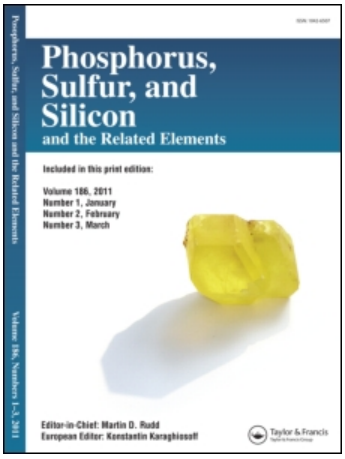

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^{31}P Nmr Determination of the Enantiomeric Composition of N-Phthaloyl-1-Aminoalkyl-Phosphonate Monoesters using 1-(1-Naphthyl)Ethylamine and Ephedrine as the Chiral Agents

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^{31}P NMR DETERMINATION OF THE ENANTIOMERIC COMPOSITION OF N-PHTHALOYL-1-AMINOALKYL-PHOSPHONATE MONOESTERS USING 1-(1-NAPHTHYL)ETHYLAMINE AND EPHEDRINE AS THE CHIRAL AGENTS

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Optically active 1-(1 -naphthyl)ethylamine as well as ephedrine with N-phthaloyl-1-aminoalkylphosphonate monoesters form in $CDCl_3$ diastereoisomeric salts distinguished in ^{31}P and in ^{1}H NMR spectroscopy. The magnetic nonequivalence of phosphonate groups are in almost all cases large enough ($\Delta\delta$ ^{31}P is up to 0.45 ppm) to determine enantiomeric excess values with a high level of accuracy. Ephedrine seems to be a better chiral agent for ee determination by means of ^{31}P NMR. The larger chemical shift dispersions $\Delta\delta$ ^{31}P NMR were recorded for the ephedrine salts. In contrast, the respective naphthylethylamine salts revealed greater $\Delta\delta$ ^{1}H NMR values.

Keywords: enantiomeric excess (ee); 1-aminoalkylphosphonates; ^{31}P NMR; magnetic nonequivalence; 1-(1-naphthyl)ethylamine; ephedrine; diastereoisomeric salts

INTRODUCTION

Optically active phosphonic acid analouges of amino acids reveal diverse and interesting biological and biochemical properties.[1,2] For proper evaluation of their biological activity enantiomeric composition of the active compound must be known. Therefore, direct and simple methods for the enantiomeric purity determination of the chiral 1-aminophosphonates and their derivatives are still desirable.

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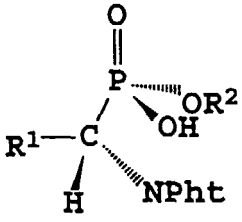

No	R^1	R^2
I	iPr	Me
II	Ph	Me
III	iPr	Bz
IV	Ph	Bz
V	Me	Me
VI	Bz	Bz
VII	iBu	Me
VIII	Bz	Me

SCHEME 1 N-phthaloyl-1-aminoalkylphosphonate monoesters I – VIII

Previously we presented methods of the enantiomeric excess (ee) determination of the free aminophosphonic acids from the ^{31}P NMR spectra of their Pd(II) complexes,[3] the ee determination of 1-hydroxyphosphonic acid esters via their diastereoisomeric phosphonodidepsipeptides.[4] To determine ee of hydroxyphosphonates[5] and aminophosphonates[6] we successfully applied optically active amines (esp. 1-(1-naphthyl)ethylamine and ephedrine). Diastereoisomeric salts formation and chiral solvating agent (CSA) methods are the quickest and simplest to perform in NMR tube, with no problem of kinetic resolution and sample racemization.[7] Recently, quinine and tertbutylphenylphosphinothioic acid were found to be effective for the ee determination of diethyl 1- and 2-hydroxyalkylphosphonates.[8]

Continuing our studies on the optically active amines as the chiral agents we report here their application to the ^{31}P NMR enantiomeric excess determination of N-phthaloyl 1-aminophosphonate monoesters.

RESULTS AND DISCUSSION

All N-phthaloyl-1-aminoalkylphosphonate monoesters studied in this work are depicted in **Scheme 1.** We have investigated the diastereoiso-

meric salts of two optically active amines, extensively employed as resolving agents or chiral solvating agents **(CSA),** i.e. (1R,2S)(-) ephedrine **[Ephe]** and R(+)-1-(1 -naphthyl)ethylamine **[R(+)NEA].**

TABLE I δ ^{31}P NMR [ppm], relaxation times T_1 [s] and phosphorus chemical shift differences Δδ ^{31}P [ppm] of N-phthaloyl-1-aminoalkylphosphonate monoesters (racemic **I-VIII**, enantiomerically pure **R-VII, S-VIII** and enantiomerically enriched **R-en-VII, S-en-VIII**) and for their diastereoisomeric salts with 1.5–2 molar excess of the optically active amines. All spectra recorded in $CDCl_3$ *ca.* 24 hours after preparing samples

	monoester		*δ ^{31}P NMR (Δδ) [ppm] diastereomeric salts with chiral amines*	
number	*δ ^{31}P ($CDCl_3$)*	*T_1 [s]*	*(1R, 2S)(-) Ephe ($CDCl_3$)*	*R(+) NEA ($CDCl_3$)*
I	**23.046**	**1.81**	18.099, 17.827 (0.272)	16.682, 16.614 (0.070)
II	**18.432**	**3.37**	14.660, 14.208 (0.452)	13.370, 13.189 (0.181)
III	**22.141**	**1.52**	17.248, 16.863 (0.385)	15.837
IV	**17.618**	**1.49**	13.731, 13.641 (0.090)	12.465, 12.374 (0.091)
V	**26.591**	**5.40**	18.131, 17.928 (0.203)	17.702
VI	**24.780**	**1.81**	16.419, 16.161 (0.258)	15.885, 15.775 (0.110)
VII	**26.876**	**1.10**	18.294, 18.080 (0.214)	17.702, 17.642 (0.060)
R-VII	**26.695**		18.461	17.556
R-en-VII			18.312, 18.127 (0.185)	
VIII	**25.428**	**1.60**	16.999, 16.772 (0.227)	16.590, 16.566 (0.024)
S-VIII	**25.247**		16.832	16.470
S-en-VIII			16.978, 16.799 (0.179)	

The ^{31}P NMR chemical shifts corresponding to the respective monoesters, their relaxation times T_1 (in seconds) and chemical shifts of their diastereoisomeric salts with chiral amines are collected in **Table I.** The respective ^{1}H NMR data: chemical shifts and Δδ ^{1}H NMR (in ppm), coupling constants $^2J_{PCH}$ or $^3J_{PCOH}$ (in Hz) for the selected proton groups are presented in **Table II.**

Chemical shift dispersion on the ^{31}P NMR spectra

Phosphonic group signals of diastereoisomeric salts have been found to be shifted by 4 to 9 ppm to higher field of the monoester peaks. The same shift has been observed for the first deprotonation of a phosphonate group, which means that in the presence of amine in $CDCl_3$ solution the phosphonate group exists in an ionic form. In the ^{31}P NMR method (1R,2S)(-)ephedrine was more effective as a chiral agent than R(+)-1-(1-naphthyl)ethylamine. The chemical shift differences of N-phthaloyl-1-aminophosphonic monoester diastereoisomeric salts with R(+)NEA ($\Delta\delta$ ^{31}P from 0 to 0.18 ppm) as well as (1R,2S)(-)ephedrine ($\Delta\delta$ ^{31}P from 0.09 to 0.45 ppm) were in almost all cases sufficient to permit accurate integration. The only cases in which we were unable to observe the chemical shift dispersion with optically active NEA were monoesters **III** and **V**. As expected, $\Delta\delta$ ^{31}P reached a maximum value at the 1.5–2 amine molar excess, when salt formation was complete.

TABLE II δ ^1H NMR [ppm] and the coupling constants ($^2J_{PCH}$ or $^3J_{POCH}$ [Hz]), proton chemical shift differences {$\Delta\delta$ ^1H [ppm]} of the selected N-phthaloyl-1-aminoalkylphosphonate racemic monoesters, and for their diastereoisomeric salts with 1.5–2 molar excess of the optically active amines

δ ^1H NMR [ppm], ($^2J_{PCH}$ or $^3J_{POCH}$ ([Hz]) of the monoesters			δ ^1H NMR[ppm], ($^2J_{PCH}$ or $^3J_{POCH}$ [Hz]), {($\Delta\delta$) [ppm]} of the diastereomeric salts with chiral amines	
number	*protons*	δ^1H ($CDCl_3$)	(1R,2S)(-) Ephe ($CDCl_3$)	R(+) NEA ($CDCl_3$)
I	$-OCH_3$	3.623(11.0)	3.547(10.6)	3.448(10.4) 3.418(10.4) {0.030}
II	$-OCH_3$	3.572(11.0)	3.568(10.6) 3.556(10.6) {0.012}	3.490(10.8) 3.478(10.6) {0.012}
	C* – H	5.604(24.4)	5.673(23.0) 5.661(22.8) {0.012}	5.657(22.4) 5.597(22.0) {0.060}
IV	C* – H	5.629(24.6)	5.680(22.6) 5.668(22.8) {0.012}	5.701(22.4) 5.657(22.2) {0.044}
V	$-OCH_3$	3.787(11.2)	3.646(10.4)	3.438(10.8) 3.428(10.4) {0.010}
VII	$-OCH_3$	3.773(11.0)	3.653(10.2) 3.646(10.4) {0.007}	3.485(10.4) 3.471(10.8) {0.014}
VIII	$-OCH_3$	3.804(11.0)	3.692(10.4) 3.687(10.4) {0.005}	3.536(10.4) 3.518(10.4) {0.018}

The relaxation times of monoesters dissolved in $CDCl_3$ varied from 1.1 to 5.4 s. The maximum T_1 value showed the smallest molecules of monoesters **V** ($R^1 = R^2 = Me$) and **II** (R^1=Ph and R^2=Me).

Additionally, downfield shifted single peaks (pairs of peaks for the racemic phosphonate monoesters) occurred on the spectra when we used more than a 2 molar excess of the amine component. For example we observed for diastereoisomeric salts of **VII** and **Ephe** two pairs of peaks at 18.486 and 18.358 ppm ($\Delta\delta$ ^{31}P =0.148 ppm) and 20.528 and 19.898 ppm ($\Delta\delta$ ^{31}P =0.63 ppm). On the basis of a chemical shifts comparison signals shifted to downfield would be assigned to the ion-pairs. Most probably, more stable, the solvent separated ion-pairs (peaks shifted downfield) are created from the larger aggregates of ions (upfield shifted peaks). The same effects we studied previously for N-phthaloyl-1-aminophosphonic acids. [6]

Chemical shift dispersion on the ^1H NMR spectra

The chemical shift differences of the diastereoisomeric salts we studied on the well separated peaks of the methyl ester group protons (-OCH_3) in case of **I, II, IV, V, VII** and **VIII** and for **II** and **IV** on the ***C-H** protons attached to the asymmetric carbon atoms. Proton methyl ester group signals of diastereoisomeric salts have been found to be shifted by 0.06 to 0.35 ppm to higher field of the monoester peaks. In all cases proton signals of NEA salts were shifted twice more than the corresponding signals of the Ephe salts. Contrary to the methyl ester peaks, protons attached to the asymmetric carbon atoms of diastereoisomeric salts have been found to be shifted by 0.02 – 0.06 ppm to the lower field of the monoester signals.

Contrary to the ^{31}P NMR spectra, R(+)-1-(1-naphthyl)ethylamine was more effective as a chiral agent than (1R,2S)(-)ephedrine. The chemical shift differences ($\Delta\delta$ ^1H) of the methyl ester group protons (-OCH_3) and the protons attached to the asymmetric carbons (***C-H**) of N-phthaloyl-1-aminophosphonic monoester diastereoisomeric salts were always larger with R(+)NEA in comparison to the respective (1R,2S)(-)ephedrine salts. The $\Delta\delta$ ^1H values were not in all cases sufficient to permit accurate integration ($\Delta\delta$ ^1H from 0.01 up to 0.06 ppm for the NEA salts).

The only cases in which we were unable to observe by means of ^1H NMR the chemical shift dispersion of the methyl ester group protons were monoester **I** and **V** salts with optically active Ephe.

Enantiomeric Excess Determination of N-Phthaloyl-1-Amino-alkylphosphonate Monoesters

^{31}P NMR spectra of R(+)NEA or (IR,2S)(-)Ephe diastereoisomeric salts usually showed two separated peaks when the racemate or enantiomerically enriched samples were used and a single peak in the case of optically pure compound.

Enantiomerically pure R-VII and S-VIII were obtained from the respective, enantiomerically pure 1-aminoalkylphosphonic acids.[9] Single ^{31}P NMR peaks were received for monoesters R-VII, S-VIII and for their respective salts. The enantiomerically pure monoesters indicate that their synthesis undergo with no racemisation procceses.

Using different mixtures of preweighted enantiomeric composition of **R-VII** and **racemic VII** or **S-VIII** and **racemic VIII** we recorded the pairs of signals with the baseline resolution almost in all cases. The peak area from the standard ^{31}P NMR spectrum was a measure of diastereoisomeric composition which is related directly to the enantiomeric composition of the original mixture. The agreements with accuracy from 0.25–2 % between known preweighted compositions and ^{31}P NMR determined values were obtained.

CONCLUSIONS

We herein report the use of optically active 1-(1-naphthyl)ethylamine and ephedrine as the convenient chiral agents for the enantiomeric purity determination of the N-phthaloyl-1-aminophosphonate monoesters by means of ^{31}P NMR. The advantages of the method are that it is quick and simple to perform. The accuracy of the method may be improved by the choice of other solvents and cosolvents.

EXPERIMENTAL

All N-phthaloyl-1-aminoalkylphosphonate monosters studied in this work were obtained according to the previously described procedures[10] and monoesters by selective cleavege of one ester group using DABCO (1,4-diazabicyclo[2.2.2]octane).[11]

The protons decoupled by inverse gated methods ^{31}P NMR and standard ^{1}H NMR spectra of the phosphonates and their salts (concentrated 0.05 – 0.1 mmol ml^{-1}) in $CDCl_3$ were recorded on the FT-NMR spectrometer Varian-Gemini 200 at 81.0 MHz for phosphorus or 200 MHz for protons. An 85% H_3PO_4 solution was used as an external reference for the ^{31}P NMR and internal reference TMS for the ^{1}H NMR spectra . Typical conditions for ^{31}P NMR spectra: spectral width 4000 Hz, number of scans 5–20 and digital resolution 0.3 Hz per data points. The T_1 values were measured by the inversion recovery method. The accuracy of the quantitative analysis can be improved by using the proper aquisition and processing parameters while recording spectra: flip angle and repetition time correlated with T_1, resolution enhnancement functions, phasing and baseline correction before integration.

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References

[1] B. Dhawan and D. Redmore, *Phosphorus, Sulfur and Silicon,* **32,** 119, (1987).
[2] P. Kafarski and B. Lejczak, *Phosphorus, Sulfur and Silicon,* **63,** 193, (1991).
[3] Z. Glowacki, M.Topolski, E. Matczak-Jon and M. Hoffmann, *Magn. Reson. Chem.,* **27,** 922, (1989).
[4] a. Z. Glowacki and M. Hoffmann, *Phosphorus, Sulfur and Silicon,* **55,** 169, (1991) 4.b. Z. Glowacki and M. Hoffmann, *Phosphorus, Sulfur and Silicon,* **63,** 171, (1991).
[5] Z. Glowacki, M. Hoffmann and J. Rachoń, *Phosphorus, Sulfur and Silicon,* **82,** 39, (1993).
[6] Z. Glowacki and M. Hoffmann, *Phosphorus, Sulfur and Silicon,* **104,** 21, (1995)
[7] 7.a. W.H. Pirkle and D.J. Hoover, NMR Chiral Solvating Agents, in Topics in Stereochemistry, vol.13 , p.263, 1982. b. G.R. Weisman, Nuclear Magnetic Resonance Analysis Using Chiral Solvating Agents in Asymmetric Synthesis, ed. J.D. Morrison, vol 1, p. 153, Academic Press, New York 1983 7.c. M. Mikolajczyk, J. Omelańczuk, M.Leitloff, J. Drabowicz, A. Ejchart and J. Jurczak, *J. Am. Chem. Soc.,* **100,** 7003, (1978).
[8] E. Zymańczyk-Duda, M. Skwarczyński, B. Lejczak and P. Kafarski, *Tetrahedron: Asymm.,* **7,** 1277,(1996).
[9] P. Kafarski, B. Lejczak and J. Szewczyk, *Can. J Chem.,* **61,** 2425, (1983).
[10] M. Hoffmann and Cz. Wasielewski, *Rocz. Chem.,* **50,** 139, (1976).
[11] M. Hoffmann, *Phosphorus, Sulfur and Silicon,* in press.