

N-(2-Nitrophenyl)proline: An Intramolecular Hydrogen Bond Forming Reagent for the Determination of the Absolute Configuration of Primary Amines

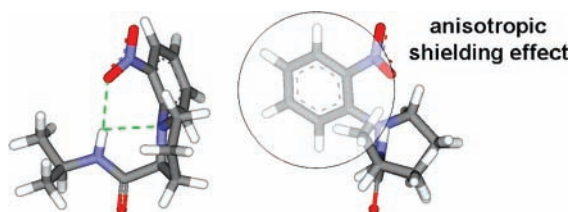
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ABSTRACT



N-(2-Nitrophenyl)proline (2-NPP) amides of primary amines have a conformational preference for intramolecular hydrogen bonding. Because of the strong and selective anisotropic effects on the amine substituents, the absolute configuration of α -chiral primary amines can be assigned by comparing the ^1H chemical shifts of diastereomeric 2-NPP amides.

Determination of the absolute configuration of chiral molecules is a key problem in the study of natural products and asymmetric synthesis, and one of the most convenient and widely used methods for absolute configuration determination is ^1H NMR spectroscopy.¹ In this method, the chiral substrate is derivatized with the two enantiomers of a chiral derivatizing agent (CDA), and the ^1H NMR spectra of the two resulting diastereomers are compared. Interpretation of the chemical shift difference ($\Delta\delta^{RS} = \delta(R) - \delta(S)$) based on the representative conformations of the diastereomers allows the absolute configuration of the chiral substrate to be assigned. Several CDAs have been developed for different classes of compounds, and for the cases of α -chiral primary amines, Mosher's α -methoxytrifluoromethylphenylacetic acid (MTPA, **1**)² and Trost's α -methoxyphenylacetic acid (MPA, **2**)³ are the two most frequently used reagents. Because of the complexity of the conformational distribution, however, the amides derived from these reagents show small $\Delta\delta^{RS}$ in general and the development of more efficient CDAs is still required.⁴

Here, we report that *N*-(2-nitrophenyl)proline (2-NPP, **3**) can be used as a new CDA for primary amines showing sufficiently large $\Delta\delta^{RS}$ values. Unlike MTPA and MPA, NPP has a cyclic structure in which the aryl and carboxylic acid groups are constrained through a five-membered ring (Figure 1). Once a primary amine is linked to the NPP carboxylic acid group through an amide bond, a hydrogen bond is

- (1) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117.
- (2) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
- (3) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374.
- (4) (a) Harada, K.; Shimizu, Y.; Fujii, K. *Tetrahedron Lett.* **1998**, *39*, 6245–6248. (b) López, B.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1999**, *121*, 9724–9725. (c) Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 4669–4675. (d) Porto, S.; Duran, J.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Org. Lett.* **2003**, *5*, 2979–2982. (e) García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2006**, *71*, 1119–1130. (f) Takeuchi, Y.; Konishi, M.; Hori, H.; Takahashi, T.; Kometani, T.; Kirk, K. L. *Chem. Commun.* **1998**, 365–366. (g) Takeuchi, Y.; Segawa, M.; Fujisawa, H.; Omata, K.; Ludwig, S. N.; Unkefer, C. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4617–4619.

Figure 1. Structures of MTPA, MPA, and NPP reagents.

expected to be formed between the amide hydrogen and proline nitrogen (N^{Pro}) atoms. Both the cyclic structure and the intramolecular hydrogen bond can help to reduce the molecule's conformational flexibility and stabilize a representative conformation where the substrate and the NPP phenyl ring with an anisotropic effect are in close proximity.

To investigate the utility of NPP reagents, we prepared diastereomeric NPP amides of α -chiral amines with diverse structures. (*S*)- and (*R*)-2-NPP were synthesized from L- and D-proline, respectively, by a nucleophilic aromatic substitution reaction with 1-fluoro-2-nitrobenzene. The acids were then coupled with chiral primary amines **5**–**14** (R = H) of known absolute configuration. The ^1H signals from the amine substrate were assigned by using COSY and other NMR spectroscopic methods and the chemical shifts were compared for both diastereomers to obtain the $\Delta\delta^{RS}$ values (Figure 2).

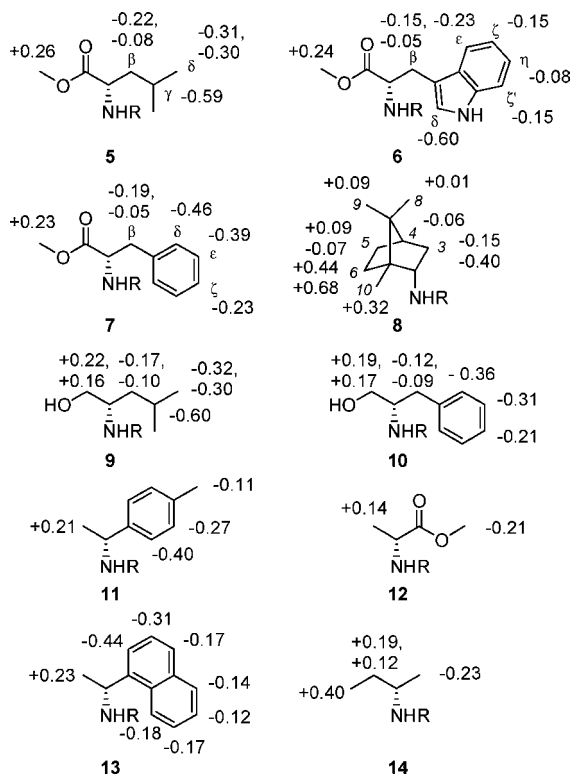


Figure 2. $\Delta\delta^{R5}$ values of 2-NPP diastereomeric amides (R = 2-NPP) of chiral amines **5–14**. ^1H NMR spectra were recorded in CDCl_3 .

All the tested compounds showed the same trend in their proton chemical shift differences. If the general structure of an α -chiral primary amine is represented as in Figure 3, the

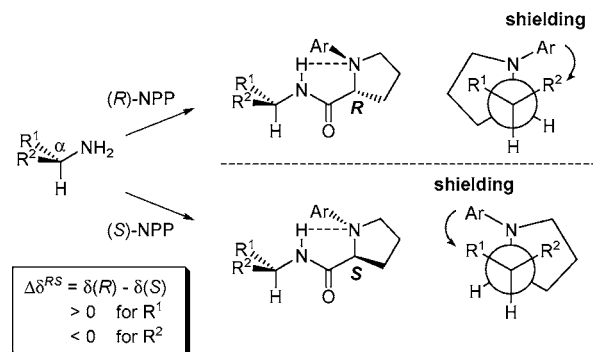


Figure 3. Representative conformations of (*R*)- and (*S*)-NPP amides. Intramolecular hydrogen bonds are indicated by dashed lines. In the Newman projection, the amide bond is omitted for clarity.

$\Delta\delta^{RS}$ values of the NPP amides are always positive for the R¹ substituent and negative for the R² substituent. This consistent and uniform distribution of the chemical shift differences could be explained on the basis of the amide conformation shown in Figure 3. In this model conformation, the C α -H, N-H, and C=O bonds adopt an *all-anti* arrangement as in MTPA and MPA amides,¹ and the C=O and C-N^{Pro} bonds are also depicted in an *anti* relationship because this conformation can be stabilized by the intramolecular hydrogen bond between the amide hydrogen and proline nitrogen atoms. In (*R*)-NPP amides, the aryl group and the R² substituent are located on the same side of the amide plane so the anisotropic shielding of the R² substituent is expected. In (*S*)-NPP amides, the aryl group is on the opposite side of the plane and the R¹ substituent is under the shielding effect. Thus, the $\Delta\delta^{RS}$ values should be positive for the protons on the R¹ group and negative for the protons on the R² group. In general, the $\Delta\delta^{RS}$ absolute values of the 2-NPP amides are considerably larger than the values reported for the corresponding MTPA and MPA amides (Table 1), suggesting that 2-NPP can be used as a more error-free reagent for assigning the absolute configuration of chiral amines.

The conformational preference of 2-NPP amides was further investigated by using conformational search and ab initio calculations.⁵ In the lowest energy conformation of the (*S*)-2-NPP amide of isopropylamine (Figure 4), the (C α -H)-(N-H) and (C=O)-(C-N^{*Pro*}) bonds are in *anti* arrangements and the amide hydrogen and the proline nitrogen atoms are separated by 2.3 Å. The two methyl groups from the amine substrate are located on the opposite sides of the amide plane and the one corresponding to the

(5) Spartan'06 (Wavefunction, Inc.) was used for the calculations. A Monte Carlo conformation search was performed by using the MMFF force field to find the lowest energy conformation, which was then used as an initial structure for the ab initio geometry optimization (RTH/6-31G**).

Table 1. Selected $\Delta\delta^{RS}$ Values of the Diastereomeric Amides **5–8** Obtained with Different CDAs

	R =	MTPA ^a	MPA ^b	2-NPP	4-NPP
5	OCH ₃	−0.02	−0.06	0.26	0.07
	γ -CH	0.23	<i>c</i>	−0.59	−0.14
	δ -CH ₃	0.10/0.08	0.13/0.08	−0.31/−0.30	−0.13/−0.07
6	OCH ₃	−0.02	−0.06	0.24	0.03
	δ -CH	0.40	0.23	−0.60	−0.29
	ζ' -CH	0.02	0.10	−0.15	−0.05
7	OCH ₃	−0.03	−0.07	0.23	0.06
	δ -CH	0.25	0.19	−0.46	−0.24
	ϵ -CH	0.13	0.09	−0.39	−0.20
	ζ -CH	0.07	0.02	−0.23	−0.08
	3-CH _{endo}	0.07	0.11	−0.40	−0.12
8	CH _{exo}	0.07	0.08	−0.15	−0.03
	6-CH _{endo}	<i>c</i>	−0.06	0.68	0.28
	CH _{exo}	<i>c</i>	−0.07	0.44	0.19
	10-CH ₃	−0.08	−0.19	0.32	0.07

^a From ref 7. The values originally reported in ref 7a are $\Delta\delta^{SR}$ rather than $\Delta\delta^{RS}$ values. ^b From ref 8. ^c Not available.

R¹ group is located on the same side with the 2-nitrophenyl group. Interestingly, the nitro group is located in close proximity to the amide group enabling additional intramolecular hydrogen bonding between the nitro oxygen and the amide hydrogen atoms; the calculated distance between the two atoms is 2.2 Å and the N–H···O bond angle is 173°.

To investigate the effect of this additional hydrogen bond, we prepared a new set of diastereomeric amides from *N*-(4-nitrophenyl)proline (4-NPP, **4**), which in turn was synthesized from 1-fluoro-4-nitrobenzene. The $\Delta\delta^{RS}$ values obtained with 4-NPP have the same signs as those obtained with 2-NPP

(Table 1), suggesting that 4-NPP and 2-NPP amides adopt similar conformations. However, the $\Delta\delta^{RS}$ absolute values are significantly larger for the 2-NPP amides than for the corresponding 4-NPP amides, in which the nitro group is located at the *para* position of the phenyl ring and therefore cannot form a hydrogen bond with the amide group.⁶

Although detailed calculation studies are required to fully understand the relationship between the $\Delta\delta^{RS}$ values and the position of the electron-withdrawing substituent, the large $\Delta\delta^{RS}$ value of the 2-NPP amides is presumably due to the hydrogen bonding between the 2-nitro and the amide groups. Formation of this additional hydrogen bond increases the energy barrier for the (C=O)–(C–N^{Pro}) bond rotation and therefore stabilizes the *anti* conformation further. The hydrogen bond also restricts the rotation of the phenyl ring and stabilizes the rotamer in which the aromatic ring faces toward the amine substrate (Figure 4). These two factors can contribute together to increase the population of the conformer in which one of the amine substituents is located in the shielding region of the anisotropic group, resulting in the large $\Delta\delta^{RS}$ values of the 2-NPP amides.

In conclusion, we have presented an NMR spectroscopic method for the determination of the absolute configuration of α -chiral primary amines that is based on 2-NPP, a new CDA readily prepared by a single-step synthesis. Unlike MTPA and MPA amides, 2-NPP amides have a conformational preference for intramolecular hydrogen bonding between the chiral auxiliary and the amide group. As a result, significantly large $\Delta\delta^{RS}$ values were obtained with 2-NPP diastereomeric amides, providing a more reliable way to assign the absolute configuration of the amines.

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Supporting Information Available: Synthetic details and characterization data for compounds **3–14**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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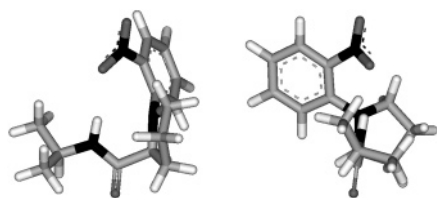


Figure 4. The calculated structure of the (*S*)-2-NPP amide of isopropylamine: a side view onto the amide plane (left) and a front view onto the proline ring (right). Progressively darker shades of gray represent H, C, O, and N, respectively.

(6) For the 4-NPP amides, the chemical shift of the amide NH proton is 0.6–0.8 ppm smaller and the N–H stretching frequency is 16–34 cm^{−1} higher than the corresponding 2-NPP amides. See the Supporting Information for the spectral data.

(7) (a) Kusumi, T.; Fukushima, T.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, 32, 2939–2942. (b) Seco, J. M.; Latypov, S. K.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1997**, 62, 7569–7574.

(8) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, 60, 1538–1545.