Determination of the Absolute Configuration of Primary Amines in Polar NMR Solvents

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N-(2-Nitrophenyl)proline (2-NPP) can be used in a wide range of solvents as an effective chiral auxiliary for the absolute configuration assignment of α-chiral primary amines. Even in competitive hydrogen-bonding solvents, 2-NPP amides of primary amines retain the conformation preference for intramolecular hydrogen bonding and produce significant anisotropic effects on the amine substituents. As a result, the absolute configuration can be assigned by comparing the ^{1}H NMR spectra of diastereomeric 2-NPP amides recorded in polar NMR solvents.

^{1}H NMR spectroscopy is one of the most convenient and widely used methods to assign the absolute configuration of chiral compounds in solution.[1] In general, the chiral molecule is derivatized with the two enantiomers of a chiral derivatizing agent (CDA) and the NMR spectra are compared to obtain the chemical shift difference between the two resulting diastereomers ($\Delta\delta^{RS} = \delta(R) - \delta(S)$). Proper analysis of the $\Delta\delta^{RS}$ values based on the diastereomer conformations can lead to the absolute configuration assignment of the chiral substrate. Among several CDAs available for the configuration assignment of α-chiral primary amines, α-methoxyphenylacetic acid (MPA)[2] and α-methoxytrifluoromethylphenylacetic acid (MTPA)[3] are the two most widely used reagents.[4] For these reagents, however, the range of the solvent systems is limited; because the magnitude of $\Delta\delta^{RS}$ values is small and sensitive to solvent polarity, the analysis of MPA and MTPA amides has been carried out in relatively nonpolar solvents such as $CDCl_3$ and CD_2Cl_2.[1,5,6]

Recently, we have discovered that *N*-(2-nitrophenyl)proline (2-NPP) amides of α-chiral primary amines produce significantly large $\Delta\delta^{RS}$ values in $CDCl_3$.[7] In this solvent, the lowest energy conformation of 2-NPP amides is stabilized by a hydrogen-bonding network connecting the amide hydrogen, proline nitrogen, and nitro oxygen atoms (Figure 1), and the amine substituents R^1 and R^2 are under different anisotropic effect. We envisioned that this intramolecular-bifurcated hydrogen bond (H-bond) might control the 2-NPP amide conformation even in competitive hydrogen-bonding solvents, like methanol and acetone, so that the 2-NPP method could be extended to the solvent systems with better solubilizing properties for polar compounds. Here, we report that 2-NPP can be used as an effective CDA in polar solvents including dimethylsulfoxide-d_6 ($(CD_3)_2SO$), a highly polar solvent frequently used for the NMR analysis of organic compounds insoluble in $CDCl_3$.

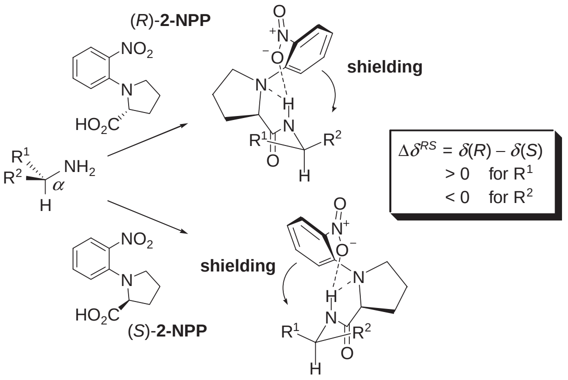

Figure 1. Conformational preference of (*R*)- and (*S*)-2-NPP amides. The hydrogen bonds connecting proline N, nitro O, and amide NH atoms are indicated by dashed lines.

Table 1. Selected $\Delta\delta^{RS}$ values of NPP–Leu–OMe ($R^1 = CO_2CH_3$, $R^2 = CH_2CH(CH_3)_2$) obtained in various NMR solvents

Solvent	ε[a]	pK_{HB}[b]	OCH_3	$C(CH_3)_2$
$CDCl_3$[c]	4.8	—	+0.26	−0.31/−0.30
C_5D_5N	12.4	1.86	+0.10	−0.16/−0.14
$(CD_3)_2CO$	20.7	1.18	+0.17	−0.23/−0.20
CD_3OD	32.7	0.82	+0.15	−0.24/−0.20
CD_3CN	37.5	0.91	+0.16	−0.25/−0.20
$(CD_3)_2SO$	46.7	2.58	+0.04	−0.10/−0.05

[a]From ref 11. [b]The value reported for the corresponding nondeuterated solvent in ref 9b. [c]From ref 7.

To test the solvent dependence of the $\Delta\delta^{RS}$ value, the ^{1}H NMR spectra of (*R*)- and (*S*)-2-NPP amides of L-leucine methyl ester (NPP–Leu–OMe) were recorded in five common NMR solvents (Table 1).[8] The $\Delta\delta^{RS}$ values obtained in these solvents have the same signs as those obtained in $CDCl_3$, suggesting that 2-NPP amides retain the same conformational preference in the tested solvents. As expected, the largest $\Delta\delta^{RS}$ values were observed when the spectra were recorded in $CDCl_3$ and smaller values in the hydrogen-bonding solvents. While there is some relationship between the solvent dielectric constant (ε) and the $\Delta\delta^{RS}$ value, it is clear that the solvent polarity scale is not sufficient to account for the observed variations.

To study the effect of solvent competition on the intramolecular H bonds and, in turn, on the $\Delta\delta^{RS}$ values, hydrogen-bonding properties of the solvents were compared. Figure 2 shows the correlation between the $\Delta\delta^{RS}$ absolute value ($|\Delta\delta^{RS}|$) and the H-bond acceptor scale (pK_{HB}) of the solvent, originally developed by Taft and co-workers to quantify the strength of H-bond acceptors.[9] In general, smaller $|\Delta\delta^{RS}|$ values were observed in better H-bond-accepting solvents presumably because solvent competition reduces the population of the representative conformation stabilized by the intramolecular H-bonds. One noticeable exception was CD_3OD, which has both H-bond-accepting and -donating properties so its competitive hydrogen-bonding ability could not be estimated properly from the H-bond accepter scale alone.

Among the tested solvents, $(CD_3)_2SO$ is the best at hydro-

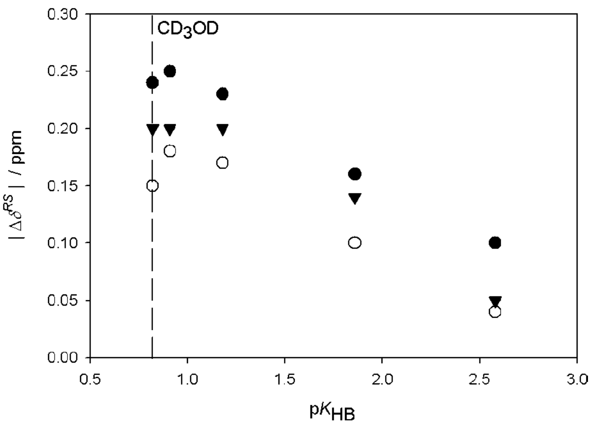

Figure 2. Correlation of the $|\Delta\delta^{RS}|$ of NPP–Leu–OMe with solvent H-bond acceptor strength (○, OCH$_3$; ▼ and ●, C(CH$_3$)$_2$).

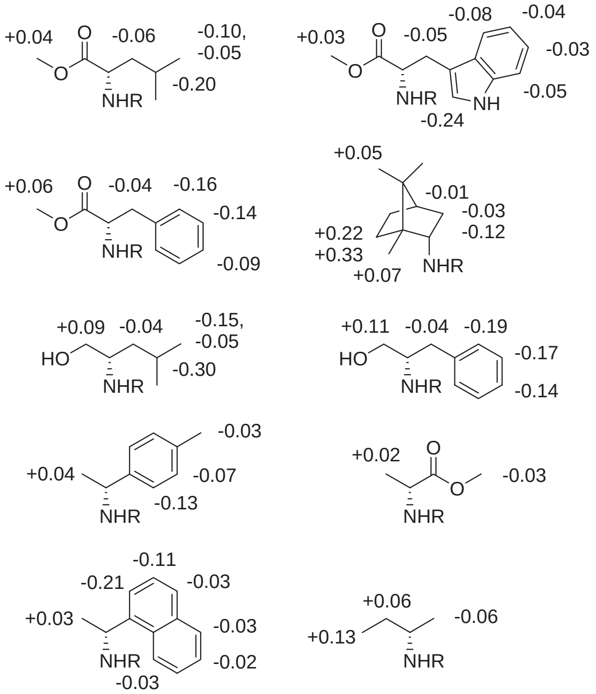

Figure 3. Selected $\Delta\delta^{RS}$ values of diastereomeric 2-NPP amides (R = 2-NPP). Chemical shift data were collected in (CD$_3$)$_2$SO.

gen-bond-accepting ability with a strongly polarized bond to oxygen. Although the $\Delta\delta^{RS}$ values obtained in (CD$_3$)$_2$SO are significantly smaller than those obtained in other solvents, the absolute values are still comparable to the values reported for the corresponding MPA and MTPA amides in CDCl$_3$,[5,10] suggesting that 2-NPP can be used in (CD$_3$)$_2$SO as a CDA producing modest $\Delta\delta$ values.

To check the general applicability of 2-NPP in (CD$_3$)$_2$SO, we examined more 2-NPP amides with diverse structures. The ^{1}H signals from the chiral substrate were assigned using COSY and other NMR spectroscopic methods, and their chemical shifts were compared to obtain the $\Delta\delta^{RS}$ values, which are summarized in Figure 3 along with the structures of the amines. In all cases, the $\Delta\delta^{RS}$ values are positive for the R^1 substituent and negative for the R^2 substituent and this general trend is fully consistent with the representative conformational models shown in Figure 1. These results demonstrate that the spatial positions of the R^1/R^2 substituents and, in turn, the absolute configuration of the chiral center can be assigned successfully on the basis of the $\Delta\delta^{RS}$ values obtained in (CD$_3$)$_2$SO.

In summary, we have shown that 2-NPP can be used to assign the absolute configuration of α-chiral amines in commonly used polar solvents. Solvent effects on the $\Delta\delta^{RS}$ value could be understood in terms of solvent competition on hydrogen-bonding interactions. Even in a highly competitive solvent such as (CD$_3$)$_2$SO, 2-NPP amides retain the conformational preference for intramolecular hydrogen bonding and produce selective anisotropic effects on the amine substrate. To our knowledge, 2-NPP is the first CDA for primary amines providing modest to large $\Delta\delta^{RS}$ values in a wide range of solvents. This 2-NPP method should find its application to amine compounds which are insoluble in nonpolar solvent systems recommended for the MPA and other methods.

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References and Notes

1 a) J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* **2004**, *104*, 17. b) T. J. Wenzel, *Discrimination of Chiral Compounds Using NMR Spectroscopy*, Wiley-Interscience, Hoboken, NJ, **2007**.
2 B. M. Trost, J. L. Belletire, S. Godleski, P. G. Mcdougal, J. M. Balkovec, J. J. Baldwin, M. E. Christy, G. S. Ponticello, S. L. Varga, J. P. Springer, *J. Org. Chem.* **1986**, *51*, 2370.
3 a) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512. b) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.
4 For other CDAs for amines, see: a) T. Oshikawa, M. Yamashita, S. Kumagai, K. Seo, J. Kobayashi, *J. Chem. Soc., Chem. Commun.* **1995**, 435. b) R. Chinchilla, L. R. Falvello, C. Najera, *J. Org. Chem.* **1996**, *61*, 7285. c) Harada, Y. Shimizu, K. Fujii, *Tetrahedron Lett.* **1998**, *39*, 6245. d) J. M. Seco, E. Quiñoá, R. Riguera, *J. Org. Chem.* **1999**, *64*, 4669. e) Y. Takeuchi, M. Segawa, H. Fujisawa, K. Omata, S. N. Lodwig, C. J. Unkefer, *Angew. Chem., Int. Ed.* **2006**, *45*, 4617.
5 S. K. Latypov, J. M. Seco, E. Quiñoá, R. Riguera, *J. Org. Chem.* **1995**, *60*, 1538.
6 MPA has been used in a single derivatization method where the Ba^{2+}-induced chemical shift changes are monitored in CD$_3$CN. See: a) B. López, E. Quiñoá, R. Riguera, *J. Am. Chem. Soc.* **1999**, *121*, 9724. b) R. García, J. M. Seco, S. A. Vázquez, E. Quiñoá, R. Riguera, *J. Org. Chem.* **2006**, *71*, 1119.
7 H. C. Ahn, K. Choi, *Org. Lett.* **2007**, *9*, 3853.
8 For the synthesis of the 2-NPP amides, see Ref. 7.
9 a) D. Gurka, R. W. Taft, *J. Am. Chem. Soc.* **1969**, *91*, 4794. b) C. Laurence, M. Berthelot, *Perspect. Drug Discovery Des.* **2000**, *18*, 39. c) C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed., Wiley-VCH, Weinheim, **2003**.
10 T. Kusumi, T. Fukushima, I. Ohtani, H. Kakisawa, *Tetrahedron Lett.* **1991**, *32*, 2939.
11 *NMR Solvent Data Chart*, Cambridge Isotope Laboratories, Inc., Andover, MA.

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