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Chiral *t*-butylphenylphosphinothioic acid in NMR analysis of tertiary amine oxides with a stereogenic nitrogen atom

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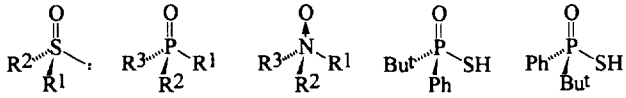
Abstract: The enantiomers of tertiary amine oxides **3** show NMR spectral nonequivalence in the presence of (−)-(*S*)- or (+)-(*R*)-*t*-butylphenylphosphinothioic acid **4**. It is observed even for the ϵ-methyl protons and is large enough to determine the ee values of **3** having long alkyl chains. The enantiomeric thioacids **4** induce also an extremely large magnetic nonequivalence of the geminal N-methylene protons in **3**. © 1997 Elsevier Science Ltd

Chiral sulfoxides **1**[1] and phosphine oxides **2**[2] play an important role in the stereochemistry of hetero-organic compounds and especially in asymmetric synthesis. However, the nitrogen analogues of **1** and **2**, i.e. chiral tertiary amine oxides **3**, are less known and investigated. At the beginning of this century Meisenheimer and his coworkers[3] resolved some asymmetric N,N-dialkylarylamine oxides via diastereoisomeric salts with optically active α-bromo-camphorosulfonic and tartaric acids. More recently, Toda *et al.*[4] described resolutions of various amine oxides **3** by selective crystalline complexation with optically active host compounds. Optically active N-oxides **3** were also obtained by chemical asymmetric oxidation of tertiary amines albeit with very low enantiomeric purity.[5] Consequently, the methods for determining enantiomeric purity[4,6] and absolute configuration of **3**[6,7] are few in number and of limited applicability.



1 **2** **3** (-)-(*S*)-**4** (+)-(*R*)-**4**

As part of our program involving enzyme-mediated reactions of chiral or prochiral hetero-organic substrates,[8] we became interested in chiral *t*-butylphenylphosphinothioic acid **4** as a new chiral solvating agent (CSA) for NMR analysis of heteroatom compounds containing the stereogenic sulfur and phosphorus atoms such as sulfoxides **1**[9] and phosphoryl compounds **2**.[10,11] In this paper we wish to report the most interesting feature of the thioacid **4** as CSA for chiral tertiary amine oxides **3**, namely, its ability to induce simultaneously magnetic nonequivalence of the enantiotopic methyl and methylene protons of an alkyl chain or benzyl group and an extremely large nonequivalence of the geminal N-methylene protons in **3**.

We have analyzed the ^{1}H NMR spectra of $CDCl_3$ solutions containing the free racemic amine oxides **3a–g** and their mixtures with (+)-(*R*)- or (−)-(*S*)-enantiomer of the thioacid **4**. In every case we have observed the typical doubling of the proton resonances of **3** induced by optically active **4** (see Table 1).

For example, the value of magnetic nonequivalence ($\Delta\delta$) of the N-methyl protons in **3a** is 0.130 ppm. For the C-methyl protons in this oxide the $\Delta\delta$ value is even higher and equal to 0.294 ppm. It should be pointed out that these values are much higher than those found[6] for the N- and C-methyl protons of

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Table 1. Magnetic nonequivalence of enantiomers and geminal protons of amine oxides **3** measured by ^{1}H NMR with (+)-(*R*)- or (−)-(*S*)-*t*-butylphenylphosphinothioic acid **4** as a chiral solvating agent

No	N-oxide			Chemical shift			Δδ
	R^1	R^2	R^3	δ (ppm)[a]	δ (ppm)[b]		(ppm)
3a	Ph	$\underline{CH_3}$	CH_2CH_3	3.55[c]	3.85[c]	3.98[c]	0.130
3a	Ph	CH_3	$C\underline{H}^AH^MCH_3{}^X$	3.719[d]	4.50[h]	4.72[h]	0.220
3a	Ph	CH_3	$CH^A\underline{H}^MCH_3{}^X$	3.719[d]	3.76[h]	3.90[h]	0.140
3a	Ph	CH_3	$CH^AH^M\underline{CH_3}{}^X$	1.18[e]	0.886[e]	1.18[e]	0.294
3b	Ph	$\underline{CH_3}$	$CH_2CH_2CH_3$	3.538[c]	3.828[c]	3.959[c]	0.131
3b	Ph	CH_3	$C\underline{H}^AH^MCH_2{}^XCH_3$	3.49-3.70[f]	3.623[i]	3.771[i]	0.148
3b	Ph	CH_3	$CH^A\underline{H}^MCH_2{}^XCH_3$	3.49-3.70[f]	4.357[i]	4.561[i]	0.204
3b	Ph	CH_3	$CH_2CH_2\underline{CH_3}$	0.847[e]	0.831[e]	0.839[e]	0.008
3c	$PhCH_2$	$\underline{CH_3}$	CH_2CH_3	2.977[c]	3.200[c]	3.250[c]	0.050
3c	$Ph\underline{CH^AH^B}$	CH_3	CH_2CH_3	4.40; 4.32[g]	4.73; 5.03[g]	4.82; 4.92[g]	0.089
3d	$PhCH_2$	$\underline{CH_3}$	$CH_2CH_2CH_2CH_3$	2.98[c]	3.26[c]	3.31[c]	0.050
3d	$Ph\underline{CH^AH^B}$	CH_3	$CH_2CH_2CH_2CH_3$	4.33; 4.38[g]	4.733; 5.097[g]	4.86; 4.97[g]	0.127
3e	$PhCH_2$	$\underline{CH_3}$	$CH_2(CH_2)_3CH_3$	2.966[c]	3.216[c]	3.251[c]	0.035
3e	$Ph\underline{CH^AH^B}$	CH_3	$CH_2(CH_2)_3CH_3$	4.31; 4.37[g]	4.71; 5.02[g]	4.67; 4.71[g]	0.035
3e	$PhCH_2$	CH_3	$CH_2(CH_2)_3\underline{CH_3}$	0.883[e]	0.809[e]	0.846[e]	0.037
3e	$PhCH_2$	CH_3	$C\underline{H}^AH^MCH_2{}^X(CH_2)_2CH_3$	3.070[e]	3.480[i]	3.530[i]	0.050
3e	$PhCH_2$	CH_3	$CH^A\underline{H}^MCH_2{}^X(CH_2)_2CH_3$	3.070[e]	3.150[i]	3.250[i]	0.100
3f	$PhCH_2$	$\underline{CH_3}$	n-C_7H_{15}	3.036[c]	3.238[c]	3.274[c]	0.036
3g	$PhCH_2$	$\underline{CH_3}$	i-C_3H_7	2.85[c]	3.150[c]	3.230[c]	0.080

[a] in a free N-oxide; [b] in complex with **4**; [c] singlet; [d] quartet; [e] triplet; [f] multiplet; [g] AB system; [h] quartets of doublets; [i] triplets of doublets

3a in the presence of (+)-(*S*)-2,2,2-trifluorophenylethanol – a commonly used CSA (Δδ=0.019 ppm for N–CH_3 and 0.028 ppm for C–Me). Interestingly, in the case of a mixture of the amine oxide **3e** and (−)-(*S*)-**4** two nicely separated (Δδ=0.037 ppm) triplets of the pentyl methyl protons are observed in the ^{1}H NMR spectrum which demonstrates the efficiency of the present method of enantiomer analysis of chiral amine oxides **3**.

Figure 1a shows the proton spectrum of the free racemic oxide **3a** indicating that the diastereotopic N-methylene protons are isochronous and appear as a typical quartet. However, in the presence of (+)-(*R*)-**4** these protons become nonequivalent and show (Figure 1b) an AMX_3 pattern (two sets of quartets of doublets for each diastereoisomeric solvate, 32 lines altogether) with the unexpectedly large geminal magnetic nonequivalence values equal to 0.74 and 0.82 ppm.

The induced enantiomer nonequivalence is also large and different for these two methylene protons (Δδ=0.220 and 0.140 ppm). Similarly, the N-methylene protons of **3e**, which appear in the proton spectrum as a triplet, show typical AMX_2 pattern after addition of (+)-(*R*)-**4** with the geminal magnetic noneqivalence values of 0.330 and 0.280 ppm. A very large value of geminal magnetic nonequivalence is also observed for the solvates of **3b** with (+)-(*R*)-**4** (Δδ=0.734 and 0.796 ppm).

In conclusion, we have demonstrated that chiral *t*-butylphenylphosphinothioic acid **4** is a versatile and very promising CSA for the NMR ee determination of tertiary amine oxides **3**. It is obvious that the spectral nonequivalence observed is due to the formation of the corresponding diastereoisomeric

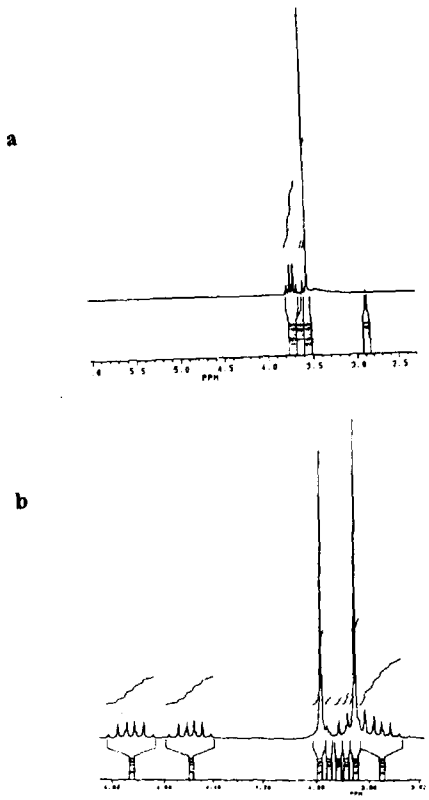

Figure 1. ^{1}H NMR spectra of amine oxide **3a**: **a**, alone; **b**, complex with (−)-(*S*)-**4**.

salts. The elucidation of their structures and correlation of the absolute configuration of **3** by the NMR–CSA method are in progress.

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