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Chiral *t*-Butylphenylphosphinothioic Acid: A Useful Chiral Solvating Agent for Direct Determination of Enantiomeric Purity of Alcohols, Thiols, Amines, Diols, Aminoalcohols and Related Compounds.

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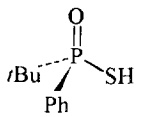
Dedicated to Professor Ekkehard Fluck on the occasion of his 65th birthday.

Abstract: Enantiomers of *t*-butylphenylphosphinothioic acid were found to be useful chiral solvating agents (CSAs) for ^{1}H-NMR determination of enantiomeric excess (ee) of many classes of chiral organic compounds, such as alcohols, diols, thiols, mercaptoalcohols, amines, aminoalcohols, hydroxyacids and related compounds. Copyright © 1996 Elsevier Science Ltd

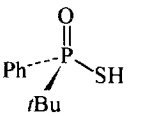
The increasing tendency to use chiral pharmaceuticals as single enantiomers as well as the recent progress in enantioselective synthesis stimulated extensive investigations on the methods for determination of enantiomeric purity and absolute configuration of chiral compounds[1]. Among the techniques used for this purpose, the NMR methods have found so far a widest application. The conversion of the mixture of enantiomers into diastereoisomeric species, which are distinguishable in NMR spectra, is typically achieved by three types of chiral auxiliaries i.e. chiral lanthanide shift reagents (CLSRs), chiral derivatizing agents (CDAs) and chiral solvating agents (CSAs). The first two of them have some limitations that have been discussed in the recent review by Parker[1a]. For example, CLSRs do not form complexes with many classes of organic compounds. Chiral derivatizing agents, on the other hand, require formation of the covalently bonded diastereoisomers prior to NMR analysis. The derivatization step should be carefully done to avoid a possible kinetic resolution and racemization of the reacting partners as well as to achieve complete condensation. When discussing derivatizing agents, it is interesting to point out that achiral bifunctional derivatizing agents have also been employed for the enantiomeric analysis of chiral compounds, especially of chiral alcohols and thiols[1b,2]. In this case, chiral and achiral (meso) diastereoisomers exhibiting different chemical shifts are formed which permits calculation of enantiomeric purity of the investigated sample.

However, the most advantageous and simple approach to enantiomeric ratio determination is based on the use of chiral solvating agents (CSAs). They form with enantiomeric pair diastereoisomeric solvation complexes which are in dynamic equilibrium and show nonequivalent spectra[3].

Among the CSAs reported in the literature, (-)-(S)- and (+)-(R)- *t*-butylphenylphosphinothioic acid **1** turned out to be very useful in the determination of enantiomeric purity of chiral heteroatom compounds containing the stereogenic phosphorus, sulfur and nitrogen atoms such as phosphoryl compounds[4], sulfoxides[5] and aminoxides[6]. We found now that the application of the chiral thioacid **1** as a CSA is much wider and that it can conveniently be used to determine enantiomeric content of chiral alcohols, thiols, amines, diols, aminoalcohols, mercaptoalcohols and related compounds[7].



(-)-(S)-**1**



(+)-(R)-**1**

The standard conditions for enantiomer analysis by ^{1}H-NMR using **1** as a CSA are following: to an NMR tube containing (+)-**1** (ca 4-8 mg) dissolved in $CDCl_3$ (0,5 ml) the investigated compound (0.8 eq in respect to **1**) is added and ^{1}H-NMR spectrum is recorded.

Table 1 summarizes the data on racemic alcohols **2** and thiol **3**. In some cases optically active alcohols **2d**, **2e**, **2g** were analyzed in order to compare the values of enantiomeric purity determined by weight and by rotation with results obtained by the present method. A typical ^{1}H-NMR spectrum of racemic 3,3-dimethyl-butanol-2 **2a** in the presence of (+)-(R)-**1** is shown in Fig.1. As can be seen, the magnetic nonequivalence due to the formation of diastereoisomeric solvates is visible for three groups of protons i.e. the *t*-butyl (A), methyl (B) and methine (C) protons. Although the chemical shift differences are not so large (1.8, 3.5 and 1.1 Hz for A,B and C, respectively), it is easy to distinguish both enantiomeric alcohols **2a** and to determine their ratio by integration. In this context, it is important to note that the values of magnetic nonequivalence $\Delta\delta$ may be increased by lowering the temperature of the investigated sample. Fig. 2 illustrates this temperature effect on the $\Delta\delta$ values of the A,B,C protons in the alcohol **2a**. It reveals also that a substantial increase of $\Delta\delta$ is observed for the protons which are closer to the stereogenic carbon atom. For example, the $\Delta\delta$ value for the methine proton C in (±)-**2a** is ca 20 times greater at -70°C than that at room temperature. For the methyl protons B one observes only twofold increase. A similar trend of the temperature dependence of $\Delta\delta$ of diastereoisomeric solvates formed by sulfoxides and naturally occuring amines with optically active alcohols was earlier observed by Anet et al[8] and Jochims et al[9].

A very high sensitivity of the present method of enantiomeric analysis of chiral alcohols is best demonstrated by observation of magnetic nonequivalence in ^{1}H-NMR spectra of the diastereoisomeric solvates formed by (+)-(R)-**1** with benzyl alcohol-d_1 **2g** and isopropyl alcohol -d_3 **2h** in which the stereogenicity at carbon is due to isotopic H→D substitution.

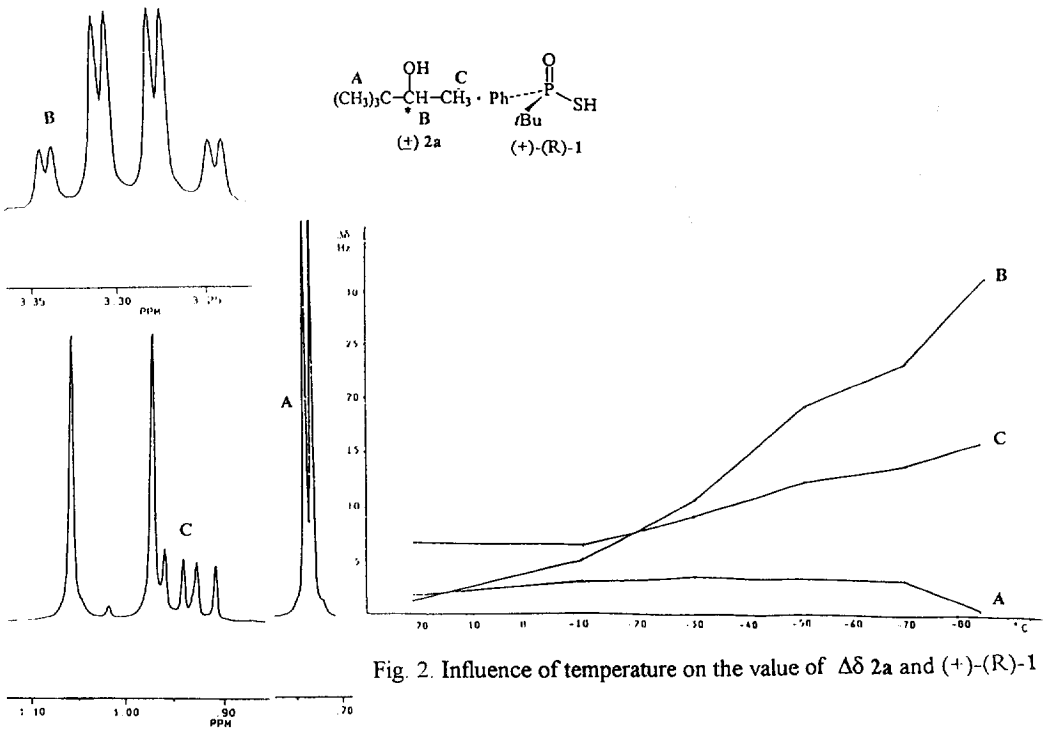
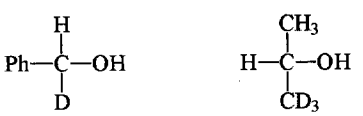


Fig. 2. Influence of temperature on the value of Δδ **2a** and (+)-(R)-1

Fig. 1 ^{1}H-NMR spectrum of racemic **2a** and (+)-(R)-1

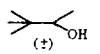
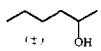
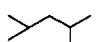
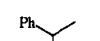
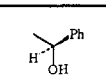
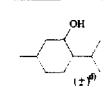
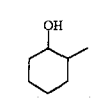
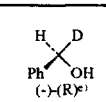
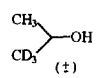
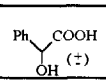
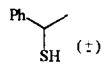


2g **2h**

In the case of (-)-**2g**, $[\alpha]_D$= -0.61 (neat)[10], the ^{1}H-NMR spectrum recorded at 500 MHz showed two overlapped triplets for the methine proton separated from each other by 2.5 Hz. The enantiomeric excess of this sample estimated from the spectrum was found to be 34% (enantiomeric ratio 33:67). This value is in a very good agreement with the purity of this alcohol calculated from rotation equal to 34.7%. The chemical shift difference of the methyl protons in the diastereoisomeric solvates between (+)-(R)-**1** and (±)-**2h** was 5.7 Hz in the ^{1}H-NMR spectrum recorded at 200 MHz. Interestingly, in the commercially available and distributed as enantiomerically pure (-)-(S)-methylbenzyl alcohol **2d**, $[\alpha]_D$= - 47.5, we found by our method 4% of the (+)-(R)-enantiomer.

The use of the chiral thiophosphinic acid **1** as a CSA is especially useful for the determination of enantiomer composition of diols and other bifunctional compounds such as mercaptoalcohols and aminoalcohols. Until now the methods for enantiomer analysis of these compounds are few in number and of limited applicability[11]. The values of Δδ and other data for a selected range of this type of compounds are

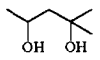
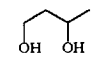
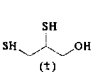
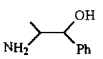
Table 1. ^{1}H-NMR Nonequivalences and Enantiomeric Ratios (er's) of Racemic and Optically Acitve Alcohols and Thiols Determined in the Presence of (+)-(R)-**1**.

No	Alcohol Structure	Solvent	Protons, multiplicity	Chemical shifts δ [ppm]	Δδ [ppm]	Δδ [Hz]	Er
2a	 (±)	$CDCl_3$	$(CH_3)_3C$ 2s CH_3 2d CH 2q	0.8688 0.8628 1.1047 1.0931 3.4975 3.4959	0.0060 0.0116 0.0036	1.8 (2.8)[a] 3.5 (5.1)[a] 1.1 (2.0)[a]	50:50
2b	 (±)	$CDCl_3$	CH_3 2d	1.1739 1.1664	0.0075	1.8	50:50
2c	 (±)	$CDCl_3$	$(CH_3)_2$ 2x2d CH_3 2d	0.8822 0.8735 0.8735 0.8637 1.1678 1.1567	0.0097 0.0098 0.0111	1.7 1.7 2.2	50:50
2d	 (±)	$CDCl_3$	CH_3 2d	1.3281 1.3078	0.0203	10.1[b]	50:50
2d	 (-)-(S)[c]	C_6D_6	CH_3 2d	1.3173 1.2997	0.0176	8.8	96:4
2e	 (±)[d]	$CDCl_3$	$(CH_3)_2C$ 2x2d CH_3 2d	0.8978 0.8916 0.8771 0.8689 0.7766 0.7690	0.0062 0.0082 0.0076	2.3 1.7 2.3	50:50
2e	(-), 94.9% (+), 5.1%	$CDCl_3$	CH_3 2d	0.7771 0.7692	0.0079	1.6	94:6
2f	 (±),cis-trans mix.	$CDCl_3$	CH_3-*t* 2d CH_3-*c* 2d	0.9748 0.9671 0.9153 0.9084	0.0077 0.0069	1.6 1.4	
2g	 (-)-(R)[e]	$CDCl_3$	CH 2t			2.5[b]	33.67
2h	 (±)	$CDCl_3$	CH_3 2d	1.1367 1.1079	0.0288	5.7	50:50
2i	 (±)	$CDCl_3$	CH 2s	5.2220 5.1981	0.0239	4.8	50:50
3	 (±)	$CDCl_3$	CH_3 2d CH 2q	1.6740 1.6726 4.2488 4.2262	0.0014 0.0226	0.4 5.1	50:50

a. in C_6D_6; b. measured on a Varian 500 MHz; c. $[\alpha]_D^{20}$-47.5; d. prepared from (+) and (-) enantiomers;

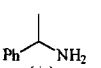
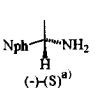
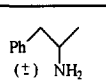
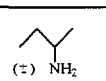
e. $[\alpha]_D^{20}$-0.61 (neat).

Table 2. ^{1}H NMR Nonequivalences and Enantiomeric Ratios of Racemic Diols, Mercaptoalcohols and Aminoalcohols Determined in the Presence of (+)-(R)-**1**.

No	Structure	Solvent	Protons, multiplicity	Chemical Shift δ[ppm]	Δδ [ppm]	Δδ [Hz]	Er
4a	 (±)	$CDCl_3$	CH_3CH 2d $(CH_3)_2C$ 2d CH_2 2ABX	1.1853 1.1762 1.2471 1.2418 1.2862 1.2747	0.0091 0.0053 0.0115	1.8 1.1 2.3	50:50
4b	 (±)	$CDCl_3$	CH_3 2d CH m CH_2 m	1.2078 1.2025	0.0053	1.0 2.9 1.4	50:50
4c	 (±)	$CDCl_3$	CH_2Cl 2ABX CH_2OH 2ABX			A4.0 B6.2 A2.9 B5.0	
4d	 (±)	$CDCl_3$	CH_2OH 2d	3.7647 3.7579	0.0068	1.4	
4e		$CDCl_3$	CH_3 2d CHOH 2d $CHNH_2$ 2q	0.8575 0.7939 3.5198 3.2208 5.1612 4.9971	0.0636 0.229 0.1644	19.1 59.8 32.8	36.7:63.3 65:35 35.3:64.7

a. gravimetric composition from pure enantiomers

Table 3. ^{1}H NMR Nonequivalences and Enantiomeric Ratios of Racemic and Optically Active Amines Determined in the Presence of (+)-(R)-**1**.

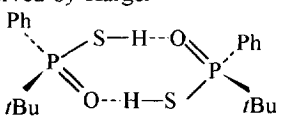
No	Structure	Solvent	Protons, multiplicity	Chemical shift δ [ppm]	Δδ [ppm]	Δδ [Hz]	Er
5a	 (±)	C_6D_6 $CDCl_3$ Py	CH_3 2d CH 2q CH_3 2d CH 2q CH_3 2d	1.3272 1.3029 4.0308 3.9478 1.4887 1.4098 4.2753 4.1411 1.7298 1.6889	0.0244 0.0930 0.0789 0.1342 0.0409	4.9 15.8 28.1 4.5	50:50
5b	 (-)-(S)[a]	$CDCl_3$	CH_3 2d CH 2q	1.6629 1.5814	0.0815	16.3 6.9	29:71
5c	 (±)	$CDCl_3$	CH_3 2d	1.1636 1.1066	0.057	11.4	50:50
5d	 (±)	$CDCl_3$	CH_3 2t	0.7984 0.7420	0.0564	11.3	50:50

a. $[\alpha]_D^{20}$-24.7 (MeOH).

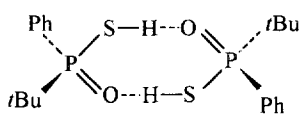
collected in Table 2. Among the data quoted in this table, the extremely large values of chemical shift differences for norephedrine are worthy of emphasis.

In our previous paper[12] on ^{1}H, ^{13}C and ^{31}P NMR nonequivalence of diastereoisomeric salts of chiral, racemic phosphorus thioacids with optically active amines we noted very high values of $\Delta\delta$ for the salt of the thioacid **1** with α-phenylethylamine and α-naphthylethylamine. It has been found now that both enantiomeric forms of **1** are suitable for the determination of enantiomeric ratio of chiral amines. As the interactions between components acid **1**-amine in diastereoisomeric salts are stronger than those in diastereoisomeric solvates with alcohols, the chemical shift differences, $\Delta\delta$, of the appropriate diastereotopic signals are as a rule greater. Only in the case of N,N-dimethyl-α-phenylethylamine we did not observe separation of diastereotopic signals.

The spectral nonequivalence observed for a long range of organic compounds in the presence of (+)- or (-)-**1** is, in our opinion, due to at least two factors. The first is the presence of the aromatic ring in **1** and its diamagnetic shielding effect. The second one is connected with a specific structural feature of this thioacid which is a proton donor and simultaneously hydrogen bond acceptor. Therefore, it can form solvates with other compounds utilizing its acidic and basic centers. The formation of the homo- and hetero-dimeric structures **6** by this acid best illustrates these acidic and basic properties and accounts for the chiral self-discrimination of enantiomers of **1** observed by Harger[13]

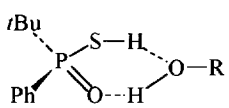


6a

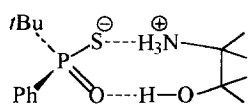


6b

The magnetic nonequivalence observed by us with alcohols and aminoalcohols may be caused by the formation in equilibrium of the structures **7** and **8** in which the acid **1** acts as a bidentate ligand interacting with its acidic and basic ends with a partner.



7



8

The proposed structure **8** should be rather rigid, more compact and more stable than **7** because it is stabilized by stronger acid-amine interactions. For this reason, such a large chemical shift nonequivalence is recorded for norephedrine. Further studies on the application of the chiral acid **1** for the determination of enantiomeric composition and absolute configuration of chiral compounds as well as on confirmation of the proposed structural models of solvates are in progress.

Acknowledgments:

We are grateful to Dr. Alan E. Sopchik (Department of Chemistry, University of Utah, Salt Lake City, USA) for the measurements of the alcohols **2d** and **2g** on a Varian 500 instrument.

Experimental

All boiling and melting points are uncorrected. Solvents were distilled and dried by conventional methods. ^{1}H-NMR spectra were measured with Bruker AC-200, MSL-300 and Varian 500 instruments. The spectra were obtained with 2793 Hz, data point with 24K and processing with zero-filling to 48K. Chloroform-d_1 was used from Dr. Glaser AG Basel and benzene-d_6 was supplied from the Institute of Atomic Energy, Otwock-Świerk, Poland. Optically active benzyl-d_1 alcohol was synthesized according to the procedure described by Streitwieser and Wolf[10a]. Propanol-2-d_3 was obtained from acetaldehyde and methyl-d_3-magnesium iodide according to a general procedure for the synthesis of alcohols described in Houben-Weyl[14]. Optically active 2-methyl benzyl alcohols were available from Aldrich. All other chiral compounds tested were commercially available.

Racemic *t*-butylphenylphosphinothioic acid 1 was obtained by the modified Hoffmann and Schellenbeek[15] method as follows:

To *t*-butylmagnesium chloride prepared from magnesium (14.6g, 0.6 mol) and t-butyl chloride (55g, 0.6 mol) in ether (400ml) dichlorophenylphosphine (71.6g, 0.4 mol) in ether (50ml) was added dropwise over a period of 45 min. at -35°C. Then, the mixture was warmed to room temperature and left to stand overnight. After refluxing for 2 hrs, the mixture was acidified with diluted 1:1 hydrochloric acid at 10°C. Three layers are usually formed. Two upper organic layers were separated and dried over $MgSO_4$. After concentration, benzene (200ml) and dicyclohexylamine (72.5g, 0.4 mol) were added to the residue at room temperature. To the resulting mixture, elemental sulfur (12.8g, 0.4 mol) was added in small portions at 35÷50°C and after that the mixture was warmed for 1 hr at 60°C. To the mixture concentrated to half of a volume, a solution of NaOH (20g in 100ml H_2O) was added at 10÷15°C and the amine was extracted with benzene (2x30ml). The water solution was acidified with concentrated hydrochloric acid (80ml) and the partially precipitated acid **1** was extracted with chloroform (4x30ml) and dried over $MgSO_4$. The chloroform solution was concentrated to dryness and the crude product (66g) was crystallized from hexane-benzene to give 64g (74.7%) of the acid **1**, m.p. 120-123°C; lit.[15] 126-127°C; ^{31}P-NMR δ=96.4 ppm ($CDCl_3$).

Resolution of *t*-butylphenylphosphinothioic acid 1 was accomplished by a slightly modified procedure described by Haynes et al[16].

To a solution of the racemic acid **1** (49.0, 0.229 mol) in ether (850ml) (-)-α-methylbenzylamine (27.7g, 0.229 mol) was added slowly at room temperature, shaking the mixture from time to time. The crystals of the salt (+)-**1**• (-)amine were filltered off on the next day (47.5g) and crystallized from ethyl acetate (ca. 0.5l) to give the salt; 25.5g, $[\alpha]_D^{22}$+22.5 9(c, 0.93, MeOH). From this salt optically active (+)-**1**, 16g, $[\alpha]_D^{22}$+26.4 (c, 1.88, MeOH) was isolated by a standard way.

The (-)-enantiomer of the acid **1**, which is present in the ether solution, was separated by concentration of the mother liquor, dissolving the residue in water (50ml), addition of a solution of NaOH (5g in 20ml water) and extraction of (-) amine with ether (4x20ml). The aqueous layer was acidified with concentrated hydrochloric acid (20ml) and the liberated (-) acid **1** was extracted with $CHCl_3$ (4x20ml). The chloroform solution was dried over $MgSO_4$ and evaporated to give (-)-**1**, 17.6g, $[\alpha]_D^{22}$-16.7, (c, 1.0, MeOH)]. The (-) acid **1** so obtained was treated with (+)-α-methylbenzylamine (9.9g, 0.082 mol) in ether (300ml). The precipitated salt (-)-**1**• (+)amine, 20.5g, $[\alpha]_D^{22}$-22.7 (c, 1.27, MeOH)] was crystallized from ethyl acetate (ca. 200ml) to give the salt, 16.5g, $[\alpha]_D^{22}$-24.4 (c,1.08, MeOH), from which the acid (-)-**1** was liberated by a standard procedure; 10.0g, $[\alpha]_D^{22}$-28.4 (c, 1.77, MeOH).

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