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^1H, ^{31}P, and ^{13}C Nuclear Magnetic Resonance Nonequivalence of Diastereomeric Salts of Chiral Phosphorus Thio Acids with Optically Active Amines. A Method for Determining the Optical Purity and Configuration of Chiral Phosphorus Thio Acids[1,2]

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Abstract: It was shown that diastereomeric salts of chiral phosphorus thio acids with optically active amines have different proton, phosphorus, and carbon NMR spectra in nonpolar solvents. The magnetic nonequivalence observed has been utilized for the first time for the direct determination of the enantiomeric content and optical purity of chiral phosphorus thio acids. In order to test the sensitivity of this method methylmethyl-d_3-phosphinothioic acid and *O*-methyl-*O*-methyl-d_3-phosphorothioic acid, which are chiral because of deuterium substitution, have been synthesized. The diastereomeric (−)- or (+)-1-(1-naphthyl)ethylamine salts of both acids exhibit different ^1H NMR spectra. The effect of solvent and optically active amines on the magnitude of magnetic nonequivalence, $\Delta\delta$, was investigated and pyridine was found to be a very good solvent for the investigated diastereomeric salts. A correlation between the absolute configuration of *O*-alkylalkylphosphonothioic acids and the NMR chemical shifts of their (−)-1-phenylethylamine salts has been observed in proton and phosphorus NMR spectra.

The recently developed NMR methods for determining enantiomeric or diastereomeric purity are based on the fact that diastereotopic nuclei are, in principle, anisochronous and should have different chemical shifts and different coupling constants.[4]

The magnetic nonequivalence of diastereomers in which the chiral centers are linked covalently in a single molecule was noted for the first time by Mateos and Cram.[5] This phenomenon was widely used to establish the composition of diastereomeric mixtures and thereby the enantiomeric purity of chiral substances from which these stereoisomers were prepared by means of *chiral derivatizing agents*.[4] In some cases empirically derived correlations of configuration and NMR chemical shifts for diastereomeric esters and amides have been reported.[6]

Similar nonequivalence of the NMR spectra was observed by Pirkle[7,4c] for a mixture of enantiomers in *chiral solvents*. In this case, unstable solvation diastereomers are formed as a consequence of interactions between the solute and solvent. Because of this, the enantiomers have different chemical environments and show different chemical shifts. Their integration provides a direct measure of the enantiomeric purity of the solute. In addition to the determination of enantiomeric or optical purities, Pirkle has also reported on the correlation of absolute configuration of chiral carbon,[8] sulfur,[9] and nitrogen[10] centers with the relative chemical shifts of enantiotopic nuclei in optically active solvents.

Recently, *chiral lanthanide shift reagents* have been prepared and found to induce the NMR spectral nonequivalence of enantiomers.[4c,11] The approach to determination of optical purity utilizing diastereomeric complexes with chiral shift reagents is very advantageous because the chemical shift differences observed are generally large and a wide range of chiral compounds can be studied.

In addition to diastereomeric solvates and complexes with chiral shift reagents, *diastereomeric salts* belong to dynamic diastereomeric systems the NMR spectra of which should be different provided that they are taken in nonpolar solvents. It is interesting to note that diastereomeric salts are systems in which there are stronger interactions between the components (acid–amine) than in the solvates investigated by Pirkle and, therefore, the NMR chemical shift differences ($\Delta\delta$) should be

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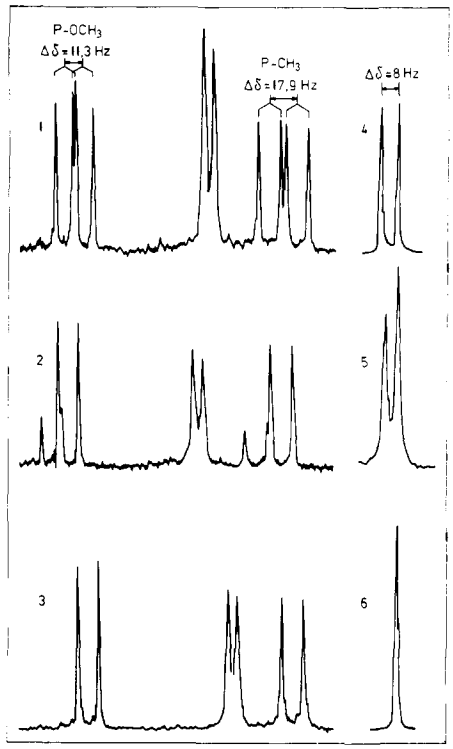


Figure 1. ^{1}H NMR (1-3) and ^{31}P{^{1}H} NMR (4-6) spectra of the salts of *O*-methylmethylphosphonothioic acid (**1a**) with (+)-1-(1-naphthyl)ethylamine: 1, (±)-**1a** (+)-NpEA; 2, (−)-**1a** ([α]$_{589}$ −2.06°, benzene) (+)-NpEA; 3, (−)-**1a** ([α]$_{589}$ −4.41°, benzene) (+)-NpEA; 4, (±-**1a** (+)-NpEA; 5, (−)-**1a** ([α]$_{589}$ −0.3°, chloroform) (+)-NpEA; 6, (−)-**1a** ([α]$_{589}$ −2.8°, chloroform) (+)-NpEA.

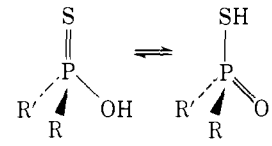
more marked. Although the first example of the NMR nonequivalence of the diastereomeric 1-phenylethylamine salts of chiral carboxylic acids was reported by Horeau[12] as early as 1968, there are limited studies on diastereomeric salts published so far.[13]

Continuing our studies[14,15] on the resolution, transformations, and absolute configuration of chiral phosphorus monothio acids (**1**) we turned our attention to the NMR methods for determining optical purity and configurational correlations. Since the majority of thio acids **1** are resolved by the classical method involving the crystallization of diastereomeric salts, this system was chosen for investigations. In this paper we describe our full results on the ^{1}H, ^{31}P, and ^{13}C NMR nonequivalence of diastereomeric salts of chiral phosphorus thio acids (**1**) with optically active amines as well as the utilization of this phenomenon for determination of the optical purity and configurational correlations of acids **1.**

Results and Discussion

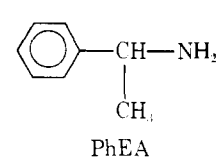
^{1}H NMR Nonequivalence of Diastereomeric Salts of Chiral Phosphorus Thio Acids (1) and Determination of Their Enantiomeric and Optical Purity. In the first part of the present study we investigated the ^{1}H NMR spectra of a series of the diastereomeric salts obtained from chiral *O*-alkylalkylphosphonothioic acids (**1a–g**) and optically active 1-phenylethylamine (PhEA) and 1-(1-naphthyl)ethylamine (NpEA).

It has been found that these salts form diastereomeric dynamic systems the ^{1}H NMR spectra of which show typical anisochronism of the diastereotopic *P*-methyl and *P*-methoxy groups. The general features of the ^{1}H NMR spectra are exemplified by the diastereomeric (+)-1-(1-naphthyl)ethylamine [(+)-NpEA] salts of racemic, partially resolved, and optically pure *O*-methylmethylphosphonothioic acid (**1**) shown in Figure 1.

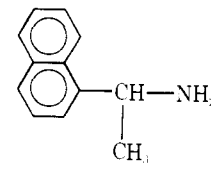


1

a, R = Me; R' = MeO
b, R = Me; R' = EtO
c, R = Me; R' = *i*-PrO
d, R = Me; R' = *n*-BuO
e, R = Et; R' = MeO
f, R = *i*-Pr; R' = MeO
g, R = *t*-Bu; R' = MeO
h, R = Et; R' = EtO
i, R = *i*-Pr; R' = EtO
j, R = Ph; R' = MeO
k, R = Ph; R' = Me
l, R = Ph; R' = Et
m, R = Ph; R' = *t*-Bu
n, R = NphO; R' = MeO
o, R = MeO; R' = MeS



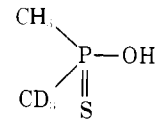
PhEA



NpEA

We also demonstrated that the method for determining the enantiomeric and optical purity of chiral phosphorus monothio acids based on the ^{1}H NMR spectral nonequivalence of diastereomeric salts is accurate. Thus, we prepared the (−)-PhEA salt from the acid **1a** containing 0.33 mol of the levorotatory acid and 0.67 mol of the racemic acid. The ratio of integrated intensities of the two diastereotopic *P*-methyl resonances in the ^{1}H NMR spectrum of this salt was found to be 0.662:0.338, which is very close to the expected enantiomeric (−)-**1a**:(+)-**1a** ratio equal to 0.665:0.335 in the sample of **1a** used.

In this context it is especially interesting to note that the ^{1}H NMR nonequivalence was observed also in the case of diastereomeric salts of chiral methylmethyl-d_3-phosphinothioic acid (**2**) and *O*-methyl-*O*-methyl-d_3-phosphorothioic acid (**3**)



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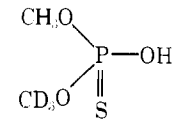

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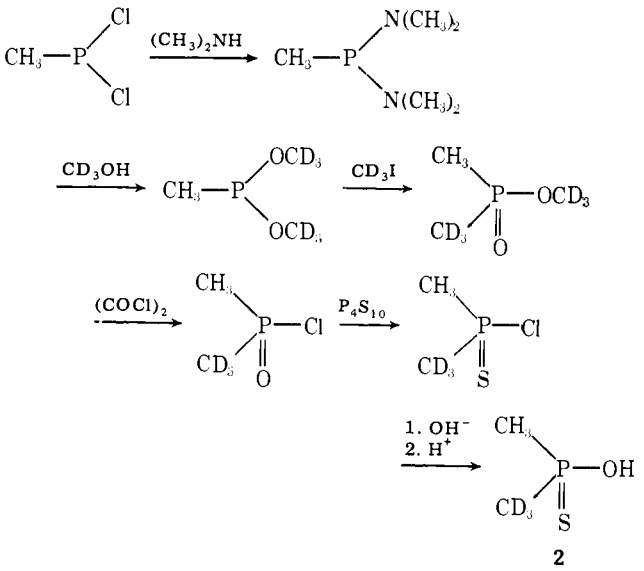
in which the chirality on phosphorus is due to the isotopic H → D substitution. The synthesis of the acid **2** and **3**[16] was carried out as shown in Schemes I and II, respectively.

In spite of the fact that the chirality at phosphorus in both thio acids **2** and **3** is only slightly marked by isotopic substitution, fairly large chemical shift differences were observed for the diastereomeric NPEA salts. In the case of the salt of (±)-**2** with (+)-NpEA the value $\Delta\delta$ = 4.1 Hz (in $CDCl_3$) was found for the diastereotopic *P*-methyl groups. As expected, the magnitude of nonequivalence observed for the diastereotopic *P*-methoxy signals in the salt of (±)-**3** with (−)-NpEA was lower, $\Delta\delta$ = 3.1 Hz (in $CDCl_3$).

In Table I we have summarized the values of the ^{1}H NMR chemical shift differences, $\Delta\delta$, for the diastereomeric (−)-PhEA salts of chiral phosphorus thio acids **1** as well as the relationship between the relative positions of the diastereotopic resonance signals in the diastereomeric salts and the chirality at phosphorus in **1.** An inspection of the results in Table I reveals that the (−)-1-phenylethylamine salts of (−)-*O*-alkylmethylphosphonothioic acid (**1a–d**) having the *S* configuration at phosphorus[14] show their *P*-methyl resonances at lower field than do their diastereomers. Similarly, the *P*-methoxy group resonance in the (−)-PhEA salts of (−)-*O*-methylalkylphosphonothioic acids **1a** and **1e, f,** in which the chirality at phosphorus is *S*,[14] are at lower field position with respect to signals of alternate diastereomers. Thus, the sense of magnetic nonequivalence[17] is the same for the *P*-methyl and *P*-methoxy

Scheme I. Synthesis of Methylmethyl-d_3-phosphinothioic Acid (**2**)



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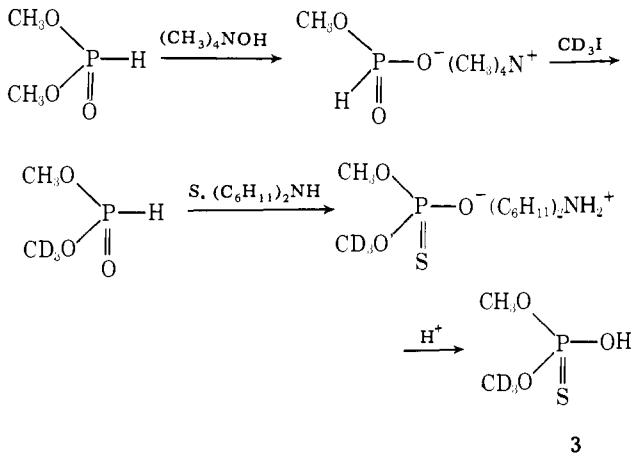
Scheme II. Synthesis of *O*-Methyl-*O*-methyl-d_3-phosphorothioic Acid (**3**)



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group and low for (*S*)-(−)-*O*-alkylalkylphosphonothioic acids (**1**). Once the correlation between the chirality at phosphorus in *O*-alkylalkylphosphonothioic acids **1** and the sense of magnetic nonequivalence of their diastereomeric salts was recognized and found to be unchanged within this class of chiral phosphorus thio acids it is believed that the magnetic nonequivalence of diastereomeric salts can also be used to determine the relative or absolute configuration of other chiral phosphorus monothio acids. However, it would be too difficult and risky to propose now a simple conformational model of a molecule of diastereomeric salt which could satisfactorily explain the observed direction of chemical shifts.

It is necessary to point out that, as it was shown in our previous studies,[18] such factors as temperature, concentration of the salt in solution, and the optical purity of the salt components do not change the sense of the magnetic nonequivalence of the diastereomeric salts but only change its magnitude. This is due to the fact that in nonpolar solvents, particularly in those having weak ionizing properties, the diastereomeric salts exist in the following equilibrium:

$$A_RH + A_SH + 2B_R \underset{K_2}{\overset{K_1}{\rightleftharpoons}} \begin{matrix} A_RHB_R \overset{K_3}{\rightleftharpoons} A_R^- + B_RH^+ \\ A_SHB_R \overset{K_4}{\rightleftharpoons} A_S^- + B_RH^+ \end{matrix}$$

Table I. Proton Chemical Shift Differences, $\Delta\delta$ (Hz), and Sense of Magnetic Nonequivalence for Diastereomeric Salts of Chiral Phosphorus Thio Acids **1** with (−)-1-Phenylethylamine

thio acid **1**[a]	$\Delta\delta$, Hz	solvent	sense of nonequivalence
1a, *Me*(MeO)P(S)OH	9.2	CCl_4	low for (−)-*S*
	9.9[b]	CCl_4	
	7.9[b]	$CDCl_3$	
1a, Me(*Me*O)P(S)OH	0.9	CCl_4	low for (−)-*S*
1b, *Me*(EtO)P(S)OH	18.9	CCl_4	low for (−)-*S*
	12.6[c]	CCl_4	
	10.5[c]	$CDCl_3$	
1c, *Me*(*i*-PrO)P(S)OH	6.9	CCl_4	low for (−)-*S*
	8.8[d]	$CDCl_3$	
	8.6[d]	C_6H_6	
1d, *Me*(*n*-BuO)P(S)OH	18.6	CCl_4	low for (−)-*S*
1e, Et(*Me*O)P(S)OH	2.9	CCl_4	low for (−)-*S*
1f, *i*-Pr(*Me*O)P(S)OH	0.6	CCl_4	low for (−)-*S*
1g, *t*-Bu(*Me*O)P(S)OH	4.2	CCl_4	low for (−)-*S*
	6.7	$CDCl_3$	
	4.4	C_6H_6	
	6.5[e]	$CDCl_3$	
1k, Ph*Me*P(S)OH	14.4	CCl_4	low for (+)-*R*
1n, (NphO)(*Me*O)P(S)OH	3.2	CCl_4	

[a] Diastereotopic groups for which $\Delta\delta$ are given are italicized; the values of $\Delta\delta$ refer to racemic acids **1** unless specified otherwise; sense of nonequivalence was estimated in an independent experiment; measured at 60 MHz with the exception of the salt of **1d**, **1g**, **1k**, and **1n**, spectra of which were recorded at 100 MHz. [b] The value refers to 78% optically pure (−)-**1a**. [c] The value refers to 70% optically pure (−)-**1b**. [d] The value refers to 70% optically pure (−)-**1c**. [e] The value refers to 65% optically pure (+)-**1g**.

The components appearing on the left side of the equation, i.e., free enantiomeric acids and free optically active bases, as well as the completely dissociated components, i.e., enantiomeric anions and ammonium cations, cannot cause magnetic nonequivalence. It can be caused only by the nondissociated forms of the salt, i.e., A_RHB_R and A_SHB_R, the existence of which in the form of ion pairs or aggregates is favored by nonpolar solvents and low temperatures.[19] In addition to chloroform, carbon tetrachloride, and benzene, pyridine was found to be a very advantageous solvent for the diastereomeric salts. Firstly, diastereomeric salts of thio acids **1** are well soluble in pyridine, and, secondly, in the majority of cases we observed much larger differences in chemical shifts of the diastereotopic signals in pyridine than in benzene and other solvents. This special effect of pyridine is clearly demonstrated by the data collected in Table II in which a comparison of $\Delta\delta$ values for diastereomeric salts in benzene and pyridine is given.

It is obvious that the greater diamagnetic anisotropy of π electrons of the pyridine ring, as compared with that of the benzene ring, as well as the better association properties of pyridine due to its more polar character and the possibility of hydrogen bond formation could explain the effect of pyridine on the enhancement of the chemical shift differences. However, in contrast to pyridine, 2-methylpyridine, and 2,6-dimethylpyridine, in the case of 2,4-dimethylpyridine we observed quite small values of $\Delta\delta$ and in 2,4,6-trimethylpyridine the magnetic nonequivalence of the (+)-PhEA salt of **1f** disappeared completely. These data tend to support the view that both electronic and steric factors play an important part in solvation of diastereomeric salts and in causing the nonequivalence of their ^{1}H NMR spectra.

Furthermore, we found that the value of $\Delta\delta$ is dependent on the concentration of pyridine and 2-methylpyridine in solution. The value increases with increasing concentration up to a certain maximum and then it remains practically constant (see

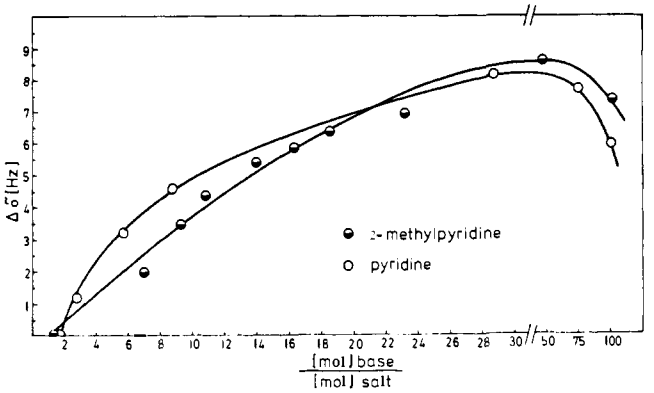


Figure 2. Changes of the $\Delta\delta$ value for the diastereomeric salts of *O*-methylisopropylphosphonothioic acid (**1f**) with (−)-1-phenylethylamine depending on the concentration of pyridine bases.

Table II. Proton Chemical Shift Differences, $\Delta\delta$ (Hz), at 60 MHz for Diastereomeric Salts of Chiral Phosphorus Thio Acids **1** with (−)-1-Phenylethylamine in Benzene and Pyridine

thio acid **1**[a]	$\Delta\delta$ in benzene	$\Delta\delta'$ in pyridine	$\Delta\delta'/\Delta\delta$
1a, Me(*Me*O)P(S)OH	1.8	3.4	1.9
1a, *Me*(MeO)P(S)OH	11.5	3.4	0.3
1c, *Me*(*i*-PrO)P(S)OH	2.5	4.5	1.8
1e, Et(*Me*O)P(S)OH	10	4.0	4.0
1f, *i*-Pr(*Me*O)P(S)OH	0.6	6.0	10.0
1g, *t-Bu*(MeO)P(S)OH	0.0	2.9	∞
1g, *t*-Bu(*Me*O)P(S)OH	2.7	4.5	1.7
1j, Ph(*Me*O)P(S)OH	1.75	2.5	1.4
1o, (MeS)(*Me*O)P(S)OH	1.0	1.75	1.75

[a] Diastereotopic groups for which $\Delta\delta$ are given are italicized.

Figure 2). This indicates that the diastereomeric salts existing as ion pairs or aggregates are surrounded by several tens of molecules of pyridine base.

By comparing the magnetic nonequivalence caused by the use of various amines (Table III) it can be observed that the diamagnetic anisotropy of the aromatic ring present in optically active amines is of principal importance. Both in benzene and pyridine optically active (+)-2-butylamine does not cause the nonequivalence of the diastereomeric salts with thio acids **1f**. (−)-*N*,*N*-Dimethylmenthylamine behaves similarly. Also in the case of (−)-*N*-benzyl-1-phenylethylamine we observed very low values of $\Delta\delta$. Probably in this case the diamagnetic shielding effects of the two aromatic rings cancel each other or the greater ease of dissociation of the salt decreases the value of $\Delta\delta$. The latter factor is also quite probable since the chemical shift difference ($\Delta\delta$) of the diastereotopic methoxy protons in the salt of thio acid **1f** with optically active (−)-*N*,*N*-dimethyl-1-phenylethylamine was found to be much smaller than that observed for PhEA itself. On the other hand, the strong magnetic nonequivalence of diastereomeric salts was observed with 1-(1-naphthyl)ethylamine as the amine component. This phenomenon is well known in NMR spectroscopy and it is connected with high diamagnetic anisotropy of the condensed aromatic rings.[22]

Finally, it should be pointed out that thiophosphonic acids which are not readily resolvable by means of their diastereomeric salts with 1-phenylethylamine show very low values of magnetic nonequivalence in such salts. This could suggest that in such cases where strong magnetic nonequivalence is observed for diastereomeric salts the ion pairs or larger aggregates exist in solution in more compact forms, which increases the diamagnetic shielding effect of the phenyl ring on both the alkyl and alkoxy groups of the thio acid.

Table III. Chemical Shift Differences, $\Delta\delta$ (Hz), at 60 MHz, for Diastereotopic Methoxy Protons in the Salt of Racemic *O*-Methylisopropylphosphonothioic Acid (**1f**) with Optically Active Amines in Pyridine

optically active amine	$\Delta\delta$, Hz
(−)-1-phenylethylamine	6.0
(−)-1-*p*-nitrophenylethylamine	4.0
(−)-*N*-benzyl-1-phenylethylamine	1.3
(−)-*N*,*N*-dimethyl-1-phenylethylamine	1.3
(−)-*N*-benzylidene-1-phenylethylimine	3.8[a]
(−)-1-(1-naphthyl)ethylamine	7.3
(+)-1-(2-naphthyl)ethylamine	4.6
(−)-ephedrine	2.9
(−)-menthylamine	0.0
(+)-2-butylamine	0.0

[a] Measured in CCl_4.

^{31}P NMR Nonequivalence of Diastereomeric Salts of Chiral Phosphorus Thio Acids (1). The optical purity and configuration of the enantiomeric phosphorus thio acids (**1**) can be determined easily by ^{1}H NMR spectroscopy only if the spectral patterns of the enantiotopic nuclei are simple and the spectra of the diastereomeric salts of **1** show clear-cut differences. However, in the case of thio acids **1** containing branched alkyl and alkoxyl groups connected with phosphorus the diastereotopic protons gave overlapping signals and accurate measurements of the integrated intensities were not possible.

This difficulty can be overcome by applying ^{31}P NMR spectroscopy since we found that the diastereomeric salts of chiral phosphorus thio acids **1** also have different ^{31}P NMR spectra and, which is undoubtedly most advantageous, it was possible by means of the ^{1}H heteronuclear decoupling to simplify all the complex ^{31}P NMR spectra of the diastereomeric salts and to reduce them to two signals only corresponding to the enantiomeric thio acids **1**. The spectra of *O*-methylmethylphosphonothioic acid (**1a**) salts with (+)-NpEA are typical and best illustrate the first example of the magnetic nonequivalence of diastereomeric dynamic systems in ^{31}P NMR spectra (Figure 1).

^{31}P NMR chemical shift differences, $\Delta\delta$, between the diastereomeric salts of chiral phosphorus thio acids (**1**) and optically active (−)-PhEA and (−)-NpEA are collected in Table IV. As in the case of ^{1}H NMR spectra, the values of $\Delta\delta$ are usually greater when (−)-NpEA is used as the amine component. Although there is no clear relationship between the structure of thio acid **1** and the magnitude of magnetic nonequivalence, it seems that the presence of a bulky group bonded directly to phosphorus gives rise to a decrease in $\Delta\delta$ (compare $\Delta\delta$ for (−)-PhEA salts of **1a, 1e, 1f** and **1g**). In this context, however, it is interesting to point out that the surprisingly high value of $\Delta\delta$ = 24.4 Hz was noted for the salt of phenyl-*tert*-butylphosphinothioic acid (**1m**) with (−)-NpEA.

As for configuration determination, an inspection of the data in Table IV reveals the most important fact that the salts of the levorotatory *O*-alkylalkylphosphonothioic acids, having the configuration *S* at the phosphorus atom,[14,15] exhibit the same, low sense of the magnetic nonequivalence.

Similarly, the same sense of magnetic nonequivalence in ^{31}P NMR spectra has been observed for other series of homochiral thio acids—alkylphenylphosphinothioic acids **1k, 1l,** and **1m**. In this case it is low for the (+)-NpEA salts of the dextrorotatory phosphinothioic acids in which the chirality at phosphorus is *R*.[14,23]

Thus, in addition to the measurements of enantiomeric or optical purity of chiral phosphorus thio acids (**1**), correlations of their relative or absolute configurations based on the ^{31}P NMR nonequivalence of diastereomeric salts are also possible.

Table IV. Phosphorus Chemical Shift Differences, $\Delta\delta$ (Hz), at 24.3 MHz, and Sense of Magnetic Nonequivalence for Diastereomeric Salts of Chiral Phosphorus Thio Acids **1**

thio acid **1**		salt with (−)-PhEA			salt with (−)-NpEA	
structure	δ, ppm	δ, ppm[a]	$\Delta\delta$, Hz, in benzene	sense of nonequivalence	δ, ppm[a]	$\Delta\delta$, Hz, in $CDCl_3$
1a, Me(MeO)P(S)OH	89.6	75.0	2.0	low for (−)-*S*	77.9	8.0
1b, Me(EtO)P(S)OH	87.5	73.1	2.1	low for (−)-*S*	75.3	6.6
1c, Me(*i*-PrO)P(S)OH	84.2	71.5	6.4	low for (−)-*S*		
1d, Me(*n*-BuO)P(S)OH	88.1	73.2	3.5	low for (−)-*S*	75.3	5.4
1e, Et(MeO)P(S)OH	95.9	81.5	2.1	low for (−)-*S*		
1h, Et(EtO)P(S)OH	95.3	81.6	2.1	low for (−)-*S*	81.4	0.0
1f, *i*-Pr(MeO)P(S)OH	98.3	83.7	1.2	low for (−)-*S*	88.8	1.7
1i, *i*-Pr(EtO)P(S)OH	98.6	83.5	1.1	low for (−)-*S*	93.0	0.0
1k, PhMeP(S)OH	78.5	36.9	0.0	low for (+)-*R*[b]	60.2	6.6
1l, PhEtP(S)OH	85.3	67.6	0.0	low for (+)-*R*[b]	68.9	5.1
1m, Ph-*t*-BuP(S)OH	97.0	77.8	7.8	low for (+)-*R*[b]	79.0	24.4
1n, (NphO)(MeO)P(S)OH	59.0	53.8	0.0		54.2	1.3

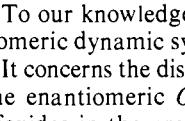
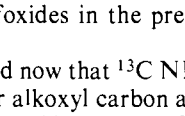
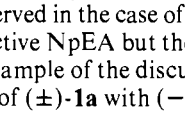
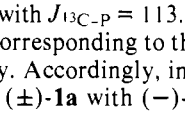
[a] Center of multiplet. [b] (+)-NpEA.

^{13}C NMR Nonequivalence of Diastereomeric Salts of Chiral Phosphorus Thio Acids (1). In view of the increasing interest in the application of ^{13}C NMR spectroscopy in stereochemical studies[24] we turned our attention also to the possibility of distinguishing between diastereomeric salts by means of this technique. To our knowledge the ^{13}C NMR nonequivalence of diastereomeric dynamic systems has been reported only in one case.[25] It concerns the distinguishing by ^{13}C NMR spectra between the enantiomeric *O,O*-dimethylphosphorylmethyl-*p*-tolyl sulfoxides in the presence of chiral lanthanide shift reagent.

We found now that ^{13}C NMR chemical shift differences of the alkyl or alkoxyl carbon atoms bonded to phosphorus can also be observed in the case of the diastereomeric salts of **1** with optically active NpEA but the $\Delta\delta$ values are rather small. The simplest example of the discussed nonequivalence is provided by the salt of (±)-**1a** with (−)-NpEA. In the ^{13}C NMR spectrum of the free acid **1a** there are two doublets centered at δ 21.31 ppm with $J_{^{13}C-P}$ = 113.3 Hz and δ 52.04 ppm with $J_{^{13}C-P}$ = 5.9 Hz corresponding to the methyl and methoxy carbons, respectively. Accordingly, in the ^{13}C NMR spectrum of the mixture of (±)-**1a** with (−)-NpEA the resonance signal for the *P*-methyl carbon appeared as a double doublet with $\Delta\delta$ = 6.35 Hz, indicating the presence of the two diastereomeric salts. No doubling was observed for the *P*-methoxy carbon atoms.

The values of the ^{13}C NMR chemical shifts and the $\Delta\delta$ values for the diastereomeric salts investigated are listed in Table V.

Table V. ^{13}C NMR Data (60 MHz) for Diastereomeric Salts of Some Chiral Phosphorus Thio Acids **1** with (−)-1-(1-Naphthyl)-ethylamine in $CDCl_3$

thio acid **1**	δ, ppm	$J_{^{13}C-P}$, Hz	$\Delta\delta$, Hz[b]
1a 	^{1}C 22.2 and 21.8	100.5	6.35
	^{2}C 51.6	3.9	
1b 	^{1}C 20.0[a]	102.8	4.6
	^{2}C 57.7	6.1	
	^{3}C 12.75[a]		
1d 	^{1}C 22.9[a]	101.3	3.6
	^{2}C 65.1	5.0	
	^{3}C 32.8	3.7	
	^{4}C 18.7		
	^{5}C 13.7		
1m 	^{1}C 34.9	73.2	1.5
	^{2}C 23.9		

[a] Average values taken from the normal spectra. [b] Magnetic nonequivalence values were estimated from the expanded spectra.

Conclusions

This work demonstrated that diastereomeric salts of chiral phosphorus thio acids with optically active amines may be distinguished by proton, phosphorus, and carbon NMR spectroscopy. ^{1}H NMR nonequivalence was observed also in the case of diastereomeric salts of chiral methylmethyl-d_3-phosphinothioic acid and *O*-methyl-*O*-methyl-d_3-phosphorothioic acid in which the chirality at phosphorus is due to the isotopic H → D substitution.

Fairly large chemical shift differences, $\Delta\delta$, were observed for diastereotopic groups in ^{1}H and ^{31}P NMR spectra which makes it possible to determine readily and with a high accuracy the enantiomeric content and optical purity of chiral phosphorus thioacids. In this respect, especially useful are the ^{31}P{^{1}H} NMR spectra in which only two singlets are observed due to the enantiomeric phosphorus thio acids forming the diastereomeric salts. Until now this approach is the only way to follow the progress and completeness of the optical resolution of chiral phosphorus thio acids.

Furthermore, it has been found that a correlation exists between the sense of magnetic nonequivalence of diastereomeric salts and the configuration of phosphorus thio acids. The (−)-1-phenylethylamine salts of (−)-*O*-alkylalkylphosphonothioic acids having the *S* configuration at phosphorus show a low sense of magnetic nonequivalence. Thus, the magnetic nonequivalence of diastereomeric salts may also be utilized to determine the relative or absolute configurations of chiral phosphorus thio acids.

Experimental Section

Instruments. ^{1}H NMR spectra were measured with Varian-HR-60, JEOL-JNM 60 HL, Tesla BS-487C, JEOL-JNM-FX60, and Perkin-Elmer R12B instruments with Me_4Si as internal standard. ^{31}P NMR spectra were recorded with JEOL-JNM 60HL and JEOL-JNM-FX60 Fourier transform spectrometers at 24.3 MHz with 85% phosphoric acid as external standard. In this paper the new convention of positive ^{31}P NMR signals to low field from H_3PO_4 is used. ^{13}C NMR spectra were measured with a JEOL-JNM-FX60 Fourier transform spectrometer with Me_4Si as internal standard. A 5–10% solution of diastereomeric salts freshly prepared from components was used for measurements.

Optical activity measurements were made with a Perkin-Elmer 241 MC photopolarimeter (sensitivity ±0.002°).

Reagents and Materials. Solvents and commercial reagents were distilled and dried by conventional methods before use. Optically active 1-phenylethylamine supplied by Fluka AG and Merck-Schuchardt was used. Optically active 1-(1-naphthyl)ethylamine and 2-butylamine supplied by Norse Laboratories Inc. were used without purification. Optically active *N,N*-dimethylamines were prepared according to the literature.[26] Optically active 1-phenylethylamine was converted into its *p*-nitro derivative according to Nerdel.[27] Condensation of optically active 1-phenylethylamine with benzaldehyde leading to the corresponding Schiff base was carried out as described by Roelofsen and Bekkum.[28] (−)-Menthylamine was obtained according to the procedure described by Voisin and Gastambide.[29]

Thio acids **1** were resolved into optical antipodes via diastereomeric salts with suitable optically active amines according to the literature procedures which have been summarized in the recent review by Mikołajczyk and Leitloff.[15]

Dimethyl-d_3 Methylphosphonite. To tetramethyl methylphosphonodiamidite[30] (10.0 g) methanol-d_3 (60 g) was added at room temperature under nitrogen. The reaction mixture was then heated for 5 h at 100–120 °C. Dimethyl-d_3 methylphosphonite formed was isolated by distillation: 5.6 g (65%); bp 30–34 °C (100 mmHg); n^{21}_D 1.4117; ^{1}H NMR (neat) δ 1.14 (d, 3 H, CH_3P, $^2J_{H-P}$ = 8.7 Hz).

Methyl-d_3 Methylmethyl-d_3-phosphinate. The ester prepared above (5.6 g, 0.0491 mol) was treated with a few drops of methyl-d_3 iodide and heated for 6 h at 100 °C. The crude product was filtered and distilled to give the analytically pure phosphinate: 5.4 g (96%); n^{20}_D 1.4290; ^{1}H NMR (neat) δ 1.25 (d, 3 H, CH_3P, $^2J_{H-P}$ = 14.7 Hz); ^{31}P NMR (CCl_4) δ 50.6.

Anal. Calcd for $C_3H_3D_6O_2P$: C, 31.60; H, 8.45. Found: C, 31.52; H, 8.65[31].

Methylmethyl-d_3-phosphinochloridate. To a solution of methyl-d_3 methylmethyl-d_3-phosphinate (4.1 g, 0.036 mol) in ether (20 mL) oxalyl chloride (5.4 g, 0.0425 mol) in ether (15 mL) was added at 0–5 °C. The reaction mixture was stirred for 4 h at room temperature. Evaporation of ether and an excess of oxalyl chloride afforded the crude phosphinochloridate as a white, hygroscopic crystals which were washed with a petroleum ether–hexane (1:1) mixture, 3 g (73%), mp 65–72 °C. It was used for further transformation.

Methylmethyl-d_3-phosphinochloridothionate. A mixture of the above prepared phosphinochloridate (2.8 g, 0.0244 mol) and phosphorus pentasulfide (1.8 g, 0.00405 mol) was heated for 6 h at 160–180 °C under nitrogen. The reaction mixture was taken up in ether. The ethereal extract after evaporation afforded the crude product which was purified by distillation: 2.5 g (80%); bp 42 °C (1.6 mmHg); n^{20}_D 1.5464; ^{1}H NMR (neat) δ 2.44 (d, 3 H, CH_3P, $^2J_{H-P}$ = 12.7 Hz); ^{31}P NMR (CCl_4) δ 90.8.

Anal. Calcd for $C_2H_3D_3PSCl$: C, 18.26; H, 4.81. Found: C, 17.57; H, 4.56.[31]

Methylmethyl-d_3-phosphinothioic Acid (2). To a solution of sodium hydroxide (1.6 g, 0.04 mol) in methanol (30 mL) phosphinochloridothionate (2.6 g, 0.01985 mol) was added. The reaction mixture was refluxed for 0.5 h, cooled, filtered, and then evaporated. The residue was dissolved in water (10 mL), acidified, and extracted with chloroform (4 × 15 mL). The chloroform solution was dried and concentrated to give thio acid **2** as a crystalline compound: mp 42–45 °C; 1.2 g (53%); ^{1}H NMR (CCl_4) δ 2.12 (d, 3 H, CH_3P, $^2J_{H-P}$ = 12.0 Hz); ^{31}P NMR (CCl_4) δ 85.0. The acid **2** was further characterized as (+)-1-(1-naphthyl)ethylamine salt, mp 165–167 °C.

Anal. Calcd for $C_{14}H_{17}O_3NOPS$: C, 59.12; H, 7.16. Found: C, 58.83; H, 7.10.[31]

Methyl Methyl-d_3 Phosphite. To a solution of dimethyl phosphite (5 g, 0.0403 mol) in methanol (15 mL) a 24.5% aqueous solution of tetramethylammonium hydroxide (16.4 g, 0.0403 mol) was added. The reaction mixture was stirred for 20 min at 40 °C. Water and methanol were evaporated under reduced pressure and the residue was dried over phosphorus pentoxide in vacuo to give the tetramethylammonium salt of monomethyl phosphite as a hygroscopic solid. It was dissolved in acetonitrite (20 mL) and treated with methyl-d_3 iodide (6.5 g, 0.0448 mol) at room temperature. The reaction solution was then stirred for 6 h at 50–60 °C. The precipitated tetramethylammonium chloride was filtered off and the filtrate was evaporated. The residue was distilled to give methyl methyl-d_3 phosphite: 3.4 g (68%); bp 55 °C (10 mmHg); n^{20}_D 1.4023; ^{1}H NMR (neat) δ 3.66 (d, 3 H, CH_3OP, $^3J_{H-P}$ = 12.0 Hz), 6.51 (d, 1 H, HP, $^1J_{H-P}$ = 682 Hz).

Anal. Calcd for $C_2H_4D_3O_3P$: C, 21.25; H, 8.44. Found: C, 20.91; H, 9.95.[31]

***O*-Methyl-*O*-methyl-d_3-phosphorothioic Acid (3).** To a solution of the phosphite prepared above (2.3 g, 0.0204 mol) in THF (20 mL) sulfur (0.96 g, 0.03 mol) was added and then a solution of dicyclohexylamine (3.6 g, 0.02 mol) in THF (15 mL) was dropped at 15–20 °C under nitrogen. The reaction mixture was stirred at room temperature for 1 h. Evaporation of the solvent afforded the salt which was treated with a 10% aqueous solution (20 mL) of sodium hydroxide. The water solution was extracted with ether (3 × 15 mL), acidified, and extracted with ether (4 × 15 mL). The ether solution obtained after extraction of the acidic aqueous layer was dried and concentrated to give 1.5 g (52%) of acid **3**: n^{20}_D 1.4804; ^{1}H NMR ($CDCl_3$) δ 2.34 (d, 3 H, CH_3OP, $^3J_{H-P}$ = 13.3 Hz), 6.15 (s, 1 H, HOP); ^{31}P NMR ($CDCl_3$ + benzene) δ 63.5.

Dicyclohexylammonium salt of **3**: mp 184–186.5 °C.

Anal. Calcd for $C_{14}H_{27}O_3NOPS$: C, 51.50; H, 9.27; H, 4.16; P, 9.47. Found: C, 51.84; H, 9.49; N, 4.65; P, 9.76.[31]

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