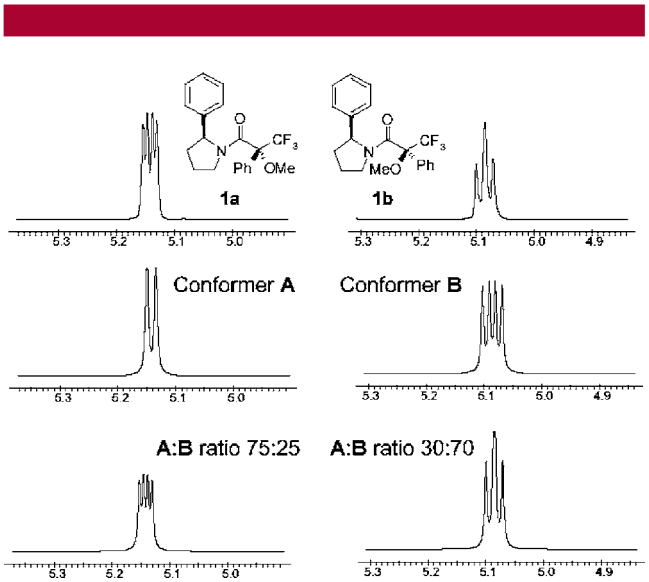

Figure 5. Experimental (top spectra) and calculated H2 signal for amides **1a** and **1b**.

of doublets, whereas in **1b** both coupling constants are similar, leading to a pseudo-triplet with an apparent coupling constant of 7.6 Hz.

The coupling constants between H2 and the C3 protons in conformers **A** and **B** were calculated by using the well-established Karplus−Altona relationship[9] in order to simulate the shape of the H2 signal that would be expected for each conformer. Figure 5 shows that neither **A** nor **B** reproduce the experimental H2 signal for any of the amides, indicating the presence of an equilibrium between both conformers that results in average coupling constant values. We have estimated the conformer ratio that provides the best fit to the experimental signal as depicted in Figure 5. Such analysis reveals that conformer **A** is the most populated geometry in **1a** whereas conformer **B** is the preferred geometry in **1b**, as previously concluded from NOE studies.

The combination of NMR and theoretical calculations therefore demonstrates that the conformational behavior of the pyrrolidine moiety in the Mosher's amides of **1** is influenced by the chirality of the MTPA auxiliary and, as a consequence, the NOEs and the proton−proton coupling constants of the pyrrolidine protons in Mosher's amides *SR* (or in its enantiomer *RS*) differ from those in the diastereomeric Mosher's amide *SS* (or in *RR*), and they can be utilized as diagnostic parameters for configurational assignment of 2-arylpyrrolidines. Conveniently, the absolute configuration of this type of compounds can be simply derived from the multiplicity of the H2 signal as follows: if the configuration of the MTPA moiety in the Mosher's amide is *R* and the H2 signal is a doublet of doublets (one of the couplings is roughly twice the other) the absolute configuration of the amine under examination is *S*, whereas if this signal is an apparent triplet (both couplings are similar) the absolute

(8) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *4*, 123.

(9) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

configuration is *R*. Conversely, if the configuration of the MTPA auxiliary is *S*, H2 appears as a triplet in the (*S*)-2-arylpyrrolidine and as a doublet of doublets in the (*R*)-2-arylpyrrolidine.

The validity of the procedure was verified for 2-arylpyrrolidines **2** and **3** whose absolute configurations were also known (*S* and *R*, respectively).[10,11] Both compounds were converted into the corresponding Mosher's amides **2a** and **3a**, in which the configuration of the chiral auxiliary is *R*, and **2b** and **3b** in which the configuration is *S*. Again, the ^{1}H spectra of all the amides show splitting of signals arising from the *anti* and *syn* rotamers. The diagnostic H2 signal of the most abundant *anti* rotamer appears between 5.0 and 5.2 ppm as a doublet of doublets in two derivatives (**2a** and **3b**) and as a pseudotriplet in the other two (**2b** and **3a**) as shown in Figure 6. According to the aforementioned rule the

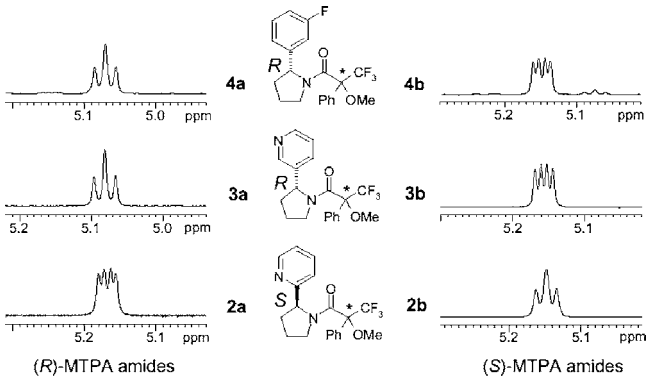

Figure 6. H2 signal for amides **2a**−**4a** and **2b**−**4b**.

absolute configuration is *S* for **2** and *R* for **3**. Hence, the correct configuration was elucidated, confirming the reliability of the approach. Furthermore, the methodology was applied to a compound of unknown configuration, 2-arylpyrrolidine **4**. Both Mosher's derivatives were prepared, **4a** and **4b**, in which the configuration of the MTPA stereogenic carbon atom is *R* and *S*, respectively. The H2 signal of the *anti* rotamer appears as a pseudotriplet (J = 7.3 Hz) in **4a** and as a doublets of doublets (J = 8.2 and 4.0 Hz) in **4b**, revealing that the configuration of **4** is *R*.

In short, we have introduced a novel concept for the assignment of the absolute configuration of a chiral amine that takes advantage of the conformational differences exhibited by the chiral substrate in the corresponding Mosher's amides, and demonstrated its usefulness for the determination of the absolute configuration of 2-arylpyrrolidines. To the best of our knowledge, this is the first example in which the absolute configuration of a chiral compound is determined from proton−proton coupling constants rather than from comparison of proton chemical shifts,[3] opening new avenues for the configurational assignment of chiral compounds. It is worth emphasizing the fact that, although both Mosher's amides are needed to ascertain the existence of conformational differences between diastereoisomers and identify a diagnostic NMR parameter that can be correlated with the absolute configuration, only a single Mosher's amide is required for application of the method in related compounds. The approach is advantageous over the standard Mosher's procedure described by Hoye et al. for cyclic amines that involves the identification of the resonances of both the *anti* and *syn* rotamers.[6] Further work to extend this novel approach to 2-alkyl and 3-substituted pyrrolidines is in progress and it will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopy data for **1a**−**4a** and **1b**−**4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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