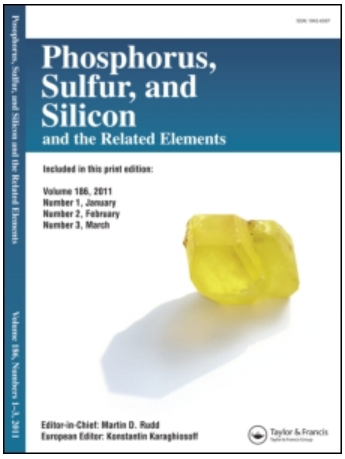

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DIRECT ^{31}P NMR DETERMINATION OF THE ENANTIOMERIC COMPOSITION OF 1-HYDROXYALKYLPHOSPHONATES USING 1-(1-NAPHTHYL)ETHYLAMINE AS A CHIRAL AGENT

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DIRECT ^{31}P NMR DETERMINATION OF THE ENANTIOMERIC COMPOSITION OF 1-HYDROXYALKYLPHOSPHONATES USING 1-(1-NAPHTHYL)ETHYLAMINE AS A CHIRAL AGENT

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Optically active 1-(1-naphthyl)ethylamine and 1-hydroxyalkylphosphonic acids form in nonpolar solvents diastereoisomeric salts distinguished in ^{31}P NMR spectroscopy. The magnetic nonequivalence of phosphonate groups is large enough (esp. for benzyl monoesters salts $\Delta\delta^{31}P$ is up to 0.36 ppm) to determine ee values. The dependence of diastereoisomeric salts magnetic nonequivalence on concentration and enantiopurity of amine component is studied.

Key words: Enantiomeric excess; 1-hydroxyalkylphosphonates; ^{31}P NMR magnetic nonequivalence; 1-(1-naphthyl)ethylamine.

INTRODUCTION

Chiral, nonracemic 1-hydroxyphosphonates are becoming increasingly important as biologically active compounds[1–4] and useful precursors for a variety of α-substituted phosphonates.[5–6] Therefore, direct and simple methods for the enantiomeric purity determination of the chiral 1-hydroxyphosphonates and their derivatives are desirable. Recently, we proposed the ^{31}P NMR enantiomeric composition determination of 1-hydroxyphosphonic acid esters via their diastereoisomeric phosphonodidepsipeptides.[7] In this paper we report the application of optically active amines as the chiral agents for direct and simple ^{31}P NMR enantiomeric excess determination of α-hydroxyphosphonates, especially for their benzyl monoesters.

RESULTS AND DISCUSSION

Enantiomeric Excess Determination

All 1-hydroxyphosphonates and optically active amines studied in this work are depicted in Scheme 1. The ^{31}P NMR chemical shifts corresponding to the respective phosphonates and their diastereoisomeric salts are collected in Tables I–IV. We have investigated the diastereoisomeric salts of three optically active amines, extensively employed as resolving agents or chiral solvating agents (CSA), i.e. S(−)-

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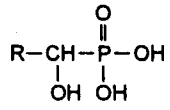
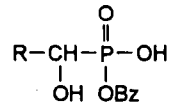


	R
1	iBu
2	iPr
3	Ph

1 - 3

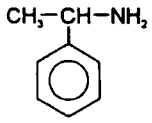
1-Hydroxyalkylphosphonic Acids 1 - 3



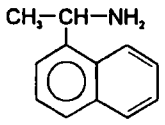
	R
4	iBu
5	iPr
6	Ph
7	n-Pr
8	Me

4 - 8

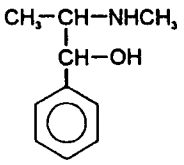
Benzyl Monoesters of 1-Hydroxyalkylphosphonic Acids 4 - 8



1-phenylethylamine
PhEA



1-(1-naphthyl)ethylamine
NEA



ephedrine
Ephe

Optically active amines.

Scheme 1

1-phenylethylamine [S(−)PhEA], (1R, 2S)(−) ephedrine [Ephe] and R(+)-1-(1-naphthyl)ethylamine [R(+)NEA] or S(−)-1-(1-naphthyl)-ethylamine [S(−)NEA].

Phosphonic group signals of diastereoisomeric salts have always been found to be shifted by ca. 5 ppm to higher field of the free acid peaks. The same shift has been observed for the first deprotonation of phosphonate group; it means that in nonpolar solvents proton transfer is complete in the resultant diastereoisomeric salts.[8]

The chemical shift differences of 1-hydroxyphosphonic acid diastereoisomeric salts with R(+)NEA as well as (1R, 2S)(−)ephedrine are not sufficient to permit accurate integration ($\Delta\delta^{31}$P lower than 0.05 ppm, Table I).

In contrast to the acids, admixtures of (+/−) 1-hydroxyphosphonic acid benzyl monoesters **4–8** with two equivalents of R(+)-1-(1-naphthyl)ethylamine in $CDCl_3$ give diastereoisomeric salts in which large ^{31}P NMR chemical shift nonequivalences were observed.

TABLE I

$\delta^{31}P$ NMR [ppm] and phosphorus chemical shift differences $\Delta\delta^{31}P$ [ppm] for 1-hydroxyphosphonic acids and for their diastereosiomeric salts with optically active amines in $CDCl_3$

	R	$\delta^{31}P$ ($\Delta\delta$) [ppm]		
		acids[1]	diastereoisomeric salts	
			(1R,2S)(-)Ephedrine	R(+) NEA
1	i-Bu	25.244	20.679	20.153 20.107(0.046)
2	i-Pr	25.023	19.564	18.714
3	Ph	20.629	16.377 16.345(0.032)	15.726 15.679(0.047)

1 acids in $CDCl_3$ with DMSO to improve solvation

TABLE II

$\delta^{31}P$ NMR [ppm] and phosphorus chemical shift differences $\Delta\delta^{31}P$ [ppm] for benzyl monoesters of 1-hydroxyphosphonic acids and for their diastereoisomeric salts with optically active amines. All spectra recorded in $CDCl_3$

	R	phosphonates	$\delta^{31}P$ ($\Delta\delta^{31}P$) [ppm] diastereoisomeric salts		
			R(+) NEA	S(-) PhEA	(-)Ephedrine
4	i-Bu	27.591	22.804 22.554(0.250)	22.540 22.454(0.096)	22.694
5	i-Pr	27.346	21.954 21.809(0.146)	21.861 21.764(0.097)	21.982
6	Ph	23.245	18.170 18.018(0.152)	18.007 17.932(0.075)	18.435
7	n-Pr	27.194	22.420 22.176(0.244)	22.045 21.948(0.097)	
8	Me	26.754	22.321 22.134(0.187)	21.938 21.870(0.068)	

TABLE III

$\delta^{31}P$ NMR [ppm] and phosphorus chemical shift differences $\Delta\delta^{31}P$ [ppm] for diastereoisomeric salt of 1-hydroxyisopenthylphosphonic acid benzyl monoester (**4**) with R(+)-1-(1-naphthyl)ethylamine in different solvents

solvent	$\delta^{31}P$ ppm	$\Delta\delta^{31}P$ ppm	R/S integration
chloroform	22.666 22.443	0.223	1.04
benzene	22.787 22.575	0.212	0.95
acetonitrile	22.564 22.469	0.095	1.03
DMSO	20.546	0.0	
pyridine	22.196	0.0	

^{31}P NMR spectra had shown two separated peaks when the racemate or enantiomerically enriched samples of **4–8** were used and a single peak in the case of optically pure compound. Values of $\Delta\delta^{31}P$ varied from 0.15 ppm (**5** and **6**) to 0.25 ppm for (**4**). For a given NEA salt, the magnitude of the shift nonequivalence was always 2–2.5 times greater than that observed using S(−)-1-phenylethylamine as the amine component.

Ephedrine tends to form diastereoisomeric salts not distinguishable in ^{31}P NMR (only for (−)ephedrine salt of 1-hydroxybenzylphosphonic acid (**3**) $\Delta\delta^{31}P$ is greater than zero).

Solvent effects are important[9-11]; addition of even a small quantity of relatively polar solvents such as DMSO or pyridine reduces nonequivalence. The highest $\Delta\delta^{31}P$ values were recorded in chloroform and in benzene. In pyridine or DMSO, in which the ions are solvent separated $\Delta\delta^{31}P$ equals zero (see Table III).

Using mixtures of R(−)(**4**) and S(+)(**4**) of pre-weighted enantiomeric composition, an excellent agreement (+/− 2%) between known compositions and ^{31}P NMR determined values were obtained (Table IV).

Magnetic Non-equivalence of Diastereoisomeric Salts

Diastereoisomeric salts formed through complete proton transfer belong to dynamic diastereomeric systems where interactions between components (chiral counterions of acid and amine) are stronger than for typical chiral solvating agents (CSA).[9,10] Therefore, the chemical shift differences are more marked ($\Delta\delta^{31}P$ up to 0.35 ppm).

Different dependence of $\Delta\delta$ on the chiral agent concentration is observed in the case of diastereoisomeric salts and for a typical solvating agent. For studied salt of (+/−)(**4**) with S(−)NEA, $\Delta\delta^{31}P$ reaches a maximum value at 1:1 stoichiometry, when salt formation is complete (see the plot in Figure 1). In this dynamic system,

TABLE IV

Enantiomeric excess determination of enantiomerically enriched monoester (**4**) using 2-molar equivalents of optically active NEA as the chiral agent

	ee % by weighing[1]		$\delta^{31}P$ ($\Delta\delta^{31}P$)	ee from spectra[2]	E %[3]
R(+) NEA as the chiral agent					
1	100	R(-)(**4**)	22.666		
2	56.7		22.745 22.562 (0.183)	57.6	1.6
3	16.67		22.810 22.573 (0.237)	17.01	2.0
4	0.00	(racemate)	22.780 22.528 (0.252)	0.99	1.0
S(-) NEA as the chiral agent					
5	53.6		22.710 22.397 (0.313)	52.7	1.7
6	43.3		22.732 22.418 (0.314)	44.0	1.7
7	0.00	(racemate)	22.672 22.409 (0.263)	0.74	0.8

1 - prepared by weighing racemate and optically pure R(-) (**4**)
2 - calculated from diastereoisomeric composition of salts
3 - percent error of measurment

magnetic non-equivalence can be caused only by diastereoisomeric ion pairs (stoichiometry 1:1), the existence of which is favored by nonpolar solvents. Additional amounts of amine can accelerate the exchange processes and the life-time of diastereoisomeric ion-pair is shortened. In consequence, the reduction of $\Delta\delta^{31}P$ is observed.

For a typical CSA, nonequivalence increases with an increase in concentration of solvating agent until the chiral solute is completely solvated, until approximately 3 molar equivalents of CSA are present.[9a]

The linear dependence of $\Delta\delta$ (see Figure 2) with enantiomeric composition has been observed previously[12] and is consistent with the different association constants in diastereoisomeric salt formation. The changes of $\Delta\delta^{31}P$ are large, as a result of strong interactions (ca. 0.1 ppm with changing molar ratio of S(+)(**4**)/R(−)(**4**) from 0.1 to 1). The plots on the Figure 2 illustrate the practical consequence of $\Delta\delta$ dependence on the enantiomeric composition of searched solute. Using R(+)NEA

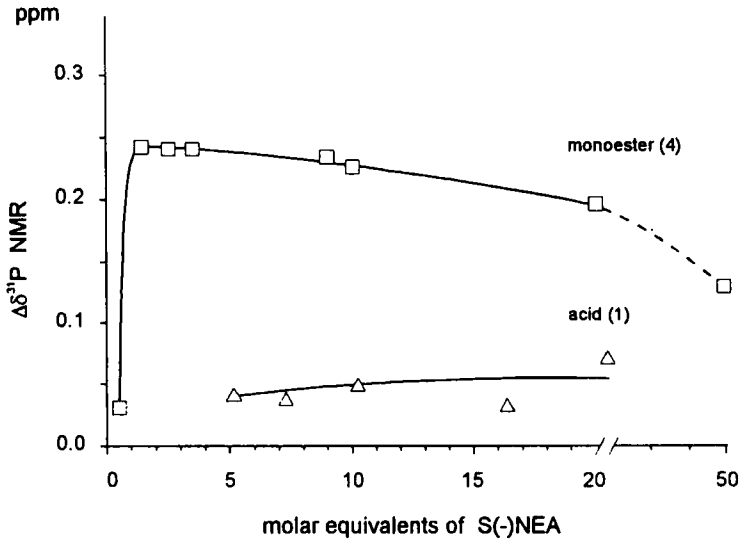


FIGURE 1 Changes of the $\Delta\delta^{31}$P NMR value for the diastereoisomeric salts of (+/−) 1-hydroxyisopenthylphosphonic acid (**1**) and benzyl monoester of (+/−) 1-hydroxyisopenthylphosphonic acid (**4**) with S(−)NEA depending on the excess of S(−)NEA.

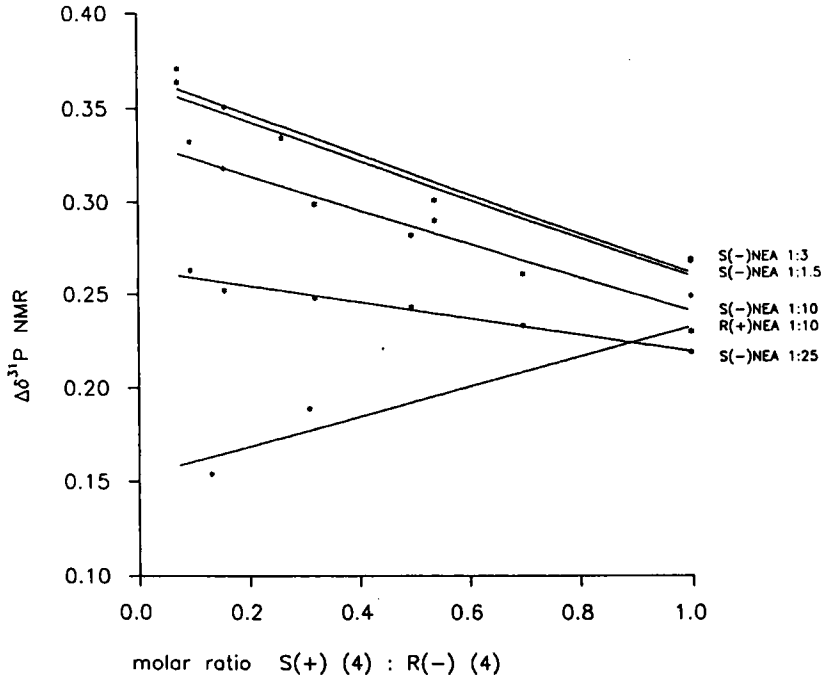


FIGURE 2 Dependence of the $\Delta\delta^{31}$P NMR value on the enantiomeric composition of (+/−) 1-hydroxyisopenthylphosphonic acid benzyl monoester (**4**) in diastereoisomeric salts with enantiomerically pure S(−) or R(+)NEA. Molar excess of NEA changed from 1:1.5 to 1:25.

for the sample enriched in R(−)(**4**) (molar ratio 0.1) $\Delta\delta^{31}P$ = 0.16 ppm, by replacing the amine with its antipode i.e. with S(−)NEA the value of nonequivalence is doubled and equals 0.33 ppm.

The variations of $\Delta\delta^{31}P$ with the substituent R at the hydroxyphosphonates asymmetric centre for the NAE and PhEA diastereoisomeric salts of (+/−)(**4**) are presented on the Figure 3. The magnitude of nonequivalence, $\Delta\delta^{31}P$, is not strongly correlated with the solute structure (esp. in case of R = iPr). On the other hand, for all NEA salts of monoesters **4**–**8**, the magnitudes of the shift nonequivalence were always greater than that observed for the respective PhEA salts.

The advantage of the CSA method, as a consequence of the fast-exchange process, is the fact, that enantiomeric purity of the CSA is not critical; it affects only the magnitude of spectral nonequivalence.[9,11] We observed a similar effect for diastereoisomeric salts of monoester (**4**) and NEA. Enantiomeric excess of enriched sample (monoester **4**, preweighted ee% = 53.58%) has been measured using a large molar excess of NEA (20 equivalents) with different enantiomeric composition as a chiral agent. We obtained the correct value, with the deviation not higher than 1%, using chiral amine S(−)NEA of ee up to 50% (75% S(−)NEA and 25% R(+)NEA, see Figure 4). The magnitude of nonequivalence has been reduced in this range from 0.283 to 0.163 ppm. The same accuracy we have also obtained using only 1.5 equivalent of NEA, the magnitude of $\Delta\delta^{31}P$ varied from 0.337 to 0.235 ppm.

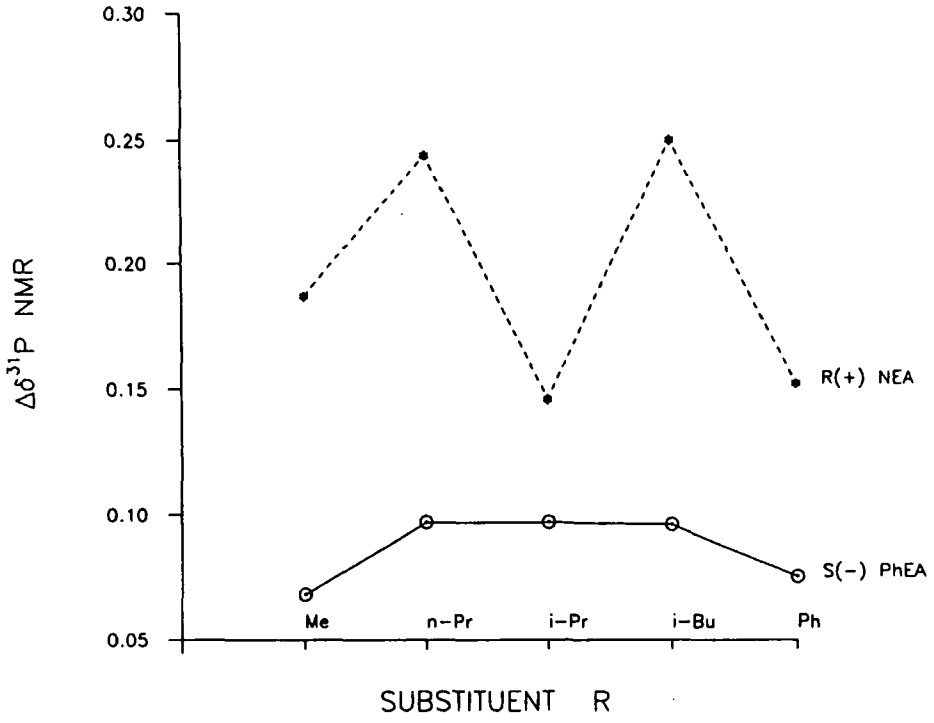
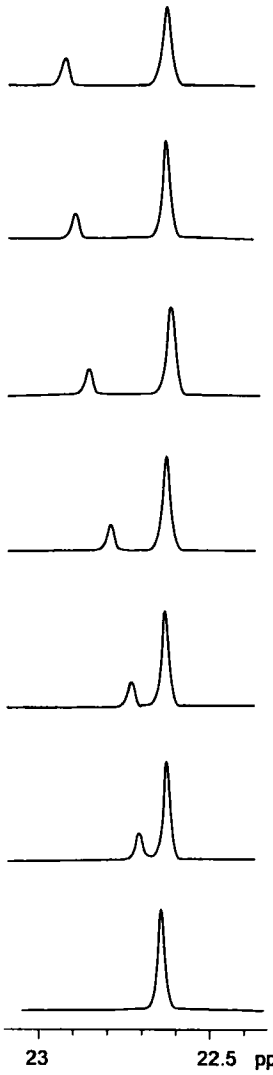


FIGURE 3 Changes of the $\Delta\delta^{31}P$ NMR value for the diastereoisomeric salts of (+/−) 1-hydroxyalkylphosphonic acid benzyl monoesters (**4**–**8**) with S(−)PhEA and R(+)NEA depending on the substituent at the asymmetric carbon atoms.



CSA enantiomeric composition		$\delta^{31}P$	$\Delta\delta^{31}P$	Integration ratio	ee % from spectrum
100	% S(-)NEA	22.825		1	
		22.542	0.283	3.298	53.47
91.7	% S(-)NEA	22.856		1	
8.3	% R(+)NEA	22.585	0.271	3.281	53.28
87.5	% S(-)NEA	22.818		1	
12.5	% R(+)NEA	22.581	0.237	3.232	52.74
75.0	% S(-)NEA	22.762		1	
25.0	% R(+)NEA	22.599	0.163	3.276	53.23
62.5	% S(-)NEA	22.706		1	
37.5	% R(+)NEA	22.619	0.087	3.158	51.90
58.3	% S(-)NEA	22.698		1	
41.7	% R(+)NEA	22.627	0.071	3.067	50.82
50.0	% S(-)NEA	22.653			
50.0	% R(+)NEA				

FIGURE 4 Variation of the $\delta^{31}P$ NMR and $\Delta\delta^{31}P$ value for diastereoisomeric salts of the enantiomeric enriched benzyl monoester of 1-hydroxyisopenthylphosphonic acid (**4**) (preweighted ee% = 53.58%) with the excess of NEA. Enantiomeric composition of NEA changed from enantiomerically pure S(−) to racemate. ^{31}P NMR spectra recorded on the Varian FT NMR spectrometer at 81.0 MHz.

CONCLUSIONS

We herein report the use of R(+) and S(−)-1-(1-naphthyl)ethylamine as a convenient chiral solvating agent for the enantiomeric purity determinations of 1-hydroxyphosphonates. In a typical experiment, the 1-hydroxyphosphonate (0.05–0.1 mmol) and S(−) or R(+)NEA (0.1–0.15 mmol) are dissolved in $CDCl_3$ and their ^{31}P NMR (proton decoupled) spectrum is recorded. NEA need not be en-

antiomerically pure, however, highly enantiomerically enriched amine is preferred to improve $\Delta\delta$ value. The concentrations of components can be used in a wide range.

EXPERIMENTAL

α-hydroxyphosphonates were obtained by previously reported procedures **1–3**[13] and **4–8**.[14] The proton decoupled ^{31}P NMR spectra of the phosphonates and their salts (0.1–0.2 mmol ml^{-1}) in $CDCl_3$ (benzene, pyridine or DMSO) were recorded on a FT-NMR spectrometer Bruker AC-200 or Varian-Gemini 200 at 81.0 MHz. An 85% H_3PO_4 solution was used as an external reference. Typical conditions: spectral width 4000 Hz, number of scans 5–20 and digital resolution 0.3 Hz per data points.

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