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TETRAHEDRON: *ASYMMETRY*

Simultaneous determination of enantiomeric purity and *erythro*/*threo* relationship in chiral 1,2-aminoalcohols by NMR using (*R*)-(+)-*t*-butylphenylphosphinothioic acid

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Abstract

The rapid simultaneous determination of enantiomeric purity and *erythro*/*threo* relationship for a series of chiral 1,2-aminoalcohols is reported. Complexation with 1 equivalent (*R*)-(+)-*t*-butylphenylphosphinothioic acid results in a preferred conformation of the aminoalcohol which in turn causes the interproton dihedral angle to assume either large (*threo*) or small (*erythro*) *J* values. Measurement of the resulting vicinal coupling constant allows easy and rapid assignment of *erythro* versus *threo*.

In medicinal chemistry today the increasing emphasis placed on chiral drugs has prompted the need for quick and accurate determination of enantiomeric purity. For the bench chemist, NMR spectroscopy has proven itself to be invaluable as the tool of choice in terms of speed and ease of use for this type of assay.[1] To discretely observe the ratio of enantiomers by NMR in solution one must form diastereomers, whether through direct covalent chemical derivatization[2] or via in situ equilibrium complexes utilizing non-bonded interactions with chiral solvating agents or CSAs[3] [i.e. chiral acids and amines (electrostatic), Pirkle reagent (hydrogen bonding)], or lanthanide shift reagents[4] (addition complexes).

We were faced with determining the enantiomeric purity of a series of 1,2-aminoalcohols. It has been reported previously that the CSA (*R*)-(+)-*t*-butylphenylphosphinothioic acid (TBPTA, Fig. 1) works well with chiral amines and aminoalcohols.[5] During the course of this study, we found that not only does TBPTA produce a high degree of chemical shift non-equivalence in 1,2-aminoalcohols ($\Delta\delta$ values of up to 400 Hz) but the resulting NMR spectrum can also yield the assignment of *erythro* or *threo* for a particular compound through measurement of vicinal *J* values following complexation. To investigate this phenomenon further, we studied a series of 1,2-aminoalcohols of both known and unknown configuration (Table 1).[6]

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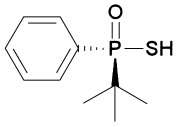
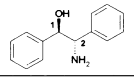
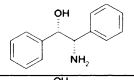
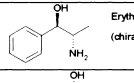
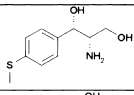
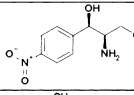
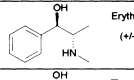
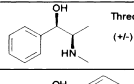
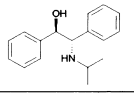
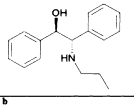
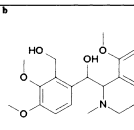
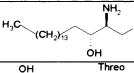
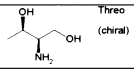


Figure 1. (*R*)-(+)-*t*-Butylphenylphosphinothioic acid (TBPTA)

Table 1
Results of complexation of (*R*)-(+)-*t*-butylphenylphosphinothioic acid with various racemic amino-alcohols

No.	Aminoalchohol structure	δ_{free} (ppm)		$\delta_{complex}$ (ppm)		$\Delta\delta$ (ppm)		$\Delta\delta\delta$ (ppm/Hz)		$^3J_{1,2}$	
		H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2	Free	Cmplx
1	 Erythro (+/-)	4.749	4.170	5.304 5.372	4.397 4.404	0.555 0.623	0.227 0.234	0.068 34	0.007 3.4	6.4	3.3
2	 Threo (+/-)	4.654	3.987	4.213 4.931	3.498 4.297	-0.441 0.277	-0.489 0.310	0.718 359	0.799 400	6.4	10
3	 Erythro (chiral)	4.518	3.193	5.150	3.382	0.632	0.189			4.8	2.6
4	 Threo (chiral)	4.595	2.978	4.673	3.140	0.078	0.162			5.2	9.5
5	 Threo (chiral)	[a]4.66	2.817	4.726	3.076	0.062	0.260			4.8	9.4
6	 Erythro (+/-)	4.758	2.803	5.365 5.447	3.232 3.246	0.607 0.689	0.429 0.443	0.083 41.4	0.014 7	4.1	1.8
7	 Threo (+/-)	4.174	2.610	4.563 4.618	3.167 3.320	0.339 0.444	0.557 0.710	0.054 27.2	0.153 76.4	8.2	9.9
8	 Erythro (+/-)	4.811	4.073	5.605 5.778	4.169 4.222	0.794 0.967	0.096 0.149	0.173 87	0.053 26	5.3	2.9
9	 Erythro (+/-)	4.819	3.895	5.559 5.717	4.163 4.178	0.740 0.898	0.268 0.823	0.158 79	0.015 7.5	5.7	2.9
10	[b]  Unknown stereochemistry and enantiomeric purity	4.713	4.03	5.961	4.924	1.248	0.894			8.9	2.3
11	 Erythro (+/-)	[c]3.25	2.461	3.822 3.848	2.797 2.826	0.569 0.595	0.336 0.365	0.025 13	0.029 15	5	3.4
12	 Threo (chiral)	3.314	2.133	3.615	2.612	0.301	0.479			4.9	7.8

a) Free in CD_3CN
b) Compound found to be enantiomerically pure and configuration deduced to be *erythro* from J value after complexation with TBPTA (unknown when purchased)
c) Both free and complexed in C_6D_6 at 60°C

Using TBPTA as the chiral agent, we observed that the vicinal *J* of the *erythro* compounds had a value of ca. 3 Hz or less after complexation. On the other hand, the *J* values of the *threo* aminoalcohols in most cases were ca. 9 Hz or greater. It seems likely that these changes reflect the formation of a strong internal hydrogen bond between the hydroxyl proton and ammonium group, as has been suggested previously by others,[7] resulting in a preferred conformation for the molecule in the presence of TBPTA. In the case of *erythro* configuration, this leads to a smaller dihedral angle in the preferred conformation than in the averaged free state, thus yielding a smaller *J* value. Conversely, when the hydroxy and amino groups of the *threo* isomer are aligned in an eclipsed fashion, as in the case of a hydrogen-bound preferred conformation, the angle between the methine protons approaches 180°, as shown in Fig. 2. This results in a much larger *J* value than in the non-complexed state, which is generally in the 4 to 6 Hz range. Therefore, the observation of the direction of change of interproton *J* values in the TBPTA complexes of 1,2-aminoalcohols should provide a rapid and efficient method of assigning configuration for these molecules.

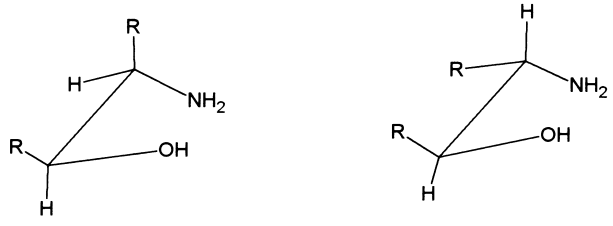


Figure 2.

The results obtained for compounds **1** and **2** are illustrative of the utility of the method. In Fig. 3, one can clearly see that a mixture of isomers is present. Upon the addition of TBPTA we get discrimination of the enantiomers, as well as from the *J* values the assignment of *erythro* versus *threo*. This method is trivial to use and we are presently looking at the possibility of determining the absolute stereochemistry with TBPTA.

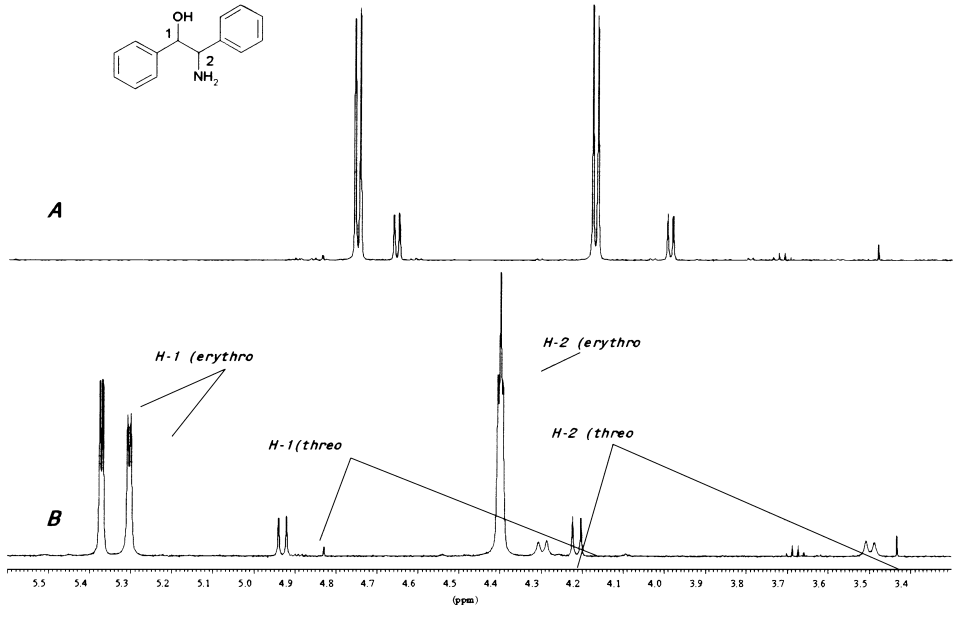


Figure 3. (*A*): An 83:17 mixture of **1** and **2** in $CDCl_3$; (*B*): Same mixture with 1 equivalent (*R*)-(+)-TBPTA

References

1. Parker, D. *Chem. Rev*. **1991**, *91*, 1441–1457.
2. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem*. **1969**, *34*, 2543–2549.
3. Pirkle, W. H.; Hoover, D. J. *Top. Stereochem*. **1982**, *18*, 263–331.
4. Fraser, R. R. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, Chapter 9, p. 173.
5. Omelanczuk, J.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2687–2694.
6. NMR spectra were obtained on a Bruker DRX-500 NMR spectrometer operating at 499.87 MHz for proton. Chemical shifts are reported in parts-per-million (ppm) and are referenced to TMS. Coupling constants *J* are in hertz (Hz). All NMR spectra were taken in $CDCl_3$ at 300°K unless otherwise noted. Aminoalcohols were either synthesized in-house or were purchased (Fluka, Sigma, Aldrich) and were used without further purification. (*R*)-(+)-TBPTA was synthesized according to the method described previously.[5] Equimolar amounts of substrate and (*R*)-(+)-TBPTA are weighed out. After obtaining a reference spectrum of the substrate in $CDCl_3$, to the contents of the NMR tube are added (*R*)-(+)-TBPTA and the resulting spectrum acquired. Once the hydroxy and amino methine protons are identified, the vicinal *J* value is measured.
7. Jen, T.; Kaiser, C. *J. Med. Chem.* **1977**, *20*, 693–698, and references cited within.