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Assignment of the absolute configuration of hydroxy- and aminophosphonates by NMR spectroscopy

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ABSTRACT

Phosphonate analogues of amino- and hydroxy acids have received considerable attention in bioorganic and medicinal chemistry due to their unique activities as peptidomimetics, being known as inhibitors of such enzymes as human renin, HIV protease and polymerase, leucine aminopeptidase and serine proteases. They have also been exploited as haptens for catalytic antibody research, herbicides, antibiotics, antiviral and anticancer agents and neuromodulators. Therefore, the demand for the asymmetric synthesis of hydroxy- and aminophosphonates should be accompanied by reliable methods for their absolute configuration assignment. NMR spectroscopy is one of the most commonly used techniques for the assignment of absolute configuration of different classes of compounds. This report describes the principles and practical aspects of applying chiral discriminating agents for the assignment of absolute configuration of 1- and 2-hydroxyphosphonates and 1- and 2-aminophosphonates by NMR spectroscopy. The report is organized in sections discussing the types of the chiral discriminating agents (including the models used for configuration assignment, if this was proposed) and the scope of their applications (with the list of all the examples of hydroxy- and aminophosphonates examined by this method). The application of the chiral derivatizing agents (CDA) and chiral solvating agents (CSA) used for these purposes, such as α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), α-methoxyphenylacetic acid (MPA), amino acids, diazaphospholidine, camphanic acid, naproxen, quinine and *t*-butylphenylphosphinothioic acid is discussed. Easy access to the selected values of the NMR chemical shifts observed for the diastereomeric species of the tested hydroxy- and aminophosphonates examined, will enable the reader to compare trends observed in spectra and subsequent absolute configuration assignment. In addition, any available complementary data confirming the configuration established by NMR (X-ray, chemical correlations, optical rotation) is also provided.

Contents

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1. Introduction

The spatial arrangement of the substituents in a molecule plays a vital role in its physicochemical and biological features. Therefore there is an unceasing demand for the asymmetric synthesis of different classes of compounds. Development of new synthetic approaches requires methods for their 'optical' efficiency assignment. To such indispensable tools belong procedures for the determination of enantiomeric purity and absolute configuration of the products.[1,2]

Enantiomers in the achiral environment can be distinguished by chirooptical methods and X-ray crystallographic analysis. However, differentiating enantiomers by chromatography, capillarly electrophoresis, mass spectrometry, and nuclear magnetic resonance requires the introduction of additional chirality into the system.[1–3] Due to interactions with chiral agents, covalently or non-covalently bonded diastereomeric species are created, with different chromatographic and spectroscopic properties.

Recently, NMR methods for the relative and absolute configuration determination have gained importance.[4–9] This stems from the common availability of NMR spectrometers and simplicity of the method, which requires a fairly small amount of the sample, without special prerequisites regarding its preparation and without the necessity for knowing the fundamentals of the technique. A recently developed method based on the use of resin-bound chiral derivatizing agents has greatly simplified the configuration assignment by circumventing any work-up procedures.[10,11] The reader interested in the assignment of absolute configuration by NMR may consult the recent reviews by Riguera et al.[6] and Harada.[9]

Amino-[12–20] and hydroxyphosphonates[21–25] constitute a class of amino acid and hydroxy acids mimics in which a planar carboxylic group is replaced by a tetrahedral phosphonic moiety. These compounds bear a close resemblance to the transition state of ester and amide hydrolysis and among hydroxy- and aminophosphonates are the known inhibitors of enzymes such as human renin,[26] HIV protease and polymerase,[27,28] leucine aminopeptidase,[29] and serine proteases.[30] They were also exploited as haptens for catalytic antibody research.[31–33] In addition, phosphonates display a broad spectrum of activities as herbicides,[34] antibiotics,[35,36] antiviral[37] and anticancer agents, and neuromodulators.[12–18] There is, therefore, a demand for the methods of enantiomeric purity (ee) determination and absolute configuration assignment of these classes of compounds.

Applications of ^{31}P NMR spectroscopy for enantiomeric purity assignment have been the subject of comprehensive reviews.[21,38,39] As yet, the absolute configuration assignment of chiral hydroxy- and aminophosphonates has not been the topic of a comprehensive review, however some aspects of this issue can be found in the review of Kolodiazhnyi devoted to the asymmetric synthesis of hydroxyphosphonates.[21] The aim of this report is to delineate the principles and practical aspects of applying chiral discriminating reagents for this purpose. We expect such compilation to be of use in choosing the most reliable and convenient reagent for the absolute configuration assignment of hydroxy- and aminophosphonates. The report is organized in sections discussing the types of chiral discriminating agent used for the purposes mentioned above. The characteristics of properly designed chiral derivatizing agents (CDAs) and chiral solvating agents (CSAs) are given in the introduction. The survey is limited to α- and β-hydroxyphosphonates most often applied in bioorganic chemistry and their amino analogues only, and covers the literature up to the end of 2008.

2. Selection of the optimal discriminating agent

Differentiation of enantiomers by NMR can be achieved either by the reaction of the CDA with the analyzed compound (thanks to the generation of a new covalent bond diastereomeric derivatives are formed)[1,2,6] or by the addition of the CSA to the analyzed compound (formation of diastereomeric associates distinguishable by NMR).[38,40,41] In both approaches, the diagnostic parameter is the chemical shift difference ($\Delta\delta$) between the corresponding nuclei in both diastereomeric species. For the purpose of this report the values of $\Delta\delta$ were in some cases calculated from the values of δ, quoted in the original publications.

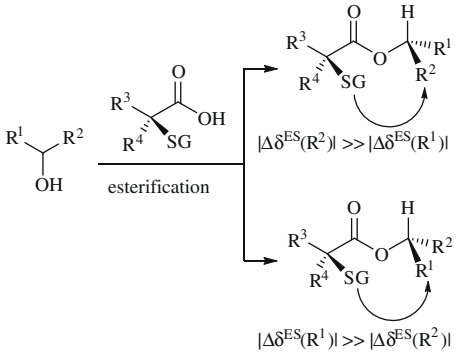
2.1. Chiral derivatizing agents (CDAs)

A properly designed CDA should have the following structural features: (a) a group enabling the formation of a covalent bond with the compound analyzed; (b) a group exerting a space-oriented anisotropic effect which selectively shields or deshields the substituents of the compound investigated; and (c) a group stabilizing one conformation of the product of derivatization.[6] Such a conformational preference, independent of the structure and configuration of the compound analyzed leads to a selective shielding or deshielding of the substituents of the substrate. It enables us to establish a correlation between the spatial arrangement of the substituents (absolute configuration) and the chemical shift differences in the NMR spectra. However, finding the preferred conformation requires more investigation on a wide range of structurally diverse compounds. Additionally, more profound analysis of the conformational equilibrium has been recently performed using theoretical calculations (optimization of the geometry and calculation of shielding/deshielding contributions), NMR (low-temperature, NOESY), and circular dichroism experiments.[6,42–45] Unfortunately, such methodical studies are exceptions for hydroxy- and aminophosphonates.[46]

In addition to the facts mentioned above, the NMR data should fulfill the following requirements: (a) the chemical shift differences, $\Delta\delta$, between the corresponding nuclei should exceed the experimental error; (b) the $\Delta\delta$ signs should be of the same among the NMR 'active' nuclei for a certain substituent; and (c) the $\Delta\delta$ signs should be positive for one substituent and negative for the other. It is also essential that no kinetic resolution should occur during the derivatization reaction. However, this can be overcome when an excess of derivatizing agent is used.

A CDA can be used in either a single or a double derivatization.[6] The first approach requires only one derivatization of the substrate. Then, by comparison of the spectra of the derivatized compound, one acquired under the standard conditions, and the other recorded after controlled shifting of the conformational equilibrium (by lowering the measurement temperature,[47–50] or by the

addition of a barium salt[51–54]), the configuration can be assigned on the basis of the $\Delta\delta$ signs. Single derivatization can also be performed by comparison of the standard spectrum of the product of derivatization with the spectrum of the substrate (esterification shift methodology, see Scheme 1).[6,55] The latter strategy was commonly applied for the phosphorus derivatives.[56–58]



SG - a group in CDA exerting shielding effect
$|\Delta\delta^{ES}(R^1)| = |\delta^E(R^1) - \delta^S(R^1)|$
$|\Delta\delta^{ES}(R^2)| = |\delta^E(R^2) - \delta^S(R^2)|$
δ^E - chemical shift of analyzed nucleus in ester
δ^S - chemical shift of analyzed nucleus in alcohol (substrate)

Scheme 1. Assignment of absolute configuration of alcohols by single derivatization, using 'esterification shift' approach.

In double derivatization (second approach), one enantiomer of the substrate is derivatized with two enantiomers of the chiral derivatizing agent (Scheme 2a) or both enantiomers of the substrate are derivatized with one enantiomer of the CDA (Scheme 2b). In both cases, two diastereomers are formed and next, by comparison of the chemical shifts of the corresponding nuclei in both derivatives, the configuration is assigned (Scheme 2). In both methods, a slightly different approach to the data analysis is preferred. When derivatization with two CDA enantiomers is applied, the differences in the chemical shifts are expressed by the parameter $\Delta\delta$ and it is its sign that defines the absolute configuration. The exact definition of this value ($\Delta\delta^{RS}$ or $\Delta\delta^{SR}$) depends on the CDA used. On the other hand, when the derivatization of the mixture of enantiomers with one enantiomer of CDA is used, a comparison of the relative positions of the signals for two diastereomeric species defines their absolute configuration ($\delta^R > \delta^S$ vs $\delta^S > \delta^R$).

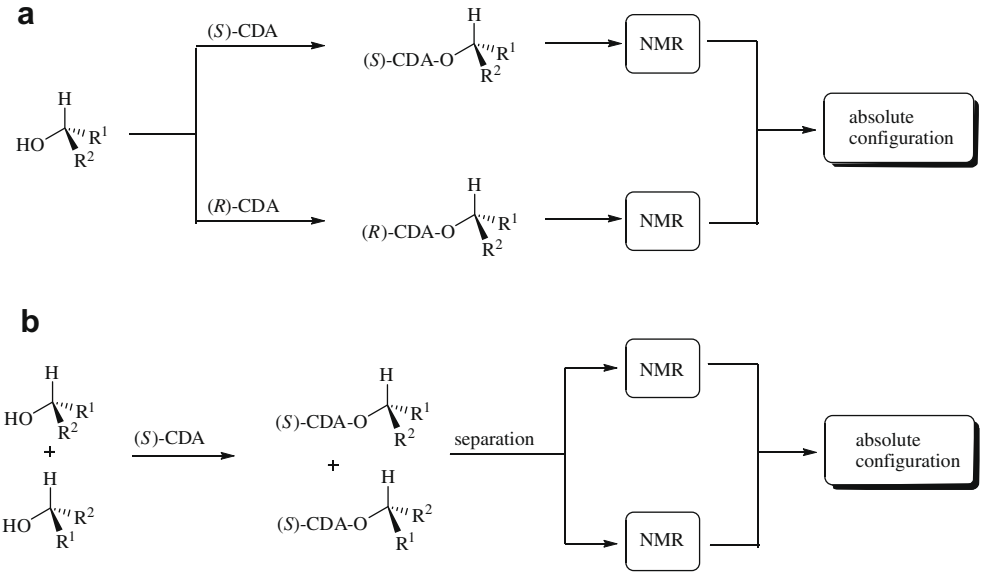
For consistency, we are presenting almost all data in the latter manner, treating the $\Delta\delta$ parameter (^{31}P NMR) presented in the tables only as an indicator of the magnitude of the difference between chemical shifts for different diastereomeric species. In this report, the $\Delta\delta$ parameter's sign has a diagnostic value only when presented in the figures and for naproxen derivatives.

2.2. Chiral solvating agents (CSAs)

Chiral solvating agents attract attention owing to the simplicity of their application in NMR analysis.[38,40,41] Due to the non-covalent interactions (hydrogen bonds and π-stacking) between the substrate investigated and the chiral solvating reagent, no derivatization is required, which means there is no need for the preparation and isolation of the product prior to the analysis. Furthermore, CSA can be of less than 100% enantiomeric purity, although the lower its enantiomeric purity, the smaller the magnitude of the chemical shifts difference. In most cases the rule applies that higher values of the $\Delta\delta$ parameter are achieved in nonpolar cosolvents, while polar solvents can considerably reduce the shift nonequivalence. Despite this, some CSAs such as cyclodextrins induce a detectable difference in chemical shifts in D_2O.[59–61] The main drawback of applying a CSA is the difficulty in proposing the conformational model, explaining the correlation between the absolute configuration and the chemical shift differences in the NMR spectra. Additionally, small differences between the chemical shifts can sometimes limit this technique. However, the advantages mentioned above still attract many research groups.[62–66]

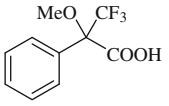
3. Absolute configuration assignment of hydroxy- and aminophosphonates by NMR

Although there is an abundance in the literature concerning the absolute configuration assignment of alcohols and amines by NMR,[6] the number of reports on the application of this approach to hydroxyphosphonates is limited, not to mention a rarity of reports on aminophosphonates. The most commonly used CDAs for this purpose are α-methoxy-α-(trifluoromethyl)phenylacetic acid

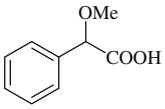


Scheme 2. Assignment of absolute configuration of alcohols by double derivatization: (a) with two enantiomers of a CDA and (b) with one enantiomer of a CDA.

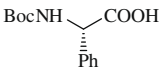
Chiral Derivatizing Agents:



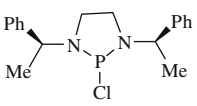
MTPA



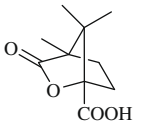
MPA



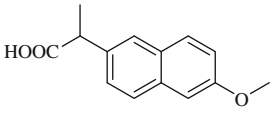
Boc-*L*-Phe



2-chloro-1,3-bis-(1-phenylethyl)-[1,3,2]diazaphospholidine

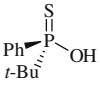


(*S*)-camphanic acid

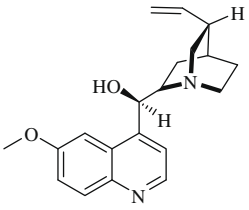


Naproxen

Chiral Solvating Agents:

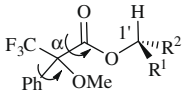


(*S*)-*tert*-butylphenylthiophosphinic acid



quinine

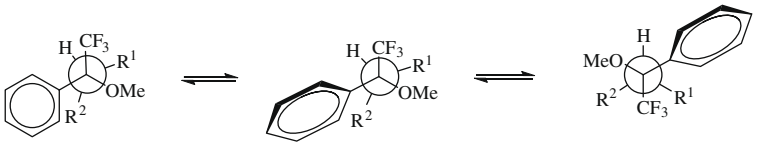
Figure 1. Common CDAs and CSAs used for the absolute configuration assignment of hydroxy- and aminophosphonates.



(*R*)-MTPA ester

a conformer consistent with the empirical Mosher model

the lowest energy conformer according to Riguera



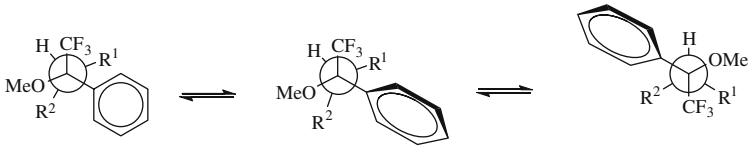
sp1 *sp 2* *ap 1*

shielding on R^2 deshielding on R^2 deshielding on R^1

(*S*)-MTPA ester

a conformer consistent with the empirical Mosher model

the lowest energy conformer according to Riguera



sp1 *sp 2* *ap 1*

shielding on R^1 deshielding on R^1 deshielding on R^2

Figure 2. The most representative conformers of the MTPA esters.[6,44]

(MTPA)[67–81] and α-methoxyphenylacetic acid (MPA, MMA) (Fig. 1).[56–58,82–90] Only isolated examples have been investigated by: 2-chloro-1,3-bis-(1-phenylethyl)-[1,3,2]diazaphospholidine,[91,92] *N*-Boc L-phenylglycine,[93] and (*S*)-(−)-camphanic acid[80] (Fig. 1). Recently, a thorough report on the application of naproxen and ibuprofen, common non-steroidal anti-inflammatory drugs, for the enantiomeric purity [(*S*)-ibuprofen and (*S*)-naproxen][94] and absolute configuration [(*S*)- and (*R*)-naproxen] assignment of hydroxy- and aminophosphonates has been published,[46] with *tert*-butylphenylthiophosphinic acid[95–97] and quinine[98–100] being use as the CSAs (Fig. 1).

The assignment of absolute configuration of hydroxy- and aminophosphonates uses ^{31}P NMR spectroscopy. The simplicity of the ^{31}P NMR spectrum after broad band decoupling of the ^{1}H enables the straightforward determination of configuration based on the relative positions of the signals.[38,39] However, the drawback of such an approach is the lack of the other signals, which could support the correctness of the ^{31}P NMR result. Therefore, ^{1}H NMR spectroscopy has sometimes been used as a complementary technique [MTPA,[68–72] MPA (double derivatization),[82–84,87–90] and naproxen[46]].

In most of the cases studied (except for naproxen derivatives), the models used were not confirmed by theoretical calculations or low-temperature NMR experiments. For MTPA and MPA derivatives of hydroxy- and aminophosphonates, the models applied for the esters and amides of MTPA and MPA of alcohols and amines were adopted directly[101–103] and abundant experimental data obtained seemed to confirm their applicability for the absolute configuration assignment of hydroxyphosphonates.

3.1. Absolute configuration assignment of hydroxy- and aminophosphonates by CDAs

3.1.1. α-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA)

α-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA)[†] was firstly used for the absolute configuration assignment of alcohols and amines by Mosher and Dale.[101,102] The structural features such as a lack of protons in the α position to the carbonyl group (avoiding racemization) together with the presence of trifluoromethyl substituent, which allows the application of ^{19}F NMR spectroscopy, made this CDA superior to other reagents at that time.

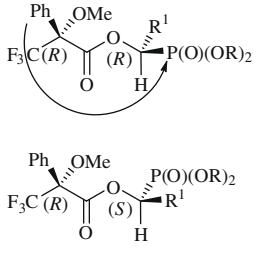
The first empirical model for the absolute configuration assignment of alcohols by MTPA was proposed by Mosher (Fig. 2).[101,102] However, some MTPA esters are known cases of not complying with the Mosher's model.[6] The explanation for such anomalies was found by extensive investigation of Riguera et al. who found out by theoretical calculations, NMR, and CD studies that MTPA esters of alcohols can be represented by the simplified equilibrium between three main conformers (Fig. 2).[44]

Riguera et al. claim that the main rotational processes involve the Cα–CO and Cα–Ph bonds.[44] In the *sp1* conformer, the carbonyl and CF_3 groups are *syn*-periplanar, whereas the phenyl is coplanar to the Cα–OMe bond. In this conformation, the R^2 substituent is shielded in the (*R*)-MTPA esters, while R^1 is shielded in the (*S*)-MTPA esters. This model complies with the Mosher model. However, in the *sp2* conformation the trends are opposite. Due to the *syn*-periplanar disposition of the CF_3 and C=O groups, together with the coplanarity of the phenyl ring and Cα–CO bond, in the (*R*)-MTPA ester, the R^2 group is deshielded, while in the (*S*)-MTPA ester it is the R^1 group which is deshielded. In the lowest energy conformation *ap1*, where the CF_3 and carbonyl groups are in the antiperiplanar relationship and the phenyl ring is coplanar with the Cα–OMe bond, in the (*R*)-MTPA ester, the R^1 substituent is deshielded while in the (*S*)-MTPA ester, the R^2 group is deshielded. Due to the combined action of these three similarly populated conformations, the differences in the chemical shifts are sometimes too small or not uniform for a given substituent to be representative. However, the Mosher model is applicable for the MTPA esters of hydroxyphosphonates, and to the best of our knowledge no incorrect assignments have been reported to date. This stems from the fact that the shielding effects in the Mosher model (Fig. 2, *sp1*) exert the same total influence on the difference between the chemical shifts ($\Delta\delta$) as the deshielding effects in the *ap1* conformer. Therefore, in the next subsection, the Mosher model for MTPA esters of hydroxyphosphonates is presented.

3.1.1.1. MTPA esters of 1-hydroxyphosphonates. For hydroxyphosphonates a few approaches for configuration assignment by MTPA have been employed.[‡] They can be classified either according to the method of derivatization, or according to the NMR signals, which are considered diagnostic. As for double derivatization two modus operandi are used: (a) standard double derivatization, in which one enantiomer of hydroxyphosphonate is derivatized separately with two enantiomers of the CDA, followed by the absolute configuration assignment on the basis of the $\Delta\delta^{SR}$ signs[§] (Scheme 2a)[69–71,105,106] or alternatively (b) derivatization of the hydroxyphosphonate (equimolar or non-equimolar mixture of enantiomers) is performed with one enantiomer of the CDA, followed by the absolute configuration assignment by comparison of the chemical shifts of the corresponding nuclei (Scheme 2b).[67,68,72,74–80,107] In most of these citations the parameter $\Delta\delta^{SR}$ is not given. Alternatively, the absolute configuration can be assigned on the basis of the chemical shifts of different NMR signals.

These approaches are listed below taking 1-hydroxyphosphonates as model. The following signals were considered diagnostic:

(a) signal of the phosphorus atom in the ^{31}P NMR spectra.[67,68,72,74–80,107,108] When the dialkylphosphono group is on the same side of the plane as the phenyl ring, it is more shielded and moves upfield, whereas the opposite disposition of the phosphono moiety and phenyl group shifts the phosphorus signal downfield (Fig. 3);



^{31}P NMR [P(O)(OR)$_2$]: $\delta^R < \delta^S$

Figure 3. Model for the assignment of the configuration of dialkyl 1-hydroxyphosphonates from the ^{31}P NMR spectra of their (*R*)-MTPA esters on the basis of the shielding effect exerted by the anisotropy cone of the phenyl ring.

(b) signal of the methoxy group of the CDA moiety in the MTPA esters of dialkyl hydroxyphosphonates with heteroaryl/aryl substituent in the α position to the phosphono group. The MeO group is more shielded by the aryl ring when both are on the same side of the MTPA plane than when they occupy the opposite sides of the plane (Fig. 4).[68] The signal

[†] MTPA is commercially available as an acid and acid chloride. By using the MTPA chloride (MTPA-Cl) for derivatization one must be aware of changing the substituent priority sequence by displacing the chlorine atom for oxygen or nitrogen.

[‡] Sometimes the hydroxyphosphonate underwent the side elimination of water under the condition required for derivatization.[104]

[§] $\Delta\delta^{SR} = \delta^S - \delta^R$.

of the methoxy group of the MTPA moiety depends on its relationship to the dialkylphosphono group (deshielding cone of the P=O bond). When on the same side of the plane as the phosphorus substituent, the methoxy group is deshielded.[72,109]

(c) signals of the protons of alkoxy groups (RO) from the dialkylphosphono substituent and/or nuclei from the non-phosphorus substituent (R^1) connected with the carbon stereogenic center, whose chemical shifts depend on their proximity to the anisotropic phenyl ring (Fig. 5).[69–71,105,106,110]

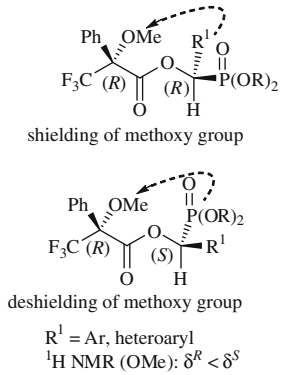


Figure 4. Model for the assignment of the configuration of dialkyl 1-hydroxyphosphonates from the ^{1}H NMR spectra (OMe group) of their (*R*)-MTPA esters based on the shielding effect exerted by the anisotropy cone of the aryl ring from the hydroxyphosphonate moiety on the methoxy group of MTPA and on the deshielding effect exerted by the anisotropy cone of the dialkylphosphono group.

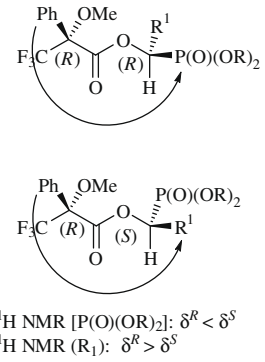


Figure 5. Model for the assignment of the configuration of dialkyl 1-hydroxyphosphonates from the ^{1}H NMR spectra of their (*R*)-MTPA esters on the basis of the shielding effect exerted by the anisotropy cone of the phenyl ring on the substituents in 1-hydroxyphosphonates.

The first application of (*R*)-MTPA for the absolute configuration assignment of 1-hydroxyphosphonates by ^{1}H NMR spectroscopy was reported by Hammerschmidt et al.[110] It confirmed the assignment made by the Horeau method.[111] For dimethyl 1-hydroxyphosphonates with an aryl substituent the signals of the methoxy (MeO) group from the (*R*)-MTPA moiety were diagnostic. The MeO group was more shielded in the esters of (*R*)-hydroxyphosphonates than in the esters of (*S*)-hydroxyphosphonates (Fig. 4).

For the (*R*)-MTPA esters of dimethyl 1-hydroxyphosphonates with an alkyl group in the hydroxyphosphonate part, the chemical shifts of the methoxy groups of dimethylphosphono substituent were diagnostic. This resulted from the mutual disposition of the phenyl ring of the (*R*)-MTPA moiety and dimethylphosphono group (Fig. 5). The protons of the dimethylphosphono group of (*R*)-MTPA esters of (*R*)-1-hydroxyphosphonates were in higher field in comparison to those of the (*R*)-MTPA esters of the (*S*)-1-hydroxyphosphonates.

In the following work Hammerschmidt et al.[67] introduced ^{31}P NMR to determine the absolute configuration of 1-hydroxyphosphonates **1**–**4** (Fig. 6). The procedure is based on the anisotropic effect exerted by the phenyl group of the MTPA on the dialkylphosphono group, as shown in Figure 5. The signals of the (*R*)-MTPA esters of (*R*)-1-hydroxyphosphonates are in the higher field compared to the signals of the (*R*)-MTPA esters of (*S*)-1-hydroxyphosphonates. Such a result complies with the Mosher model in which C(1′)H, the carbonyl, and CF_3 groups are situated in the same plane (Fig. 2, *sp1*). In the derivative in which the phenyl ring is located on the same side of the plane as the dialkylphosphono group [(*R*)-MTPA esters of (*R*)-1-hydroxyphosphonates] it is shielded more than when the phenyl ring is on the opposite side to the phosphorus substituent [(*R*)-MTPA esters of (*S*)-1-hydroxyphosphonates].

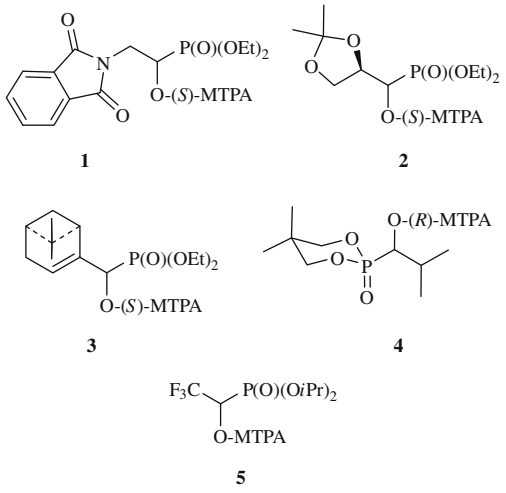


Figure 6.

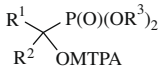
The same reasoning was applied for dialkyl [1-hydroxy-2-(4-alkoxyphenyl)ethyl]phosphonates,[74] 1-hydroxyalkylphosphonates and 1-hydroxy(aryl)alkylphosphonates,[75,107,76] and hydroxy(aryl/heteroaryl)methylphosphonates.[77,80] In many publications, the assignments presented were not supported by any experimental data.[112–116]

^{1}H and ^{31}P NMR techniques can also be combined to make the absolute configuration assignment more reliable. By comparison of the chemical shifts of the phosphorus signal and the MeO group of the MTPA moiety, the absolute configuration of thirteen 1-hydroxy(aryl)methyl- and 1-hydroxy(heteroaryl)methylphosphonates was assigned.[68]

Yuan et al.,[69] who adopted the double derivatization strategy[101,102,117] [using (*R*)- and (*S*)-MTPA enantiomers], proposed a modified approach to the absolute configuration assignment for MTPA esters of diisopropyl 1-hydroxy-1-(trifluoromethyl)methylphosphonate **5**. The presence of a CF_3 group in compound **5**, allowed the authors[69] to use ^{19}F NMR spectroscopy next to ^{1}H and ^{31}P NMR. Determination of the $\Delta\delta^{SR}$ signs allowed the configuration to be tentatively assigned (Table 1).

Diagnostic NMR data for all compounds discussed above are listed out in Table 1.

Table 1
Diagnostic ^{31}P NMR chemical shifts and ^{1}H NMR chemical shift differences of MTPA esters of 1-hydroxyphosphonates



Entry	R^1	R^2	R^3	^{31}P NMR[j]			^{1}H NMR[k] $\Delta\delta^{SR}$	Ref.
				δ^S	δ^R	$\Delta\delta^{SR}$		
1	Me	H	Me	22.68	22.26	0.42	–	67
2	Me	H	Et	–	–	–	–	113[a,b]
3	Me	H	*i*-Pr	18.04	17.53	0.51	–	67[c],113[a,b]
4	Et	H	Me	22.21	21.77	0.44	–	67,113[a,b]
5	Et	H	Et	–	–	–	–	113[a,b]
6	Et	H	*i*-Pr	17.54	17.08	0.46	–	75
7	Pr	H	*i*-Pr	17.83	17.33	0.50	–	75
8	*i*-Pr	H	Et	19.33	18.93	0.40	–	67
9	*i*-Pr	H	Et	19.37	18.95	0.42	–	75
10	*i*-Pr	H	*i*-Pr	18.79	18.64	0.15	–	75,114[a]
11	Compound **4**, Figure 6			12.59	12.55	0.04	–	73
12	*i*-Bu	H	Et	20.42	19.93	0.49	–	75
13	*i*-Bu	H	*i*-Pr	–	–	–	–	114[a]
14	*t*-Bu	H	Et	18.79	18.64	0.15	–	75
15	*t*-Bu	H	*i*-Pr	–	–	–	–	114[a]
16	(*S*)-*s*-Bu	H	*i*-Pr	18.06	17.21	0.85	–	73
17	(*R*)-*s*-Bu	H	*i*-Pr	17.71	17.60	0.11	–	73
18	C_5H_{11}	H	Me	–	–	–	–	112[a]
19	C_5H_{11}	H	Et	19.90	19.43	0.47	–	67,114[a]
20	C_5H_{11}	H	Et	19.96	19.46	0.50	–	75
21	C_5H_{11}	H	*i*-Pr	17.81	17.32	0.49	–	75,114[a]
22	C_7H_{15}	H	Et	19.97	19.47	0.50	–	75
23	C_7H_{15}	H	*i*-Pr	–	–	–	–	75
24	C_9H_{19}	H	Et	19.98	19.49	0.49	–	75,114[a]
25	*c*-C_4H_7	H	*i*-Pr	–	–	–	–	114[a]
26	*c*-C_6H_{11}	H	*i*-Pr	–	–	–	–	114[a]
27	*c*-C_7H_{13}	H	*i*-Pr	–	–	–	–	114[a]
28	*c*-$C_6H_{11}(CH_2)_2$	H	Et	–	–	–	–	114[a]
29	Compound **5**, Figure 6			9.39	8.71	0.68	–	69[d]
30	CH_2=CH	H	Et	15.78	15.39	0.39	–	79,113[a]
31	CH_2=CH	H	*i*-Pr	–	–	–	–	113[a]
32	(*E*)-CH_3CH=CH	H	Me	19.93	19.60	0.33	–	67[c]
33	CH_2=CH–CH_2	H	Et	18.56	18.20	0.46	–	107[d,e]
34	$CH_3(CH_2)_2$CH=CH	H	Me	–	–	–	–	112[a]
35	(*E*)-PhCH=CH	H	Me	–	–	–	–	112[a]
36	(*E*)-PhCH=CH	H	Et	15.97	15.61	0.36	–	79
37	PhCH=C(CH_3)	H	Me	–	–	–	–	112[a]
38	4-$MeOC_6H_4$CH=CH	H	Et	16.20	15.86	0.34	–	79
39	Bn	H	Et	19.01	18.52	0.49	–	74
40	Bn	H	Et	18.37	17.92	0.45	–	78
41	Bn	H	*i*-Pr	16.91	16.38	0.53	–	114[a], 74[f]
42	$Ph(CH_2)_2$	H	*i*-Pr	17.42	17.01	0.41	–	67
43	$BnOCH_2$	H	Me	–	–	–	–	67
44	(2*R*)-BnOCH(Me)	D	*i*-Pr	15.17	15.10	0.07	–	67
45	(2*S*)-BnOCH(Me)	D	*i*-Pr	15.65	14.14	1.51	–	67
46	4-$BnOC_6H_4CH_2$	H	Et	19.25	18.73	0.52	–	74
47	4-$MeOC_6H_4CH_2$	H	Et	19.27	18.75	0.52	–	74
48	4-$MeOC_6H_4CH_2$	H	*i*-Pr	17.00	16.45	0.55	–	74[f]
49	Compound **1**, Figure 6			16.18	15.72	0.46	–	67
50	Compound **2**, Figure 6			19.17	18.08	1.09	–	67
51	Compound **3**, Figure 6			19.55	18.64	0.91	–	67
52	Ph	H	Me	19.17	18.87	0.30	0.06[h]	67,112[a], 110[g,h]
53	Ph	H	Et	15.77	15.39	0.38	–	77
54	Ph	H	*i*-Pr	14.72	14.36	0.36	0.13	67,110[c,h]
55	2-MeC_6H_4	H	Me	19.64	19.42	0.22	0.10	68[h]
56	2-MeC_6H_4	H	*i*-Pr	15.44	15.11	0.33	0.13	68[h]
57	2-MeC_6H_4	H	*i*-Pr	15.36	14.99	0.37	–	80
58	4-MeC_6H_4	H	Et	15.97	15.61	0.36	–	77
59	4-MeC_6H_4	H	Me	–	–	–	–	112[a]
60	2-$MeOC_6H_4$	H	*i*-Pr	15.25	14.90	0.35	0.11	68[h]
61	3-$MeOC_6H_4$	H	*i*-Pr	14.58	14.20	0.38	0.13	68[h]
62	4-$MeOC_6H_4$	H	Me	–	–	–	–	112[a]
63	4-$MeOC_6H_4$	H	Et	16.11	15.76	0.35	–	77
64	4-$MeOC_6H_4$	H	*i*-Pr	14.96	14.59	0.37	–	80
65	2-ClC_6H_4	H	*i*-Pr	13.95	13.65	0.30	–	80
66	2-ClC_6H_4	H	*t*-Bu	6.70	6.61	0.09	–	80
67	4-ClC_6H_4	H	Me	–	–	–	–	112[a]
68	4-ClC_6H_4	H	Et	15.27	14.89	0.38	–	77
69	2-FC_6H_4	H	*i*-Pr	13.82	13.48	0.34	–	80
70	4-$NO_2C_6H_4$	H	Me	–	–	–	–	112[a]

(*continued on next page*)

Table 1 (*continued*)

Entry	R^1	R^2	R^3	^{31}P NMR[j]			^{1}H NMR[k] $\Delta\delta^{SR}$	Ref.
				δ^S	δ^R	$\Delta\delta^{SR}$		
71	1-Naphthyl	H	Me	14.62	14.26	0.36	0.14	68[h]
72	1-Naphthyl	H	*i*-Pr	15.01	14.70	0.31	0.17	68[h]
73	2-Naphthyl	H	*i*-Pr	19.25	19.03	0.22	0.16	68[h]
74	2-Thienyl	H	Et	15.19	14.91	0.28	0.10	68[h]
75	2-Thienyl	H	Et	14.39	14.07	0.32	—	77
76	2-Thienyl	H	*i*-Pr	13.30	12.91	0.39	0.13	68[h]
77	3-Thienyl	H	Et	15.28	15.00	0.28	—	77
78	3-Thienyl	H	*i*-Pr	14.25	13.93	0.32	0.14	68[h]
79	4-Me-2-Thienyl	H	Et	14.62	14.30	0.32	—	77
80	2-Furyl	H	Et	13.60	13.13	0.47	—	77
81	2-Furyl	H	*i*-Pr	12.36	11.80	0.56	0.11	68[h]
82	3-Furyl	H	Et	15.64	15.33	0.31	—	77
83	4-Me-2-Furyl	H	Et	13.85	13.35	0.50	—	77
84	2-Pyridyl	H	*i*-Pr	13.54	13.10	0.44	0.07	68[h]
85	3-Pyridyl	H	*i*-Pr	13.57	13.20	0.37	0.12	68[h]
86	$CH_3CH(NH_2)$	H	H	—	—	—	—	116[i]

[a] No spectroscopic data given.
[b] Absolute configuration confirmed by general rule predicting *Candida Antarctica* lipase B—catalyzed resolution.
[c] Absolute configuration determined by Horeau's method.[110,111]
[d] Absolute configuration confirmed by Kazlauskas rule.[118]
[e] Absolute configuration corroborated by the results of rabbit muscle fructose 1,6-biphosphate aldolase-promoted aldol addition.
[f] Absolute configuration confirmed by chemical correlation with 1-aminophosphonates of the known configuration.
[g] Absolute configuration determined previously by chemical correlation with 1-hydroxyphosphonate of the known configuration and circular dichroism.[119]
[h] Only selected ^{1}H NMR chemical shifts of MTPA esters of 1-hydroxyphosphonates are available.
[i] Absolute configuration confirmed by the order of elution on quinine-derived chiral anion exchanger (racemic and (*S*)-*N*-2,4-dinitrophenyl β-phenylalanine was used as a reference).
[j] $\delta^S = \delta$[*R*-MTPA-(*S*)-ester] = δ[*S*-MTPA-(*R*)-ester]; $\delta^R = \delta$[*R*-MTPA-(*R*)-ester] = δ[*S*-MTPA-(*S*)-ester]; $\Delta\delta^{SR} = \delta^S - \delta^R$.
[k] $\Delta\delta^{SR}$ for protons from OMe group in MTPA residue.

3.1.1.2. MTPA esters of 2-hydroxyphosphonates. It is assumed that for the MTPA esters of 2-hydroxyphosphonates the same conformational model as for the esters of 1-hydroxyphosphonates is valid.[72] However, due to the change of the substituent priority sequence on the stereogenic carbon center (C_2 in 2-hydroxyphosphonates and C_1 in 1-hydroxyphosphonates), there is a change of pattern in the signs of chemical shift differences. As a consequence, the ^{31}P NMR signals of the (*R*)-MTPA esters of the (*R*)-1-hydroxyphosphonate are shifted upfield relative to the signals of the corresponding (*S*)-MTPA esters (Fig. 7a). The opposite is true for MTPA esters of 2-hydroxyphosphonate, where the phosphorus atom is more shielded in the (*S*)-MTPA derivatives than in the appropriate (*R*)-MTPA esters (Fig. 7b).

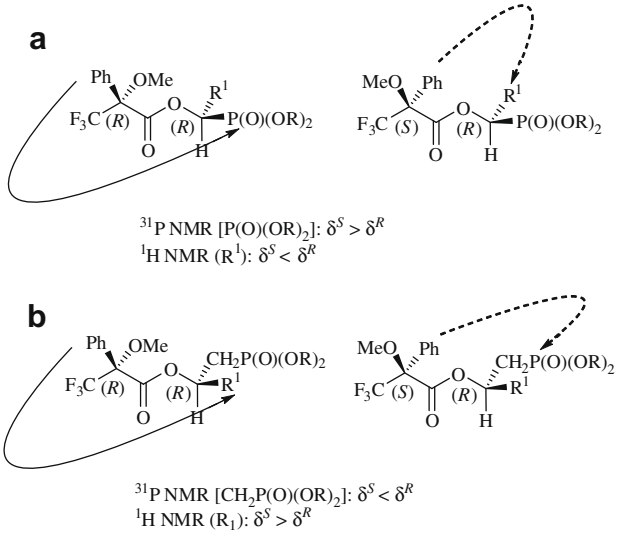


Figure 7. Comparison of the models of the (*R*)- and (*S*)-MTPA esters for the assignment of the absolute configuration of (a) (*R*)-1-hydroxyphosphonates and (b) (*R*)-2-hydroxyphosphonates.

Noyori et al. assigned the absolute configuration of diethyl and dimethyl 2-hydroxyphosphonates[70] and dimethyl *N*-acetyl-1-amino-2-hydroxyphosphonates[71] by double derivatization with both enantiomers of MTPA using ^{1}H and ^{31}P NMR (Fig. 8, compounds **6**–**14**).[117] The signs of the $\Delta\delta^{SR}$ (^{1}H and ^{31}P) were the same within one substituent connected with the stereogenic carbon center and opposite to the signs of $\Delta\delta^{SR}$ for the signals of the second group. Yuan et al.[105,106,116] used the same approach and ^{1}H NMR spectroscopy for the absolute configuration assignment of dimethyl 2-hydroxy-2-(trifluoromethyl)-ethylphosphonate, diethyl 3-chloro-, and 3-azido-2-hydroxypropylphosphonates (Fig. 8, compounds **15**–**17**).[¶]

As shown in Figure 8, the results were consistent with those of the Mosher conformational model.

Hammerschmidt et al.[72] assigned the absolute configuration of diisopropyl and diethyl 2-hydroxyphosphonates by derivatization with (*S*)-MTPA chloride and comparison of the chemical shifts in ^{31}P and ^{1}H NMR (MeO group from the MTPA moiety) of the thus obtained esters. The chemical shifts of the methoxy group protons depend on their disposition to the deshielding cone of the diethylphosphono group (Fig. 4),[109] while the phosphorus signal depends on its relation to the shielding cone of the phenyl ring (Fig. 3).

Based on the results mentioned above, Hammerschmidt et al.[72] argued that wrong assignments have been previously made for diisopropyl 2-hydroxy-2-phenylethylphosphonate,[80‖] diethyl 2-hydroxypropylphosphonate,[120,††] dimethyl 2-hydroxypropyl-

[¶] In the chloro analogue **16**, the substituent priority sequence changes and therefore, the absolute configuration on the β carbon stereogenic center is opposite to the one of the azidophosphonate **15**, although the Δδ signs stick to the same pattern in both compounds.

[‖] Although Hammerschmidt and Meier obtained the diisopropyl 2-hydroxy-2-phenylethylphosphonate with similar specific rotation values {$[\alpha]_D^{20} = +25.1$ (*c* 0.8, $CHCl_3$), ee = 91%[72] and $[\alpha]_D^{20} = +22.6$ (*c* 1.8, acetone), ee = 87%,[80]}, they ascribed them opposite configurations. It seems that Meier assigned the configuration of the phosphonate without taking into account the change of the substituent priority sequence at the stereogenic carbon center.

[††] The incorrect assignment was probably the result of ascribing the same absolute configuration to the MTPA chloride and to the ester obtained from MTPA-Cl and hydroxyphosphonate.

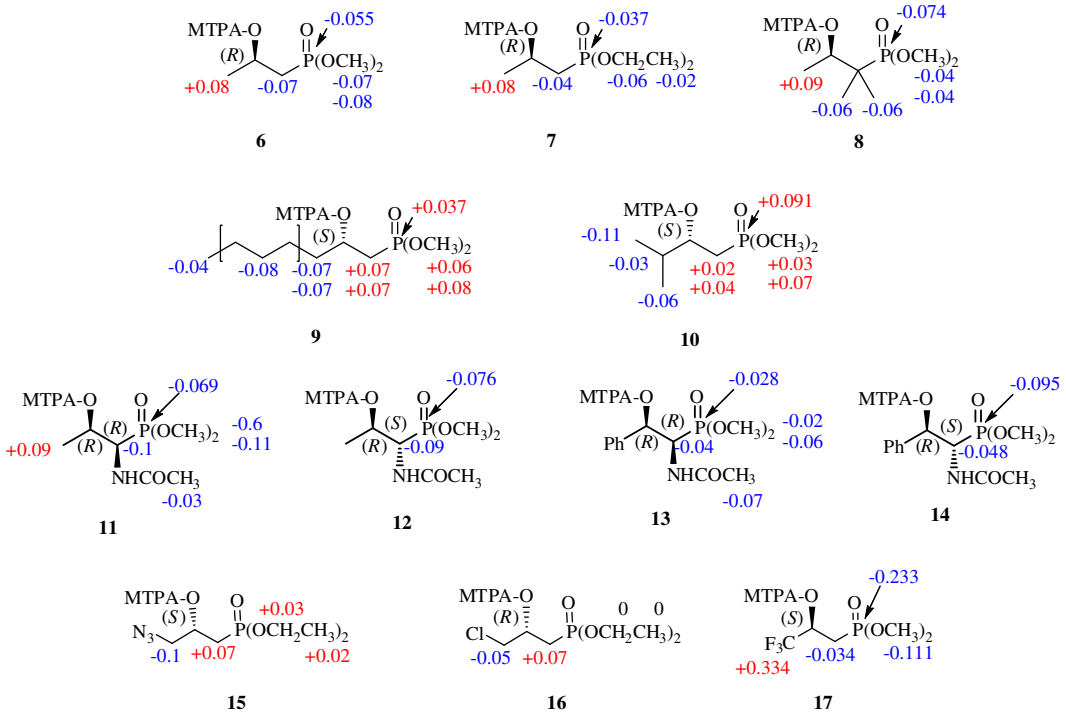


Figure 8. The differences between chemical shifts ($\Delta\delta^{SR}$) of (*S*)- and (*R*)-MTPA esters of 2-hydroxyphosphonates **6**–**17** (positive $\Delta\delta^{SR}$ values are given in red, negative $\Delta\delta^{SR}$ values are given in blue).

phosphonate,[108] and very likely also to diethyl 2-hydroxy-2-(2-pyridin-2-yl)ethylphosphonate.[108]

MTPA was also applied by Savignac et al.[115] for the absolute configuration assignment of dimethyl and diethyl 2-hydroxyphosphonates and 2-hydroxythiophosphonates and by Lindner et al.[116] for the absolute configuration assignment of the 1-amino-2-hydroxyphosphonic acids.

Diagnostic NMR data for the compounds discussed above are collected in Table 2.

In conclusion, rich experimental material (in total 112 examples presented in Tables 1 and 2), covering a wide range of structurally diverse 1-hydroxy- and 2-hydroxyphosphonates, proves the reliability of MTPA as a convenient chiral derivatizing agent for the absolute configuration assignment of hydroxyphosphonates. According to the results gathered here, no incorrect assignments were made stemming from the application of the Mosher model.

3.1.1.3. MTPA amides of aminophosphonates. The empirical model for MTPA amides is the same as that for MTPA esters.[102] According to Riguera et al.[45] the simplified conformational equilibrium for the MTPA amides of α-chiral primary amines can be reduced to three conformers (Fig. 9) where the *sp1* conformer is the favorable one.

Owing to the more favorable disposition of the substituents in the most stable conformation of the MTPA amides, compared to the most favorable conformation of MTPA esters, the $\Delta\delta^{SR}$ is larger. Therefore, no such problems as those for the MTPA esters of alcohols (small $\Delta\delta^{SR}$, uneven distribution of $\Delta\delta^{SR}$ signs) have been reported for MTPA amides derived from primary amines with an α-stereogenic center.

Despite such favorable conformational equilibria for MTPA amides, to the best of our knowledge, this reagent was used only for the configuration assignment of the MTPA amides of diethyl (1*S*,2*S*)-1-amino-2-methylcyclopropanephosphonate[122] **18** (Fig. 10) and diethyl (*R*)-1-amino-1-methylbenzylphosphonate[81] **19** (Fig. 11). Since the stereogenic center of the aminophosphonates investigated is quaternary, the Mosher model cannot be applied directly.

Fadel et al.[122] assigned the absolute configuration of MTPA amide **18**, using a model derived from theoretical calculations (MM2), supported by the values of vicinal coupling constants of the cyclopropyl ring substituents in ^{1}H NMR. However, the configurational assignment of aminocyclopropylphosphonates requires additional investigation as this assignment was not confirmed by any other complementary method and no other examples of the absolute configuration determination of this type of aminophosphonates were given.

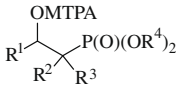
Hammerschmidt et al.[81] proposed a modified MTPA model for the amides of quaternary α-aminophosphonates **19a** and **19b**, in which the hydrogen atom, *syn*-periplanar to the carbonyl group, was exchanged for the methyl group, now being the smallest substituent on the quaternary stereogenic carbon.

According to the model shown in Figure 11, the chemical shifts of the MTPA methoxy groups were diagnostic, being moved upfield in (*R*)-MTPA-(*R*)-amide (δ = 3.45) compared to (*R*)-MTPA-(*S*)-amide (δ = 3.57). In the case of ^{31}P NMR, the chemical shift difference was minor (0.02 ppm), and the trend was opposite to that expected from the model. The absolute configuration [for (*S*)-aminophosphonic acid] was additionally confirmed by comparing the specific rotation of the derivatized title compound with the literature data for analogous compounds, the binding model elaborated for the chiral stationary phase used on HPLC for ee assignment, and finally by the retentive course of migration of the dialkylphosphono group from oxygen or nitrogen to carbon atom.

3.1.2. α-Methoxyphenylacetic acid (MPA, MMA)

α-Methoxyphenylacetic acid (MPA, MMA, Fig. 1) together with MTPA is the most widely used chiral derivatizing agent for the

Table 2
Diagnostic ^{31}P NMR chemical shifts and ^{1}H NMR chemical shift differences of MTPA esters of 2-hydroxyphosphonates



Entry	R^1	R^2	R^3	R^4	^{31}P NMR (δ)[l]			^{1}H NMR $\Delta\delta$[m]	Ref.
					δ^S	δ^R	$\Delta\delta^{SR}$		
1	Compound **6**, Figure 8				—	—	−0.055	—	70[a,b]
2	Compound **7**, Figure 8				—	—	−0.037	—	115[c], 70,121[c,j]
3	Me	H	H	*i*-Pr	24.12	24.20	−0.08	0.01	72[d]
4	Compound **8**, Figure 8				—	—	−0.074	—	70[a,b]
5	H	H	NH_2	H	—	—	—	—	116[e]
6	Compound **10**, Figure 8				—	—	−0.091	—	70[a,b]
7	*i*-Pr	H	H	Me	—	—	—	—	115[b]
8	*i*-Pr	H	H	*i*-Pr	24.99	25.30	−0.31	0.07	72
9	Bu	H	H	Me	—	—	—	—	108
10	Compound **9**, Figure 8				—	—	−0.037	—	115[b,c], 70
11	C_5H_{11}	H	H	*i*-Pr	24.41	24.50	−0.09	0.04	72
12	C_5H_{11}	H	H	Me	—	—	—	—	115[b,c,f]
13	*c*-C_3H_5	H	H	Et	—	—	—	—	115[b,c]
14	Compound **17**, Figure 8				26.21	26.44	−0.23	—	69[g]
15	Compound **15**, Figure 8				—	—	—	—	105,106[c]
16	Compound **16**, Figure 8				—	—	—	—	105,106[c,h]
17	Ph	H	H	*i*-Pr	23.18	23.43	−0.25	0.13	72
18	2-Thienyl	H	H	Et	24.70	24.82	−0.12	0.10	115[b,c], 72
19	2-Thienyl	H	H	*i*-Pr	22.43	22.63	−0.20	0.12	72
20	2-Pyridyl	H	H	Me	25.26	25.44	−0.18	—	108[k]
21	$Ph(CH_2)_3$	H	H	Me	28.08	28.19	−0.11	—	108
22	Compound **11**, Figure 8				—	—	−0.069	—	71[b,i]
23	Compound **12**, Figure 8				—	—	−0.076	—	71[b]
24	Compound **13**, Figure 8				—	—	−0.028	—	71[b]
25	Compound **14**, Figure 8				—	—	−0.095	—	71[b]

[a] Double derivatization with (*S*)- and (*R*)-MTPA.
[b] Absolute configuration supported by the BINAP-Ru reduction model for keto derivatives.
[c] No spectroscopic data given.
[d] Absolute configuration corroborated by comparison with the specific rotation of diethyl[72] and dimethyl[70] 2-hydroxypropanephosphonate of the known configuration.
[e] Absolute configuration confirmed by the order of elution on quinine-derived chiral anion exchanger.
[f] Thiophosphonate.
[g] Tentative assignment by MTPA derivatization.
[h] Absolute configuration confirmed by Kazlauskas rule.[118]
[i] Absolute configuration confirmed by using dimethyl *N*-acetyl 1-amino-2-hydroxypropylphosphonate of the known configuration.[71]
[j] The absolute configuration of diethyl 2-hydroxypropylphosphonate, obtained via the reduction of diethyl 2-oxopropylphosphonate by baker's yeast, was assigned tentatively previously,[120] by analogy to the similar reductions of 2-oxoalkanoates. Kafarski et al.[121] ascribed to diethyl 2-hydroxypropylphosphonate thus obtained the opposite configuration, unanimous with the one suggested by Hammerschmidt et al.[72]
[k] According to Hammerschmidt et al.,[72] the absolute configuration tentatively assigned to this compound is reversed.
[l] $\delta^S = \delta$[*R*-MTPA-(*S*)-ester] = δ[*S*-MTPA-(*R*)-ester]; $\delta^R = \delta$[*R*-MTPA-(*R*)-ester] = δ[*S*-MTPA-(*S*)-ester]; $\Delta\delta^{SR} = \delta^S - \delta^R$.
[m] $\Delta\delta^{SR}$ for protons from OMe group in MTPA residue.

absolute configuration assignment of secondary alcohols by NMR.[‡‡] Initially, due to the racemization problems occurring during the derivatization, MPA was less popular than MTPA. Nevertheless, optimization of the derivatization conditions introduced later on by Trost et al.[103] solved this problem.

According to the extensive studies of Riguera et al.[42] MPA esters of secondary alcohols are mainly composed of two conformers with a different orientation around the Cα–CO bond (Fig. 12).

The *sp* conformer is the most stable one, in which the MeO, and carbonyl groups are in the *syn*-periplanar disposition, in the same plane with C(1′)H. In the less stable, *ap* conformer, the methoxy and carbonyl groups are in an *anti*-periplanar disposition. For convenience, the most representative *sp* conformer can be used exclusively for the absolute configuration assignment. The model thus obtained is consistent with the empirical one proposed by Mosher.[101] By applying such an approach, the absolute configuration of the investigated alcohol can be determined directly by comparison of the chemical shifts of the protons of the corresponding nuclei. In the (*R*)-MPA ester, it is expected that strong shielding from the phenyl group is exerted on the substituent R^1 (Fig. 12). The opposite is valid for the R^2 group, which should be shielded in the (*S*)-MPA ester. Thus, the differences in the chemical shifts $\Delta\delta^{RS}$ will be positive for the R^2 substituent and negative for the R^1 substituent.

3.1.2.1. MPA esters of 1-hydroxyphosphonates. As for the MTPA esters of hydroxyphosphonates two methods of derivatization can be applied:

(a) Standard double derivatization, in which one enantiomer of the hydroxyphosphonate is derivatized with (*S*)- and (*R*)-MPA, followed by the absolute configuration assignment on the basis of the $\Delta\delta^{RS}$ signs (Fig. 1). This strategy is however very rarely applied.[84]
(b) Derivatization of two enantiomers of hydroxyphosphonate with one enantiomer of MPA followed by the absolute configuration assignment based on the comparison of their

[‡‡] The formation of the diastereomeric esters between MPA and hydroxyphosphonates is also a convenient route for hydroxyphosphonate resolution.[82,83,87,89]

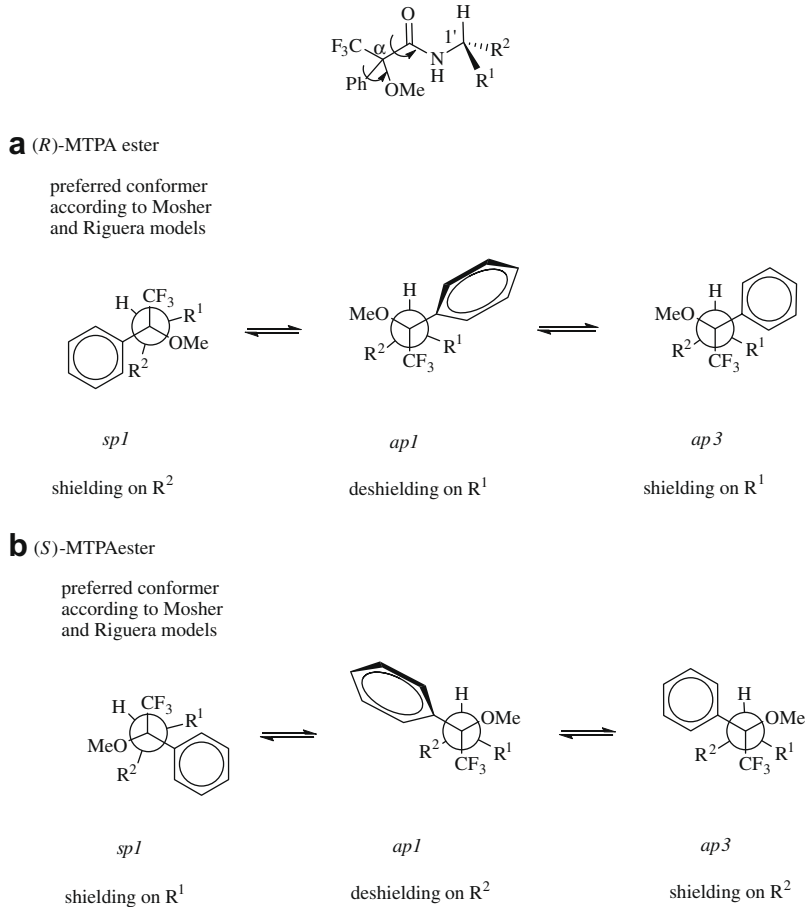


Figure 9. Shielding/deshielding effects in the three most representative conformers of the MTPA amides.[6,45]

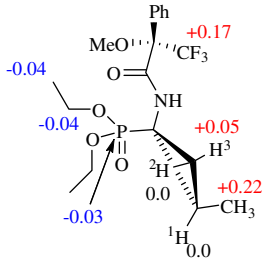


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Figure 10. Chemical shift differences ($\Delta\delta^{SR}$) between diastereomeric MTPA amides of diethyl (1*S*,2*S*)-1-amino-2-methylcyclopropanephosphonate (positive $\Delta\delta^{SR}$ values are given in red, negative $\Delta\delta^{SR}$ values are given in blue).[122]

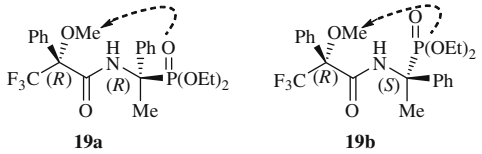


Figure 11. Model for the assignment of the configuration of the quaternary 1-aminophosphonate based on the shielding/deshielding of the methoxy group from the MTPA moiety.[81]

NMR spectra.[82,83,87–90,85,86] Such an approach is very often supported by a complementary technique (single derivatization), in which chemical shifts of the MPA ester are compared with the respective ones derived from the hydroxyphosphonate investigated (esterification shift) (Fig. 13).[56–58] Thus, the signals of both substituents (R^1 group and dialkylphosphono moiety) can be easily distinguished, since the protons of the substituent which is under the shielding cone of the phenyl ring from MPA are moved upfield, whereas the protons from the second substituent resonate at practically the same field in both the MPA ester and the free hydroxyphosphonate.

Assignments are usually made by comparison of the following signals:

(a) The phosphorus atom in the ^{31}P NMR spectra (the most common technique)[56–58,84–86,88] and the signals of protons of the substituents connected with the carbon stereogenic center in the hydroxyphosphonate moiety (Fig. 14).[82,83]
(b) Proton Cα–H for aryl substituted hydroxyphosphonates.[88] Contrary to the MTPA esters, the signal of the MeO group does not have diagnostic value, since according to the conformational model it is placed in the MPA plane, irrespective of the configuration of the derivatized compound (Fig. 15).

Based on the considerations mentioned above, Spilling et al.[56] described the derivatization of three racemic structurally diverse dimethyl 1-hydroxyphosphonates with (*R*)-MPA, leading to esters **20**–**22**, which after chromatographic separation, were

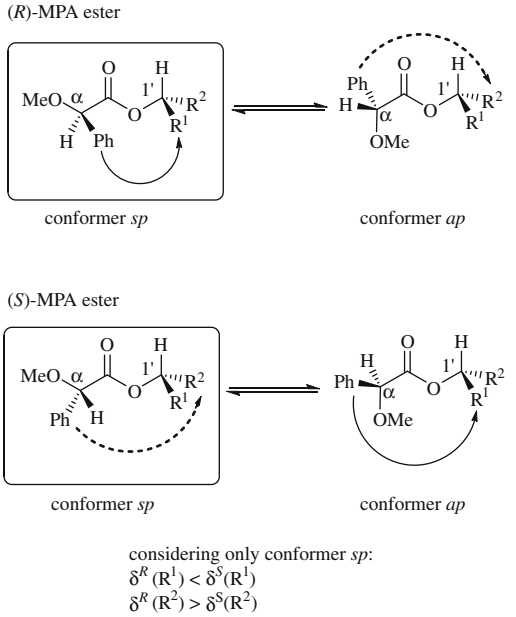


Figure 12. Conformational equilibrium in MPA esters.[6,42]

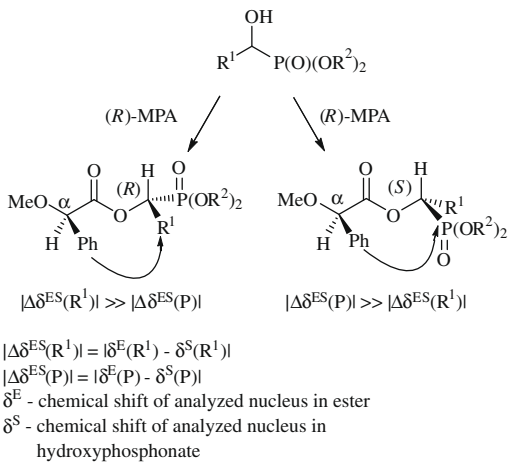


Figure 13. Assignment of configuration of dialkyl 1-hydroxyphosphonate by comparison of the chemical shifts of (*R*)-MPA esters of 1-hydroxyphosphonate with the chemical shifts of the hydroxyphosphonate (esterification shift).

subsequently analyzed by ^{31}P and ^{1}H NMR spectroscopies. Due to the shielding effect of the phenyl ring in the (*R*)-MPA esters of (*S*)-hydroxyphosphonate the dimethylphosphono group is moved upfield compared to the appropriate signal in the (*R*)-hydroxyphosphonate derivative ($\delta^S < \delta^R$).

Additionally, the complementary esterification shift technique was applied (Fig. 16, compounds **20**–**22**). Thus, in the (*R*)-MPA ester of (*S*)-hydroxyphosphonate, the protons of the dimethylphosphono group are intensely shielded, with respect to the same protons in the free 1-hydroxyphosphonate ($|\Delta\delta^{ES}(P)| = |\delta^E(P) - \delta^S(P)| = 0.2 \div 0.38$),[§§] while the protons of the second substituent connected with the carbon stereogenic center resonate at practically identical chemical shifts in the ester and in the starting

[§§] δ^S—chemical shifts of protons and phosphorus in starting 1-hydroxyphosphonate (substrate); δ^E—chemical shifts of protons and phosphorus atom in ester; $\Delta\delta^{ES} = \delta^E - \delta^S$.

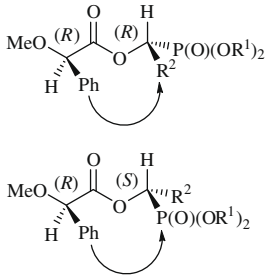


Figure 14. Model for the assignment of the configuration of 1-hydroxyphosphonates from the ^{31}P NMR and ^{1}H NMR spectra of their (*R*)-MPA esters on the basis of the shielding effect exerted by the anisotropy cone of the MPA phenyl ring on the substituents in 1-hydroxyphosphonates.

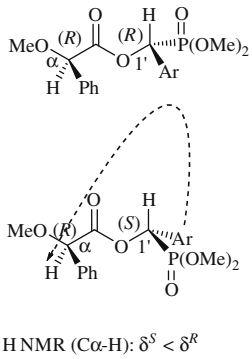


Figure 15. Model for the assignment of the configuration of 1-hydroxyphosphonates from the ^{1}H NMR spectra (Cα–H) of their (*R*)-MPA esters on the basis of the shielding effect exerted by the anisotropy cone of the aryl ring from the hydroxyphosphonate moiety.

hydroxyphosphonate ($|\Delta\delta^{ES}(R)| = |\delta^E(R) - \delta^S(R)| = 0 \div 0.13$). The opposite is valid for the (*R*)-MPA ester of (*R*)-1-hydroxyphosphonate.

Such results can be easily rationalized by the shielding effect of the phenyl ring exerted on the substituent present on the same side of the MPA plane, determined by the C(1′)H, MeO and carbonyl groups as shown in Figure 13. In the (*R*)-MPA esters of (*S*)-1-hydroxyphosphonates it is the dialkylphosphono substituent which is in the proximity of the phenyl ring, whereas in the (*R*)-MPA ester of (*R*)-1-hydroxyphosphonate the R^1 group is shielded. On the other hand, small differences in the chemical shifts between (*R*)-MPA esters of (*S*)-1-hydroxyphosphonates and free hydroxyphosphonate for the R_1 substituent and between the (*R*)-MPA esters of (*R*)-1-hydroxyphosphonates and the free hydroxyphosphonate for the dialkylphosphono group result from the similar shielding for these substituents in esters and hydroxyphosphonates.

Such an approach was also applied to the assignment of the absolute configuration of dimethyl 1-(hydroxyfarnesyl)phosphonate[57] and 5′-hydroxy 5′-phosphonate derivatives of cytidine[58] (Fig. 16, compounds **23** and **24**, respectively).

Recently, for the absolute configuration assignment of dimethyl and diethyl *meta*-substituted hydroxy(phenyl)methylphosphonates Skropeta et al.[88] have used the differences in the chemical shifts of ^{31}P NMR signals together with the differences in the chemical shifts of methine proton signals from the MPA moiety. Depending on the disposition of Cα–H to the shielding cone of the phenyl group, its signal is moved upfield or downfield (Fig. 15). For (*S*)-MPA esters of (*R*)-1-hydroxyphosphonates the signal of the

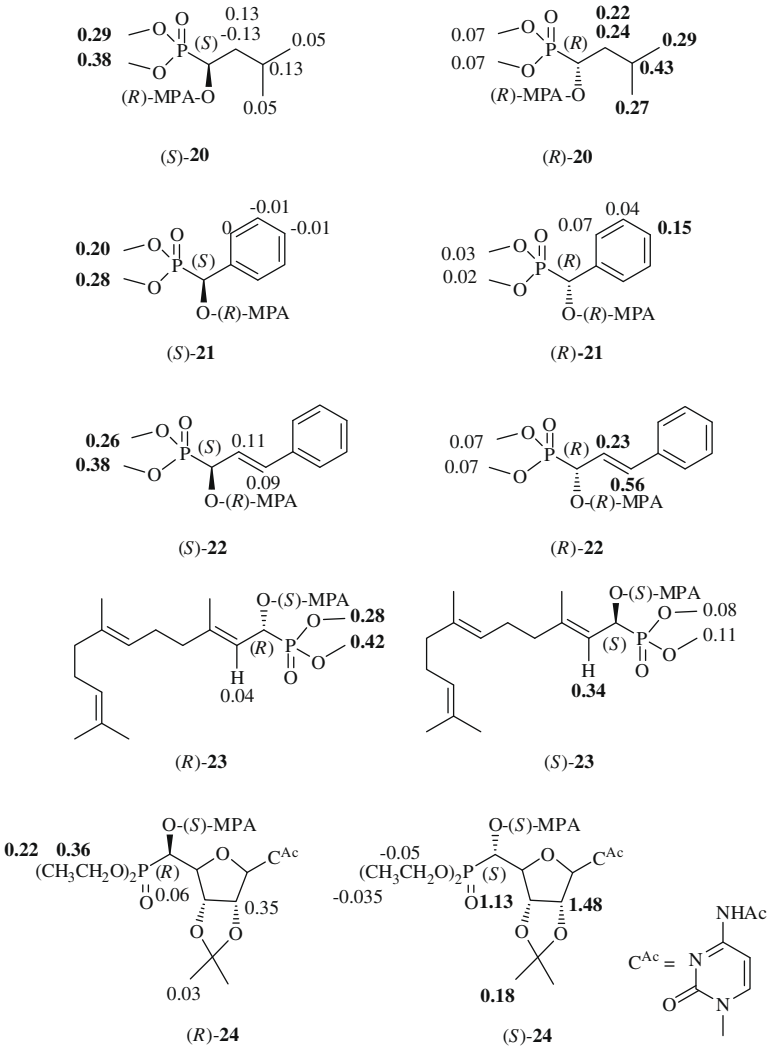


Figure 16. Esterification shifts values between the hydroxyphosphonates and their MPA esters **20**–**24** (values in bold represent the protons from the group which is most intensively shielded in ester compared to parent hydroxyphosphonate).

methine proton is more shielded than the respective one in the (*S*)-1-hydroxyphosphonate derivative. The chemical shifts differences are in the range 0.04–0.07 ppm.

The MPA esters of hydroxyphosphonates were also used for the determination of the absolute configuration of hydroxyphosphonates with two consecutive stereogenic centers. Wróblewski et al.[82,83,85] determined the absolute configuration of hydroxyphosphonates **25**–**30** (Fig. 17) assuming that the presence of one stereogenic center had no influence on the determination of the absolute configuration of the second stereogenic center. The authors, after chromatographic separation of diastereomeric (*S*)-MPA esters, assigned the configuration of the compounds **25** and **26** by comparison of their chemical shifts in ^{31}P and ^{1}H NMR. For the determination of the absolute configuration of diethyl and dimethyl *N*-Boc-2-amino-1,3-dihydroxyphosphonates **27**–**30**, only ^{31}P NMR spectroscopy was applied.

Kafarski et al.[86] applied the (*S*)-MPA ester of dimethyl *N*-Boc (1*R*/*S*,2*S*)-2-amino-1-hydroxyphosphonate **31** for the tentative assignment of its absolute configuration by ^{31}P NMR (Fig. 17). The authors also noticed, similarly to earlier observations

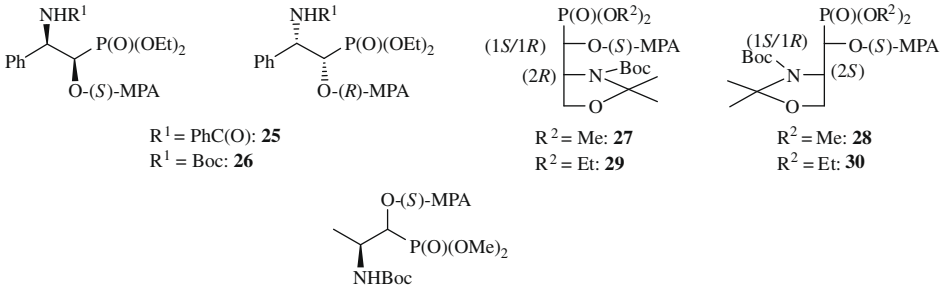


Figure 17.

Spilling,[56] the amplification of the difference in chemical shifts between signals of the diastereomeric (*S*)-MPA esters **31** ($\Delta\delta$ = 0.74 ppm) in comparison to the parent hydroxyphosphonates ($\Delta\delta$ = 0.51 ppm). This assignment was confirmed by the thorough conformational analysis of aminohydroxyphosphonates and aminohydroxyphosphonic acids.

Standard double derivatization with two enantiomers of MPA was applied by Wiemer et al.[84] for the absolute configuration assignment of *N*-acetylcytidine derivative of 5′,6′-dihydroxy-6′-phosphonate (Fig. 18).

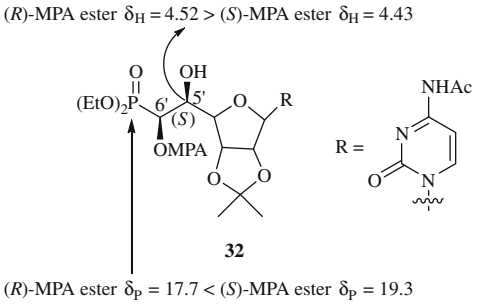


Figure 18.

The presence of two hydroxy groups in the above-mentioned dihydroxyphosphonate creates the problem of their regioselective derivatization by MPA. Moreover, for MPA, diesters a different model for the absolute configuration assignment of diesters than the one originally developed for MPA monoesters should be applied.[49,50,123–125] Luckily, after derivatization of parent dihydroxyphosphonate by (*R*)- and (*S*)-MPA, pure monoesters **32** could be isolated for further studies.[¶¶] The authors assumed no interference of the neighboring stereogenic center on the analysis and for the configuration assignment by NMR, they used the model in which the antiperiplanar disposition of two methine protons (5′-H and 6′-H) was assumed.[‖‖] Next, by comparison of the chemical shifts of the phosphorus atom and 5′-H signals the absolute configuration was assigned. In the (*S*)-MPA (5′*S*,6′*S*)-monoester **32** phosphorus atom should be relatively deshielded and the 5′-H-shielded. For the (*R*)-MPA (5′*S*,6′*S*)-monoester derivative **32**, the phosphorus atom should be more shielded and 5′-H, relatively deshielded. Opposite would be observed for the (5′*R*,6′*S*)-dihydroxyphosphonate derivative[84,126] **32**. Based on this, the authors assigned the (5′*S*,6′*S*)-configuration to product **32**, which was next confirmed by the X-ray analysis.[126]

3.1.2.2. MPA esters of 2-hydroxyphosphonates. Analogously as for the MTPA esters, the same conformational model can be applied to the MPA esters of 1-hydroxyphosphonates and 2-hydroxyphosphonates (Fig. 19).

For the (*S*)-MPA esters of 1-hydroxyphosphonates, the diethylphosphono moiety is more shielded in the (*S*)-MPA ester of (*R*)-1-hydroxyphosphonate, while the R substituent is strongly affected by the shielding cone of the phenyl ring in the (*S*)-MPA ester of (*S*)-1-hydroxyphosphonate (Fig. 19a). The contrary is observed for the (*R*)-MPA ester of (*S*)-1-hydroxyphosphonate. In turn, for the (*S*)-MPA esters of (*R*)-2-hydroxyphosphonate the R group is under the shielding cone of the phenyl ring, whereas for the (*S*)-MPA ester of (*S*)-2-hydroxyphosphonate, the diethylphosphonomethyl substituent is under aromatic ring influence (Fig. 19b).

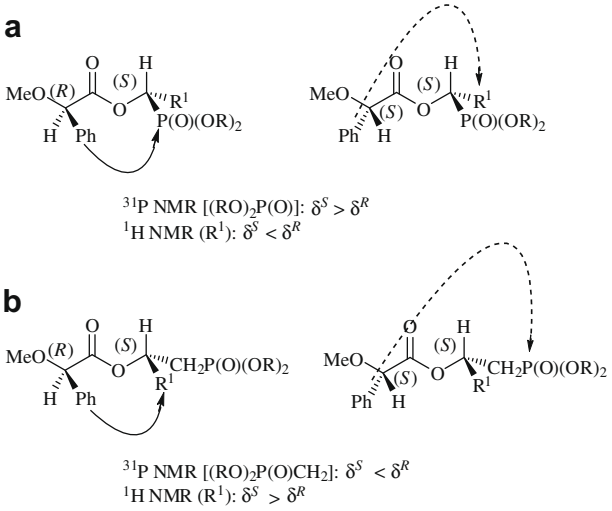


Figure 19. Comparison of the models of (*R*)- and (*S*)-MPA esters for the assignment of absolute configuration of (a) (*S*)-1-hydroxyphosphonates and (b) (*S*)-2-hydroxyphosphonates.

Ordóñez et al. used (*S*)-MPA for both the derivatization and the resolution (for selected compounds only) of thus obtained diastereomeric MPA esters of dimethyl 3-(*N*,*N*-dibenzylamino)-2-hydroxypropylphosphonate[87] **33**, dimethyl 3-[benzyl-(1-phenylethyl)amino]-2-hydroxypropylphosphonate[90] **34**, dimethyl 3-[(*S*,*S*)-*N*,*N*-bis(α-methylbenzylamino)]-2-hydroxypropylphosphonate[90] **35**, dimethyl 2-(2-*N*,*N*-dibenzylaminophenyl)-2-hydroxyethylphosphonate[89] **36**, and dimethyl 2-(2-benzyloxyphenyl)-2-hydroxyethylphosphonate[128] **37** (Figs. 20 and 21). By comparison of the chemical shifts of protons and phosphorus in both diastereomeric esters, the authors assigned their absolute configuration.[87,89,90,128] In the (*S*)-MPA esters of (*S*)-2-hydroxyphosph onates the ^{31}P and ^{1}H signals of the dimethylphosphono group were shifted more upfield than in the (*S*)-MPA ester of (*R*)-2-hydroxyphosphonates, while the protons of the second substituent connected with the carbon stereogenic center were shifted more upfield in the (*S*)-MPA ester of (*R*)-2-hydroxyphosphonates than in the ester of (*S*)-2-hydroxyphosphonate. The configurational assignment was confirmed by the single crystal X-ray analysis of diastereomerically pure (*S*)-2-(2-*N*,*N*-dibenzylaminophenyl)-2-hydroxyethylphosphonate[89] and (*R*)-3-[(*S*,*S*)-*N*,*N*-bis(α-methylbenzylamino)]-2-hydroxypropylphosphonate.[90]

Recently Ordonez et al.[128] confirmed the results of the configuration assignment for compound **37** using ^{13}C NMR (the same trend was observed between the values of chemical shifts as in ^{1}H and ^{31}P NMR, Fig. 21). In addition, the authors applied the methodology developed by Riguera et al.,[52] in which derivatized esters were subjected to $Ba(ClO_4)_2$ in MeCN-d_6. The authors observed that for most signals (^{1}H NMR), the chemical shift differences between diastereomers are slightly higher in the presence of $Ba(ClO_4)_2$ compared to the sample without a complexing agent, which confirms the preferential stabilization of the Mosher-like conformer.

Also of interest is Piotrowska and Glowacka's work[129] in which the absolute configurations of the phosphonate analogues of *cis*- and *trans*-4-hydroxyprolines have been established after N- and O-derivatization with (*S*)-MPA, by employing the Trost model and using ^{1}H NMR. However, as it concerns the γ-hydroxyphosphonates, it is not discussed here.

Although the experimental data for the MPA esters of hydroxyphosphonates are not so abundant (29 examples presented in Tables 3 and 4) as for the MTPA esters of hydroxyphosphonates, the structural diversity of the investigated compounds, coupled

[¶¶] Derivatization of the parent dihydroxyphosphonate with (*R*)-MPA gave only the monoacylated product. For (*S*)-MPA the easily separable mixture of the mono- and diacylated derivatives was obtained in a ratio of 3:2.

[‖‖] From the point of view of absolute configuration assignment by NMR the application of this model gave the same results as those for the Mosher model.

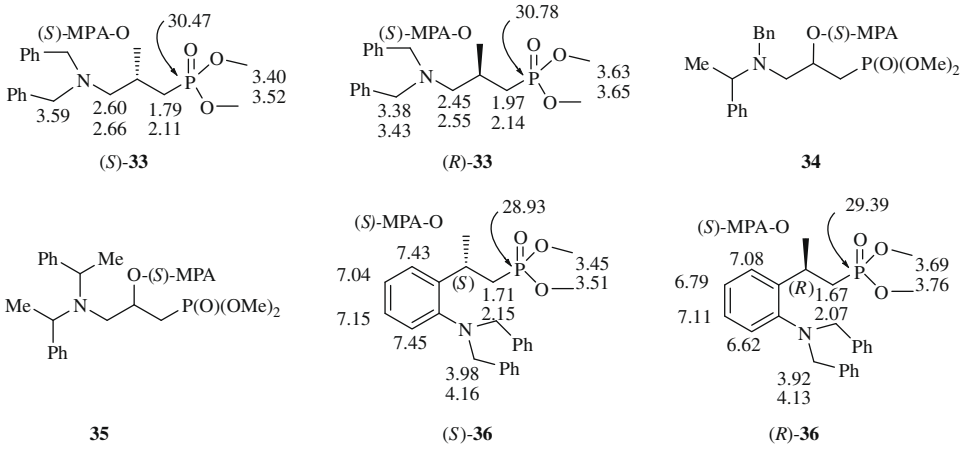


Figure 20. (*S*)-MPA esters of 2-hydroxyphosphonates and their chemical shifts in ^{1}H, ^{31}P NMR (for compounds **34**–**35** $\Delta\delta$ are not given as only (*S*)-MPA was used for derivatization[90]).

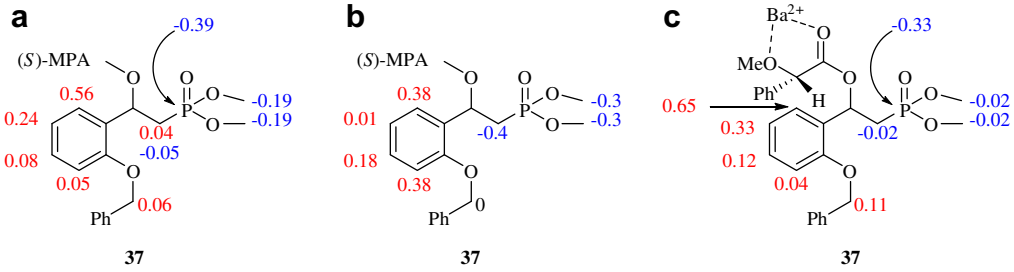


Figure 21. Chemical shift differences ($\Delta\delta^{RS}$) between the diastereomerically pure (*S*)-MPA esters of dimethyl (*S*)- and (*R*)-2-(2-benzyloxyphenyl)-2-hydroxyethylphosphonates **37**: (a) in ^{1}H and ^{31}P NMR; (b) in ^{13}C NMR; and (c) in ^{1}H and ^{31}P NMR, after complexation with $Ba(ClO_4)_2$ (positive $\Delta\delta^{RS}$ values are given in red, negative $\Delta\delta^{RS}$ values are given in blue).[128]

with the reliability of MPA as a CDA for the assignment of absolute configuration of alcohols makes this reagent a valuable tool for the determination of the absolute configuration of 1- and 2-hydroxyphosphonates.

3.1.2.3. MPA amides of 1-aminophosphonates. In the MPA amides, the most representative conformers are those in which C(1′)H, MeO and carbonyl groups are in the same plane, with the carbonyl and OMe units in the antiperiplanar disposition (Fig. 22).[43] Thus, contrary to the MTPA derivatives, the conformational model for MPA amides is opposite to the model for MPA esters.

For the convenience of analysis, the most representative *ap* conformer can be used exclusively for the absolute configuration assignment. By applying such an approach, the absolute configuration of the investigated amine derivative can be easily determined by comparison of the chemical shifts of the protons of particular substituents. In the (*R*)-MPA amide, the shielding from the phenyl group is exerted on the substituent R^2. The opposite is valid for the R^1 group, which should be shielded in the (*S*)-MPA ester. Thus the differences in the chemical shifts $\Delta\delta^{RS}$ will be positive for the R^1 substituent and negative for the R^2 substituent.

Although MPA is a common CDA for the assignment of the absolute configuration of the amines, to the best of our knowledge it was only used for the absolute configuration assignment of diallyl 1-aminobenzylphosphonates. Schmidt et al.[130] by comparison of the phosphorus chemical shifts of (*S*)-MPA amides of diallyl *meta*-substituted 1-aminobenzylphosphonates, assigned an (*S*)-configuration to those represented by the ^{31}P signal in the higher field, while an (*R*)-configuration was ascribed to those 1-aminobenzylphosphonates with ^{31}P signals in the lower field (Table 5).

Limited experimental data, however, require further confirmation to make this approach a reliable tool for the aminophosphonates' absolute configuration assignment.

3.1.3. Amino acids as chiral derivatizing agent

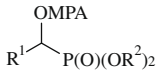
Boc-phenylglycine (BPG) was found superior to MTPA, MPA, and other aryl(methoxy)acetic acids reagents as a CDA for the derivatization of chiral primary amines.[131] The BPG amides show larger differences between the chemical shifts ($\Delta\delta$) than the appropriate MTPA and MPA derivatives due to the more convenient structural and conformational features. However, such a promising strategy was not systematically adapted to the aminophosphonates, and only a few examples of N-protected L-amino acids were used as chiral auxiliaries for the derivatization of 1-hydroxyphosphonates.[93]

Głowacki and Hoffmann applied N-protected L-amino acids (including *L*-BPG) to the absolute configuration determination of dibenzyl 1-hydroxyphosphonates.[93] They found that ^{31}P NMR signals of depsipeptides of selected L-amino acids and (*R*)-1-hydroxyphosphonates are moved downfield compared to those of depsipeptides of (*S*)-1-hydroxyphosphonates (Table 6). However, a wider applicability of this CDA for hydroxyphosphonates configuration assignment needs further confirmation on the more structurally diverse examples of hydroxyphosphonates and additional study on the conformational model.

3.1.4. Diazaphospholidine-based chiral derivatizing agents

Phosphorus-based chiral derivatizing agents and ^{31}P NMR spectroscopy can be used as a convenient tool for the assignment of the absolute configuration of alcohols, amines, and thioles.[38,39,132,133] In turn, the application of phosphorus-containing CDA for

Table 3
Diagnostic ^{31}P NMR chemical shifts and ^{1}H NMR chemical shift differences of MPA esters of 1-hydroxyphosphonates



Entry	R^1	R^2	^{31}P NMR (δ)[n]			^{1}H NMR $\Delta\delta^{o}$	Absolute configuration of MPA	Ref.
			δ^S	δ^R	$\Delta\delta^{RS}$			
1	*i*-Bu	Me	22.48	23.10	0.62	—	(*R*)	56[a]
2	Ph	Me	18.97	19.29	0.32	—	(*R*)	56[a]
3	Ph	Me	—	—	—	0.05	(*S*)	88[b,e]
4	Ph	Et	—	—	—	0.05	(*S*)	88[b]
5	Ph	Allyl	18.80	18.38	0.42	—	(*S*)	88[b]
6	PhCH=CH	Me	19.62	19.82	0.20	—	(*R*)	56[c]
7	$PhCH_2CH_2$	Me	22.15	22.75	0.60	—	(*R*)	56[d]
8	3-$PhOC_6H_4$	Me	—	—	—	003	(*S*)	88[b]
9	3-$PhOC_6H_4$	Et	17.60	17.15	0.45	0.05	(*S*)	88[b]
10	3-$PhOC_6H_4$	Allyl	18.08	17.62	0.46	—	(*S*)	88[b]
11	3-$CF_3C_6H_4$	Me	—	—	—	0.05	(*S*)	88[b,e]
12	3-$CF_3C_6H_4$	Et	17.06	16.68	0.38	0.04		88[b]
13	3-$CF_3C_6H_4$	Allyl	20.47	20.06	0.41	—		88[b]
14	Compound **23**, Figure 16		21.90	21.50	0.40	—	(*S*)	57
15	Compound **24**, Figure 16		16.17	15.92	0.25	—	(*S*)	58[f]
16	Compound **25**, Figure 17		—	—	—	—	(*S*)	82[f]
17	Compound **26**, Figure 17		—	—	—	—	(*S*)	83[g]
18	Compound **27**, Figure 17		18.95/ 19.55[h]	20.94	1.99[i]	—	(*S*)	85
19	Compound **28**, Figure 17		20.05	20.33/20.23[h]	0.28[i]	—	(*S*)	85
20	Compound **29**, Figure 17		16.01/ 16.90[h]	18.35	2.34[i]	—	(*S*)	85
21	Compound **30**, Figure 17		17.27[i]	17.84/ 17.54[h]	0.57[i]	—	(*S*)	85[j]
22	Compound **31**, Figure 17		19.60	20.35	0.75	—	(*S*)	86[k,l]
23	Compound **32**, Figure 18		17.70	19.30	1.60	—	(*S*) and (*R*)	84[m]

[a] Absolute configuration of hydroxyphosphonate confirmed previously by X-ray analysis.[56]
[b] Absolute configuration supported by the expected geometry of oxidation by (+)-8,8-(dichlorocamphor)sulfonyloxaziridine.[127]
[c] Absolute configuration confirmed by X-ray of (*R*)-MPA ester of 1-hydroxyphosphonate.[56]
[d] Absolute configuration confirmed by correlation with the sample obtained via reduction of the double bond in MPA ester of cinnamyl 1-hydroxyphosphonate of known configuration (see, entry 6 in this table).
[e] Obtained by transesterification of the appropriate diallyl phosphonates.[88]
[f] Absolute configuration supported by the comparison of chemical shifts between MPA ester and the parent hydroxyphosphonate.
[g] Absolute configuration supported by comparison with ^{1}H and ^{31}P NMR chemical shifts of diethyl analogue.
[h] Major/minor rotamers.
[i] $\Delta\delta^{RS}$ for major rotamers.
[j] Absolute configuration confirmed by chemical correlation with diethyl (4*R*,5*S*)-(5-benzoylamino-2,2-dimethyl-[1,3]-dioxan-4-yl)phosphonate (absolute configuration determined by ^{1}H and ^{13}C NMR).
[k] Absolute configuration confirmed by chemical correlation with (1*S*,2*S*)-2-amino-1-hydroxypropylphosphonic acid (comparison of specific rotation and spectroscopic parameters).
[l] Absolute configuration confirmed by NMR conformational analysis of dimethyl hydroxyphosphonate and its acid.
[m] Absolute configuration of hydroxyphosphonate confirmed by X-ray analysis.[126]
[n] $\delta^S = \delta$[*S*-MPA-(*S*)-ester] = δ[*R*-MPA-(*R*)-ester]; $\delta^R = \delta$[*S*-MPA-(*R*)-ester] = δ[*R*-MPA-(*S*)-ester]; $\Delta\delta^{RS} = \delta^R - \delta^S$. For the purpose of this review in some cases the values δ needed to be recounted for $\Delta\delta$.
[o] $\Delta\delta^{RS}$ for proton C(α)–H group in MPA residue.

organophosphorus compounds leads to two sets of phosphorus signals in ^{31}P NMR spectrum. The correlation between the chemical shifts of the derivatized compounds and the absolute configuration together with the magnitude of the chemical shift difference ($\Delta\delta_P$) allows the choice of the most diagnostic [P(III) or P(V)] signal for the configuration determination.

Kee et al.[91,92] used phosphorochloridite **38** (derived from *N*,*N*'-bis[1-(*S*)-phenylethyl]-1,2-ethylenediamine) as a convenient CDA for the derivatization of 1-hydroxy(aryl)methylphosphonates **39** (Fig. 23, Table 7). These types of chiral phosphorus-containing C_2-symmetric diamines were earlier used by Alexakis et al.[132,133] for the determination of the absolute configuration of the alcohols.

As seen from Table 7, a large chemical shift dispersion ($\Delta\delta$) was found between the phosphorus(III) nuclei (1.7–5.8 ppm), while for the phosphorus(V) nuclei the $\Delta\delta$ was much smaller (0–0.12 ppm).

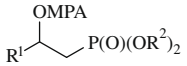
According to thorough studies of the spectroscopic features of **40**, the absolute configuration of the parent hydroxyphosphonates is assigned on the basis of the chemical shifts difference in ^{31}P NMR for the P(III) nucleus in **40**. The signals of P(III) of the (*S*)-1-hydroxyphosphonates derivatives **40** were in a lower field compared to those of the (*R*)-1-hydroxyphosphonates derivatives. These assumptions were further supported by the analysis of the chemical shifts of the methine proton of the hydroxyphosphonate moiety, and coupling constants values ($^3J_{PP}$, $^3J_{HP}$, $^2J_{HP}$) of the derivatized hydroxyphosphonates. The collected empirical data showing the same trend among these values[†††] together with the chemical shifts allowed inferring the absolute configuration of eleven 1-hydroxy(aryl)methylphosphonates with a reasonable confidence.

3.1.5. (1*S*)-(−)-Camphanic esters of hydroxyphosphonates

Derivatization of a range of 1-hydroxyphosphonates with (1*S*)-(−)-camphanic acid revealed that in the ^{31}P NMR spectra, the signals of the (*S*)-camphanic acid esters **41** of (*S*)-1-hydroxyphosphonates derivatives were shifted downfield by 0.01–0.66 ppm compared with the chemical shifts of the

[†††] For two derivatives **40** the $^3J_{PP}$ displayed opposite trend (Table 7, entries 9 and 10).

Table 4
Diagnostic ^{31}P NMR chemical shifts and ^{1}H NMR chemical shift differences of (*S*)-MPA esters of 2-hydroxyphosphonates



Entry	Compound	^{31}P NMR (δ)[e]			Ref.
		δ^S	δ^R	$\Delta\delta^{RS}$	
1	**33**	30.47	30.78	0.31	87
2	**34**	—	—	—	90[a]
3	**35**	—	—	—	90[a,b]
4	**36**	28.93	29.39	0.46	89[c]
5	**37**	29.17	29.56	0.39	128[d]

[a] No spectroscopic data given.
[b] Absolute configuration confirmed by X-ray analysis of (*R,S,S*)-**35**.
[c] Absolute configuration confirmed by Molecular Mechanics (MM) using an MMX force field for geometry minimization and energy assessment on the mandelates.[89] It seems that, the models depend on the configuration of the derivatized 2-hydroxyphosphonate and only for the (*S*)-MPA ester of (*S*)-2-hydroxyphosphonate it is consistent with the Mosher/Trost model.
[d] To determine the most stable conformer, a conformational search and geometry optimization were performed, employing Hartree–Fock with the basis set 6-311+G**.
[e] δ_S indicates for chemical shift of (*S*)-MPA ester of (*S*)-2-hydroxyphosphonate; δ_R indicates for chemical shift of (*S*)-MPA ester of (*R*)-2-hydroxyphosphonate; $\Delta\delta^{RS} = \delta^R - \delta^S$.

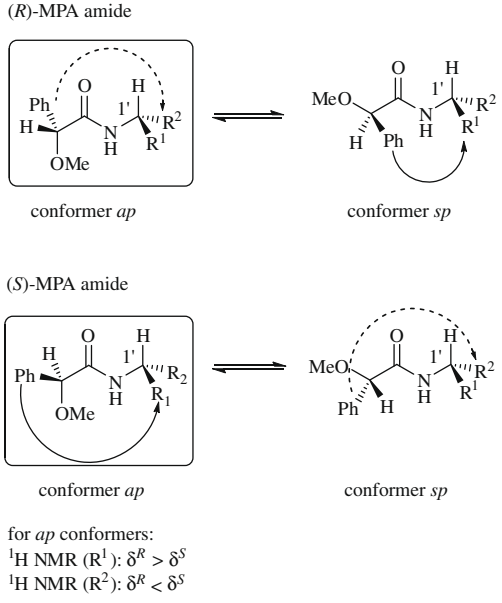
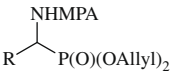


Figure 22. Conformational equilibrium in MPA amides.[43]

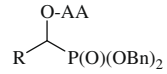
Table 5
Chemical shifts of (*S*)-MPA amides of diallyl 1-aminobenzylphosphonates[130]



Entry	R	^{31}P NMR[a]		
		δ^S	δ^R	$\Delta\delta^{RS}$
1	Ph	22.73	23.04	0.31
2	3-PhO–C_6H_4	22.15	22.48	0.33
3	3-CF_3–C_6H_4	21.86	22.17	0.31

[a] δ^S—chemical shift of (*S*)-MPA amide of (*S*)-1-aminophosphonate; δ^R—chemical shift of (*S*)-MPA ester of (*R*)-1-aminophosphonate; $\Delta\delta^{RS} = \delta^R - \delta^S$.

Table 6
^{31}P NMR chemical shifts of dibenzyl 1-hydroxyphosphonates derivatized with amino acids (AAs)[93]



Entry	R	AA	^{31}P NMR[a]		
			δ^S	δ^R	$\lvert\Delta\delta^{RS}\rvert$
1	*i*-Bu	Boc-L-Phe	21.88	22.28	0.41
2	Ph	Boc-L-Phe	18.32	18.52	0.20
3	*i*-Bu	Boc-L-Val	22.19	22.53	0.34
4	*i*-Bu	Boc-L-Leu	22.18	22.34	0.16
5	*i*-Bu	Cbz-L-Pro	22.41	22.59	0.19

[a] δ^S—chemical shift of the ester of (*S*)-hydroxyphosphonate; δ^R—chemical shift of the ester of (*R*)-hydroxyphosphonate; $\Delta\delta^{RS} = \delta^R - \delta^S$.

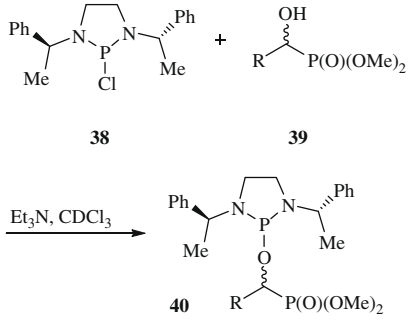


Figure 23. Application of 2-chloro-1,3-bis-(1-phenylethyl)-[1,3,2]diazaphospholidine **38** for the derivatization of dimethyl 1-hydroxyphosphonates[91,92] **39**.

Table 7
^{31}P NMR chemical shifts of **40**

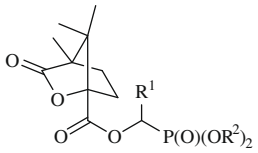
Entry	R	P(III)			P(V)		
		δ^S	δ^R	$\lvert\Delta\delta\rvert$	δ^S	δ^R	$\lvert\Delta\delta\rvert$
1	Ph[a]	127.75	122.21	5.54	23.55	23.54	0.01
2	1-Naphthyl	127.87	122.27	5.60	23.77	23.68	0.09
3	2-Naphthyl	128.13	123.37	4.76	23.47	23.47	0
4	2-BrC_6H_4	126.95	121.55	5.40	22.93	22.81	0.12
5	3-BrC_6H_4	128.78	124.02	4.76	22.74	22.71	0.03
6	4-BrC_6H_4	128.68	124.40	4.28	22.83	22.83	0
7	4-MeC_6H_4	127.64	122.16	5.48	23.78	23.77	0.01
8	4-$MeOC_6H_4$	127.91	122.53	5.38	23.85	23.85	0
9	4-$O_2NC_6H_4$	126.34	124.62	1.72	21.75	21.74	0.01
10	2-$O_2NC_6H_4$	129.73	126.62	3.11	21.84	21.80	0.04
11	2-$Ph_2PC_6H_4$	128.61	122.74	5.87	23.44	23.42	0.02

δ^S—chemical shift of the ester of (*S*)-hydroxyphosphonate.
δ^R—chemical shift of the ester of (*R*)-hydroxyphosphonate.
[a] Absolute configuration confirmed by comparison of the specific rotation with

(*R*)-1-hydroxyphosphonates esters.[80] For the (1*S*)-camphanates **41** of the diversely substituted in the phenyl ring 1-hydroxy(aryl)methylphosphonates (Table 8, entries 1–20), the magnitude of the chemical shift difference was smaller (0.01–0.11 ppm) than for appropriate (*R*)-MTPA esters (0.09–0.37). However, for the (*S*)-camphanates **41** of the 1-hydroxyalkyl- and 1-hydroxyalkenylphosphonates (Table 8, entries 21–25), the $\Delta\delta^{RS}$ was in the range of 0.07–0.66 ppm.

No model was proposed for explaining the observed trends. Based on the earlier studies it can be assumed that such a correlation exists owing to the anisotropy of the carbonyl group, selectively exerting its influence on the dialkylphosphono moiety.

Table 8
Chemical shifts of (*S*)-camphanic esters of 1-hydroxyphosphonates **41**



41

Entry	R^1	R^2	^{31}P NMR ($CDCl_3$)		
			δ^S	δ^R	$\Delta\delta^{RS}$
1	Ph	Et	16.87	16.92	0.05
2	Ph	*t*-Bu	8.08	8.12	0.04
3	Ph	*i*-Pr	14.97	15.00	0.03
4	2-ClC_6H_4	Me	18.60	18.68	0.08
5	2-ClC_6H_4	Et	16.22	16.29	0.07
6	2-ClC_6H_4[a]	*i*-Pr	14.34	14.40	0.06
7	2-ClC_6H_4	*t*-Bu	7.34	7.35	0.01
8	3-ClC_6H_4	*i*-Pr	14.16	14.20	0.04
9	3-ClC_6H_4	*t*-Bu	7.28	7.33	0.05
10	4-ClC_6H_4	*i*-Pr	14.39	14.42	0.03
11	4-ClC_6H_4	*t*-Bu	7.35	7.38	0.03
12	2,4-$Cl_2C_6H_4$	*i*-Pr	13.81	13.88	0.07
13	2-BrC_6H_4	*i*-Pr	14.39	14.45	0.06
14	2-IC_6H_4	*i*-Pr	14.72	14.81	0.09
15	2-$O_2NC_6H_4$	*i*-Pr	13.29	13.38	0.09
16	2-$MeOC_6H_4$	*i*-Pr	15.63	15.66	0.03
17	2-MeC_6H_4	*i*-Pr	15.90	15.91	0.01
18	4-MeC_6H_4	*t*-Bu	7.38	7.42	0.04
19	4-$MeO_2SC_6H_4$	*i*-Pr	13.37	13.42	0.05
20	2,6-$F_2C_6H_4$	*i*-Pr	13.33	13.44	0.11
21	$PhCH_2CH_2$	*i*-Pr	17.62	17.69	0.07
22	PhCH=CH	*i*-Pr	15.13	15.79	0.66
23	Me	*t*-Bu	11.92	12.06	0.14
24	*i*-Pr	*t*-Bu	10.98	11.21	0.23
25	*i*-Bu	*t*-Bu	12.07	12.25	0.18

δ^S—chemical shift of the ester of (*S*)-hydroxyphosphonate.
δ^R—chemical shift of the ester of (*R*)-hydroxyphosphonate.
$\Delta\delta^{RS} = \delta^R - \delta^S$.
[a] Absolute configuration confirmed by circular dichroism and X-ray analysis.

3.1.6. Naproxen (Nap)

(*S*)-Naproxen derivatives have been applied as chiral derivatizing reagents to assess the e.e. of chiral sulfoxides by ^1H NMR,[134] amino derivatives,[135] and cyanohydrins[136] by HPLC. The low price and appropriate structural features encouraged Gajda and Błażewska to apply (*S*)-naproxen for the enantiomeric purity determination of hydroxy- and aminophosphonates.[94] The promising results thus obtained led to an extension of the methodology to the absolute configuration assignment of hydroxy- and aminophosphonates by double derivatization with (*S*)- and (*R*)-naproxen.[46] This is the first example of such thorough studies on the conformational equilibrium of the naproxen derivatives of hydroxy- and aminophosphonates, supported by theoretical calculations,[‡‡‡] and low temperature NMR experiments. This confirmed the model previously proposed for the absolute configuration assignment of carboxylic acids by derivatization with alcohols[137] and enabled construction of the model for the aminophosphonates derivatives. The method is general and especially useful for aminophosphonates, for which almost no literature reports on applying CDA and NMR as a tool for the absolute configuration determination exist. According to the studies of Gajda et al.[46] naproxen esters and amides of hydroxy- and aminophosphonates are mainly composed

[‡‡‡] For geometry optimization ab initio restricted Hartree–Fock, 6-31G(d) basis set was used; condensed phase (chloroform) was included using implicit polarized continuum model with COSMO electrostatics; energy calculations were performed at the DFT level, using B3LYP functional, 6-31G(d) basis set.

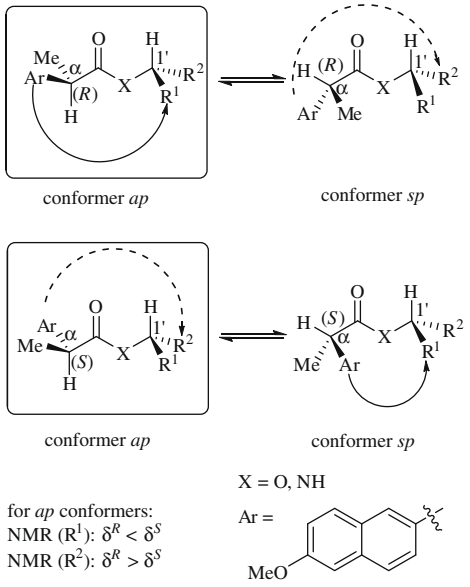


Figure 24. Conformational equilibrium in naproxen esters and amides.

of two conformers, with a different orientation around the Cα–CO bond (Fig. 24).

The most stable one is the *ap* conformer, in which Cα–H and C=O bonds are in the *anti*-periplanar disposition, in the same plane with C(1′)–H. For the convenience of application, the most representative *ap* conformer can be used exclusively for the absolute configuration assignment. As shown in Figure 24 in the (*R*)-naproxen derivative, the strong shielding from the aryl group should be exerted on substituent R^1, whereas in the (*S*)-naproxen derivative, the R^2 group is expected to be shielded.

Since the conformational models for naproxen esters and amides of hydroxyphosphonates and aminophosphonates are the same, here they will be presented together.

3.1.6.1. Naproxen esters and amides of 1-hydroxy- and 1-aminophosphonates. As for MTPA and MPA esters of hydroxyphosphonates, and also in the case of naproxen, two ways of derivatization of hydroxy- and aminophosphonates can be applied:

(a) One enantiomer or enantiomerically enriched mixture of the studied compound is derivatized with (*S*)- and (*R*)-naproxen and next, based on the values of $\Delta\delta^{RS}$ for different substituents, absolute configuration is assigned.[46]
(b) Derivatization of two enantiomers of the studied compound with one enantiomer of naproxen and next, based on the relative positions of the peaks of thus obtained diastereomeric species, absolute configuration can be assigned.

Until now, only approach (a) was described. Gajda et al.[46] applied the double derivatization technique for diethyl 1-hydroxy- and 1-aminophosphonates with defined stereochemistry using (*R*)- and (*S*)-naproxen chloride[§§§] as CDA.

[§§§] The authors[46] used enantiomerically pure (*S*)-naproxen and enantiomerically enriched (*R*)-naproxen (ee = 60%). Recently, enantiomerically pure (*R*)-naproxen has become commercially available. For the convenience of analysis, in this chapter we will refer to both (*S*)- and (*R*)-enantiomer of naproxen without defining their enantiomeric purity. In addition, as double derivatization with both enantiomers of naproxen was applied for all investigated compounds, $\Delta\delta^{RS}$ will be used as a diagnostic parameter, in which the sign will allow the determination of the absolute configuration assignment.

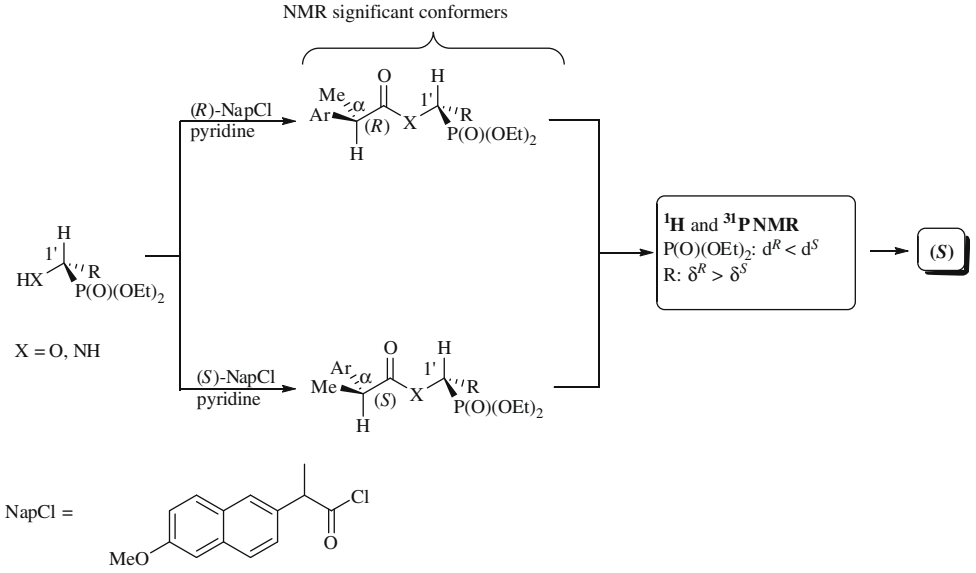


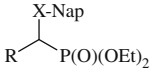
Figure 25. Assignment of the absolute configuration of (*S*)-1-hydroxy- and (*S*)-1-aminophosphonates by double derivatization with (*R*)- and (*S*)-naproxen chlorides. The opposite $\Delta\delta^{RS}$ sign pattern would be observed for the naproxen esters of (*R*)-1-hydroxy and naproxen amides of (*R*)-1-aminophosphonates (not shown).

As already mentioned, for the naproxen derivatives of both the hydroxy- and aminophosphonates, the same conformational model is valid.[46] As shown in Figure 25, the C(1′)–H, Cα–H and carbonyl group are in the same plane, with the Cα–H proton and carbonyl group in the antiperiplanar disposition. According to such a model in the derivatives of the (*R*)-naproxen and (*S*)-1-hydroxy or (*S*)-1-aminophosphonate, the diethylphosphono group is more shielded than for the (*S*)-naproxen ester or amide ($\Delta\delta^{RS}[P(O)(OEt)_2] < 0$). The R substituent is more shielded in the (*S*)-naproxen derivative compared to the (*R*)-naproxen derivative ($\Delta\delta^{RS}(R) > 0$). The opposite is valid for the naproxen esters of (*R*)-1-hydroxyphosphonates and amides of (*R*)-1-aminophosphonates ($\Delta\delta^{RS}[P(O)(OEt)_2] > 0$, $\Delta\delta^{RS}(R) < 0$). The chemical shift differences ($\Delta\delta^{RS}$) and diagnostic ^{31}P NMR chemical shifts of the naproxen derivatives of diethyl 1-hydroxy- and 1-aminophosphonates are collected in Figure 26 and Table 9.

The methodology can be additionally simplified to the use of the ^{31}P NMR (for the diethylphosphono group in ^{1}H as well as the ^{31}P NMR, the signs of $\Delta\delta^{RS}$ are the same). For the naproxen derivatives of (*R*)-1-hydroxy- and 1-aminophosphonates the chemical shift difference $\Delta\delta^{RS}$ in ^{31}P NMR is positive, whereas the negative sign of $\Delta\delta^{RS}$ confirms the (*S*) configuration of the carbon stereogenic center.

High values and homogenous signs of the $\Delta\delta^{RS}$, the same for protons and phosphorus in one substituent and opposite to the signs determined for the signals of the second substituent

Table 9
Diagnostic ^{31}P NMR chemical shift differences of (*R*)- and (*S*)-naproxen esters and amides of 1-hydroxy and 1-aminophosphonates **42–56**



Entry	Compd	X	R	^{31}P NMR ($CDCl_3$)[e]			Absolute configuration
				δ^S	δ^R	$\Delta\delta^{RS}$	
1	**42**	O	Me	21.55	21.06	−0.49	(*S*)[a]
2	**43**	O	Et	21.24	20.68	−0.56	(*S*)[a,b]
3	**44**	O	Pr	21.17	20.55	−0.62	(*S*)[a]
4	**45**	O	Bu	22.04	21.43	−0.61	(*S*)[a,b]
5	**46**	O	*i*-Bu	21.23	20.62	−0.61	(*S*)[a,b]
6	**47**	O	*t*-Bu	20.18	19.48	−0.70	(*S*)[a]
7	**48**	O	*c*-Hex	20.88	20.22	−0.66	(*S*)[a]
8	**49**	O	PhCH=CH	17.38	18.05	0.67	(*R*)[a]
9	**50**	O	4-MeC_6H_4	17.91	17.52	−0.39	(*S*)[a]
10	**51**	NH	Me	25.76	26.00	0.24	(*R*)[a,c]
11	**52**	NH	Bu	25.22	25.40	0.18	(*R*)[a,c]
12	**53**	NH	*i*-Bu	25.52	25.76	0.24	(*R*)[a,c,d]
13	**54**	NH	*c*-Hex	24.36	24.66	0.30	(*R*)[a,c]
14	**55**	NH	Bn	24.23	24.03	−0.20	(*S*)[a,c]
15	**56**	NH	4-MeC_6H_4	21.88	22.09	0.21	(*R*)[a,c]

[a] Absolute configuration supported by the oxazaborolidine-catalyzed reduction model for ketones[138] and α-ketophosphonates.[80]
[b] Absolute configuration supported by comparison with specific rotation of the appropriate diethyl 1-hydroxyphosphonates of known configuration.[76]
[c] Absolute configuration supported by chemical correlations.[76]
[d] Absolute configuration supported by comparison with specific rotation of the appropriate diethyl 1-aminophosphonate of known configuration.[76]
[e] δ^R—(*R*)-naproxen ester/amide of 1-hydroxy/ 1-aminophosphonate; δ^S—(*S*)-naproxen ester/amide of 1-hydroxy/ 1-aminophosphonate; $\Delta\delta^{RS} = \delta^R - \delta^S$.

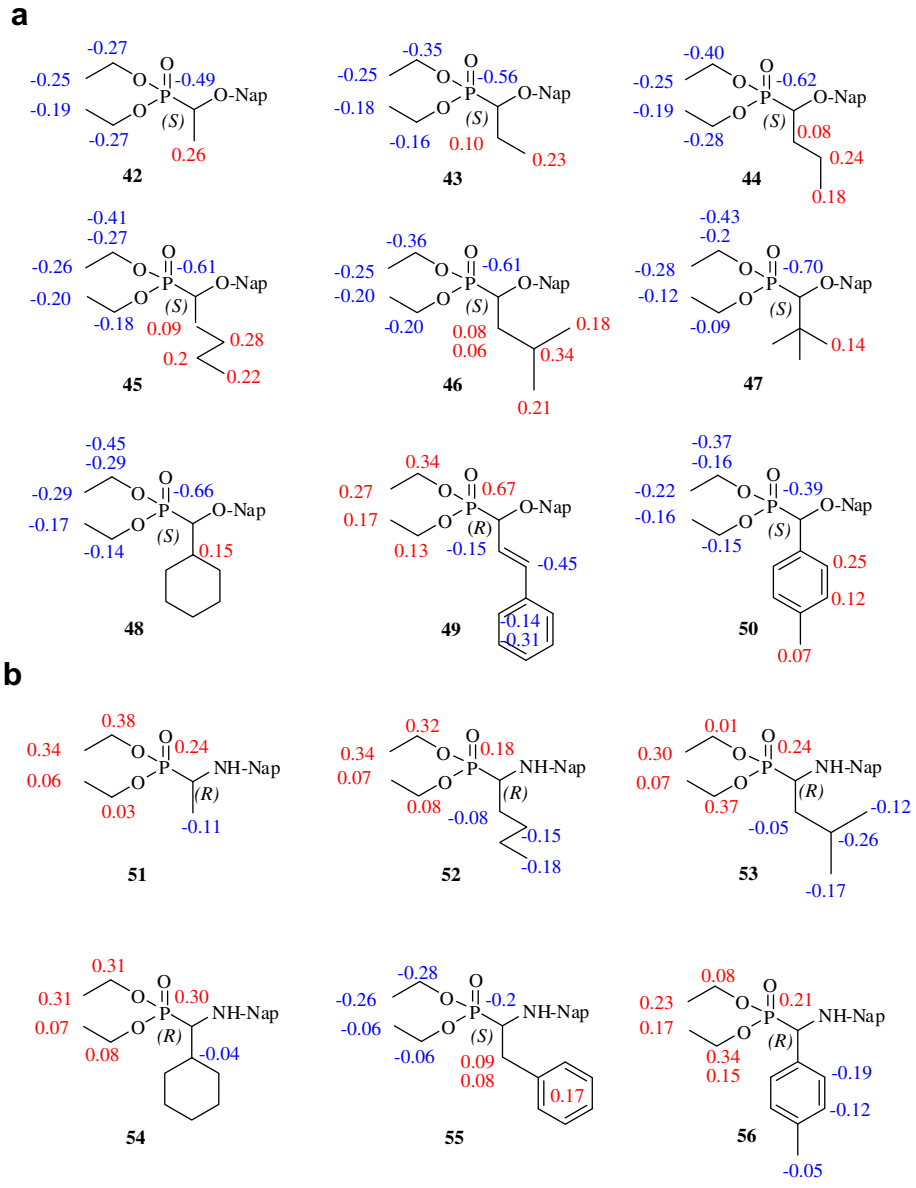


Figure 26. $\Delta\delta^{RS}$ values taken from the ^{1}H and ^{31}P NMR spectra of naproxen esters (a) and amides (b) of the appropriate diethyl 1-hydroxyphosphonates and 1-aminophosphonates of known configurations (positive $\Delta\delta^{RS}$ values are given in red, negative $\Delta\delta^{RS}$ values are given in blue).[46]

connected with the carbon stereogenic center, proved the reliability of the naproxen as a chiral derivatizing agent for 1-hydroxy- and 1-aminophosphonates. The method is especially valuable for aminophosphonates, for which very few reports exist on applying NMR for their absolute configuration determination.

3.1.6.2. Naproxen esters and amides of 2-hydroxy- and 2-aminophosphonates. Naproxen was also successfully applied as a chiral derivatizing agent to the absolute configuration assignment of 2-hydroxy- and 2-aminophosphonates[46] with defined stereochemistry. The conformational model is the same as that for the 1-hydroxy- and 1-aminophosphonates (Fig. 27a and b). Due to the change of the substituent priority sequence on the carbon stereogenic center, there is a change of pattern in the signs of the chemical shift differences. Therefore, for the (*R*)-naproxen esters of the (*R*)-2-hydroxyphosphonates, diethylphosphonomethyl group is shielded ($\Delta\delta^{RS} < 0$; $\delta^{R} < \delta^{S}$), while in the (*S*)-naproxen esters of (*R*)-2-hydroxyphosphonates it is the R group which is under the influence of the naphthyl ring ($\Delta\delta^{RS} > 0$; $\delta^{R} > \delta^{S}$; Fig. 27b). Whereas for the esters of the (*S*)-2-hydroxyphosphonates and (*R*)-naproxen the R group is shielded ($\Delta\delta^{RS} < 0$; $\delta^{R} < \delta^{S}$) and in the (*S*)-naproxen esters the diethylphosphono group is shielded by the naphthyl ring ($\Delta\delta^{RS} > 0$; $\delta^{R} > \delta^{S}$). The same model operates for 2-aminophosphonates. As shown in Figure 28, the results are consistent with the conformational model. Diagnostic ^{31}P NMR data for compounds **57**–**59** are collected in Table 10.

Also here, as for naproxen esters and amides of 1-hydroxy- and 1-aminophosphonates, the methodology can be additionally simplified to the use of the ^{31}P NMR (for the diethylphosphono group in ^{1}H as well as ^{31}P NMR the signs of $\Delta\delta^{RS}$ are the same). For the naproxen derivatives of diethyl (*R*)-2-hydroxy- and (*R*)-2-aminophosphonates the $\Delta\delta^{RS}$ in ^{31}P NMR is negative, whereas the (*S*)-configuration is described by positive value of $\Delta\delta^{RS}$.

Homogenous signs of the $\Delta\delta^{RS}$, the same for protons and phosphorus in one substituent and opposite to the signs determined for the signals of the second substituent connected with the carbon

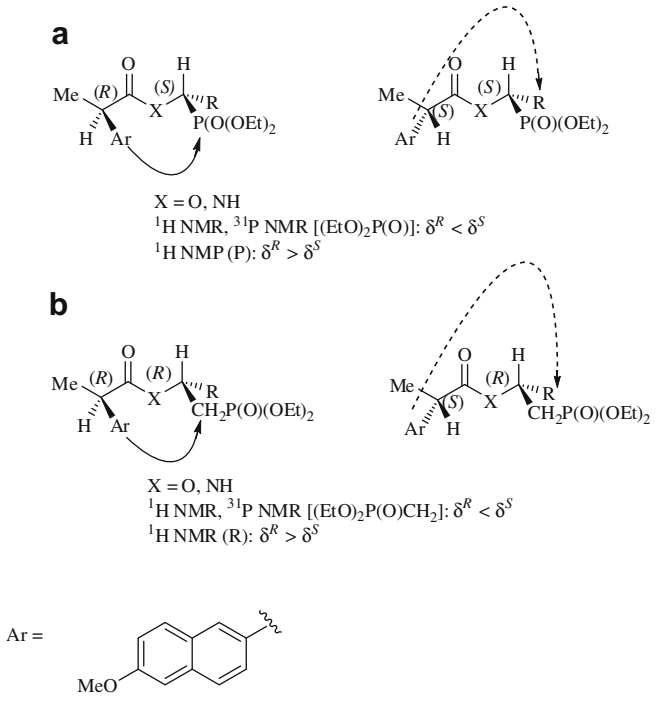


Figure 27. Comparison of the models of the (*R*)- and (*S*)-naproxen derivatives of: (a) diethyl (*S*)-1-hydroxy-/(*S*)-1-aminophosphonates; (b) diethyl (*R*)-2-hydroxy-/(*R*)-2-aminophosphonates.

stereogenic center, proved reliability of the naproxen as a chiral derivatizing agent for 2-hydroxy- and 2-aminophosphonates. However, despite the fact that the results obtained by the authors[46] were consistent with the proposed conformational model, only limited number of examples of 2-hydroxy- and 2-aminophosphonates were investigated. To confirm the applicability of this method to 2-hydroxy- and 2-aminophosphonates, further investigation on a range of structurally diverse phosphonates is necessary.

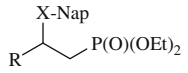
3.2. Absolute configuration assignment of hydroxyphosphonates by chiral solvating agents

3.2.1. *t*-Butylphenylphosphinothioic acid

(S_P)- and (R_P)-*tert*-Butylphenylphosphinothioic acids are used as chiral solvating agents for the enantiomeric purity assignment of structurally diverse classes of compounds.[139–142]

Hammerschmidt et al.[95–97] successfully used (S_P)-*tert*-butylphenylphosphinothioic acid for the determination of the absolute configuration of 1-hydroxyphosphonates (Table 11). For method validation, the authors used chiral hydroxyphosphonates with a defined stereochemistry. Thus, for the complexes of all (*R*)-1-hydroxyphosphonates with (S_P)-*tert*-butylphenylphosphinothioic acid the ^{31}P NMR signal of the dialkylphosphono group was shifted

Table 10
Diagnostic ^{31}P NMR[d] chemical shift differences of naproxen derivatives **57–59**



Entry	Compd	X	R	^{31}P NMR ($CDCl_3$)			Absolute configure
				δ^S	δ^R	$\Delta\delta^{RS}$	
1	**57**	O	Me	26.54	26.72	0.18	(*S*)[a]
2	**58**	O	Ph	25.69	25.72	0.03	(*S*)[b]
3	**59**	NH	Ph	27.98	27.77	−0.21	(*R*)[b,c]

[a] Absolute configuration supported by comparison with specific rotation of diethyl 2-hydroxypropanephosphonate of known configuration.[121]
[b] Absolute configuration supported by the oxazaborolidine-catalyzed reduction model for β-ketophosphonates.[80]
[c] Absolute configuration supported by chemical correlation.[76]
[d] δ^R—chemical shift of (*R*)-naproxen ester/amide of 2-hydroxy/2-aminophosphonate; δ^S—chemical shift of (*S*)-naproxen ester/amide of 2-hydroxy/2-aminophosphonate; $\Delta\delta^{RS} = \delta^R - \delta^S$.

downfield in comparison with the respective signal derived from the complex of (*S*)-1-hydroxyphosphonates. The opposite relationship was observed for the ^{1}H signals of the methine proton next to phosphorus atom (C(1′)HP, $n = 0$), which were shifted upfield for the complex of (*R*)-1-hydroxyphosphonates with (*S*)-*tert*-butylphenylphosphinothioic acid, whereas for the analogous complex of (*S*)-1-hydroxyphosphonate they were shifted downfield. The chemical shift difference in the ^{31}P NMR spectra was in the range 0.1–0.3 ppm, while in the ^{1}H NMR spectra $\Delta\delta^{RS}$ is 0.1–0.25 ppm.

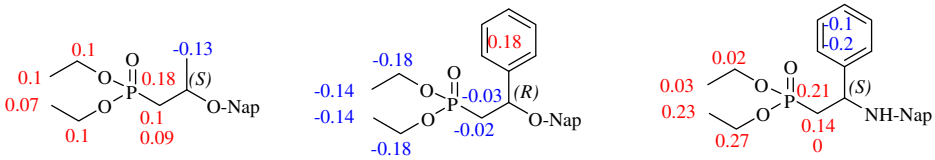
(S_P)-*tert*-Butylphenylphosphinothioic acid was also applied to the absolute configuration assignment of diethyl 2-hydroxypropylphosphonate (Table 11, entry 28). Again, the phosphorus atom signal corresponding to the complex of (S_P)-*tert*-butylphenylphosphinothioic acid and (*R*)-2-hydroxypropylphosphonate was moved downfield (0.05 ppm) compared to that of the diastereomeric complex of (*S*)-2-hydroxyphosphonate.[95] Unfortunately, according to the authors,[95–97] no general conclusions for absolute configuration assignment could be drawn for the 1-acetoxy, 1-chloroacetoxy-, 1-azido-, 1-phthalimidooxy-, 1-acyloxy-, and 1-aminooxyphosphonates.

The method seems to be reliable due to the wide range of the structurally diverse (alkyl, cycloalkyl, alkenyl, alkynyl, aryl, and heteroaryl) 1-hydroxyphosphonates investigated. However, the authors claim the necessity of using an independent method to substantiate the results.

3.2.2. Quinine

Quinine and its derivatives are frequently used as chiral solvating agent inducing NMR nonequivalence in enantiomeric mixtures.[143–146] Quinine has also found applicability in the studies on hydroxyphosphonates[99,113,147–151] using ^{31}P NMR spectroscopy.

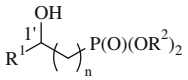
Lejczak et al.[98] and later on Kee et al.[99] used quinine as a chiral discriminating agent for the tentative absolute configuration assignment of 1-hydroxyphosphonates (Table 12, entries 1–21).



57 **58** **59**

Figure 28. $\Delta\delta^{RS}$ values calculated from the ^{1}H and ^{31}P NMR spectra of naproxen esters and amide of the diethyl 2-hydroxyphosphonates **57–58** and diethyl 2-aminophosphonate **59** of the known configurations (positive $\Delta\delta^{RS}$ values are given in red, negative $\Delta\delta^{RS}$ values are given in blue).[46]

Table 11
Diagnostic ^{31}P NMR and ^{1}H NMR chemical shifts of complexes of (S_P)-*tert*-butylphenylphosphinothioic acid and 1- and 2-hydroxyphosphonates



Entry	*n*	R^1	R^2	^{31}P NMR[b]			^{1}H NMR[c]			Ref.
				δ^R	δ^S	$\Delta\delta^{RS}$	δ^R	δ^S	$\Delta\delta^{RS}$	
1	0	Ph	*i*-Pr	20.29	20.10	0.19	4.10	4.20	−0.10	95
2	0	Me	*i*-Pr	25.08	24.85	0.23	3.97	4.12	−0.15	95
3	0	C_5H_{11}	Et	26.31	26.10	0.21	—	—	—	95
4	0	(*E*)-$CH_3CH{=}CH$[a]	Me	25.25	25.11	0.14	4.48	4.59	−0.12	95
5	0	*i*-Pr	*i*-Pr	24.38	24.11	0.27	3.65	3.86	−0.21	95
6	0	*t*-Bu	*i*-Pr	24.27	23.87	0.30	3.59	3.84	−0.25	95
7	0	*i*-Bu	*i*-Pr	25.15	24.91	0.24	4.07	4.26	−0.19	95
8	0	Bn[a]	Et	25.11	24.92	0.19	4.17	4.30	0.14	95
9	0	PhC≡C[a]	*i*-Pr	16.73	16.63	0.10	4.98	5.12	0.14	95
10	0	*c*-$C_6H_{11}(CH_2)_2$	Et	26.30	26.11	0.19	—	—	—	95
11	0	*i*-Pr	$CH_2CMe_2CH_2$	22.45	22.22	0.23	—	—	—	95
12	0	*c*-C_3H_5	*i*-Pr	23.23	23.03	0.20	3.18	3.39	−0.21	95
13	0	*c*-C_4H_7	*i*-Pr	24.32	24.03	0.28	3.73	3.92	−0.19	95
14	0	*c*-C_5H_9	*i*-Pr	24.49	24.21	0.28	3.72	3.90	−0.18	95
15	0	*c*-C_6H_{11}	*i*-Pr	24.52	24.20	0.32	3.74	3.92	−0.18	95
16	0	*c*-C_7H_{13}	*i*-Pr	24.72	24.40	0.32	3.81	4.01	−0.19	95
17	0	*c*-C_8H_{15}	Et	26.47	26.18	0.29	—	—	—	95
18	0	2-MeC_6H_4	Me	24.63	24.49	0.14	5.33	5.51	−0.18	95
19	0	2-$MeOC_6H_4$	*i*-Pr	21.29	21.14	0.15	5.73	5.90	−0.17	95
20	0	1-Naphthyl	Me	23.92	23.85	0.07	5.92	6.13	−0.21	95
21	0	2-Thienyl	Et	20.16	19.96	0.20	5.26	5.44	−0.18	95
22	0	3-Thienyl	*i*-Pr	19.98	19.80	0.18	5.06	5.23	−0.17	95
23	0	2-Furyl	*i*-Pr	18.39	18.27	0.12	5.10	5.23	−0.13	95
24	0	3-Pyridyl	*i*-Pr	18.79	18.68	0.11	4.85	5.05	−0.19	95
25	0	2-Pyridyl[a]	*i*-Pr	18.02	17.89	0.13	4.48	4.59	−0.12	95
26	0	N_3CH_2	*i*-Pr	20.99	20.80	0.19	—	—	—	96
27	0	C_5H_{11}	*t*-Bu	—	—	—	—	—	—	97
28	1	Me	Et	28.43	28.37	0.05	—	—	—	95

[a] Racemic hydroxyphosphonate was used.
[b] δ^R—chemical shift of the complex of (*R*)-hydroxyphosphonate and (S_P)-*tert*-butylphenylphosphinothioic acid; δ^S—chemical shift of the complex of (*S*)-hydroxyphosphonate and (S_P)-*tert*-butylphenylphosphinothioic acid; $\Delta\delta^{RS} = \delta^R - \delta^S$.
[c] Chemical shift differences between protons C(1′)H in both diastereomeric complexes.

In the presence of quinine, the ^{31}P NMR signals for the (*S*)-1-hydroxyphosphonates were shifted downfield (0.13–0.33 ppm) compared to the signals of (*R*)-1-hydroxyphosphonates.[98,99] These assignments were confirmed by comparing the values of the specific rotation of several investigated hydroxyphosphonates with the literature data. Quinine was also applied for the studies on the stereochemistry of diethyl 1,2-dihydroxy-2-arylethylphosphonates.[147] It was found that in the presence of quinine the signals of the diethyl *threo*-(*1S,2S*)-1,2-dihydroxy-2-arylethylphosphonates were shifted upfield by about 0.06–0.15 ppm in comparison with those of the *threo*-(*1R,2R*)-enantiomer (Table 12, entries 22–27). However, for the *erythro*-1,2-dihydroxy-2-arylethylphosphonates, the authors were unable to assign the absolute configuration using quinine. Yuan et al.[100] applied the above-mentioned approach to tentatively assign the absolute configuration of diethyl 1,2-dihydroxy-3,3,3-trifluoropropanephosphonates obtained by enzymatic kinetic resolution (Table 12, entry 28).

The large magnitudes of the chemical shift differences for the 1-hydroxyphosphonates in the presence of quinine place this method among valuable tools for the ee determination. Still, the application of quinine as CSA for the absolute configuration assignment of 1-hydroxyphosphonates requires further confirmation.

4. Conclusions

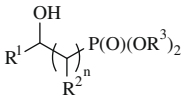
The popularity of NMR as a tool for the absolute configuration assignment comes from the wide availability of the equipment and the simplicity of the method. It obviates the need for often tedious search for crystallization conditions to allow X-ray studies, and provides the configurational answer after a few minutes acquisition.

Among other classes of organic compounds, hydroxy- and aminophosphonates take special place due to the presence of phosphorus atom in the molecule, often next to the stereogenic center. This facilitates the use of the broad band decoupled ^{31}P NMR spectroscopy for simple configuration assignment, making each enantiomer (present in the solution either as a diastereomeric ester, amide, or complex) represented by a single peak. This result is often supported by ^{1}H NMR data.

Most of the literature-reported examples of using NMR method for configuration assignment concern 1- and 2-hydroxyphosphonates, with MTPA or MPA applied as chiral derivatizing agent (CDA). For aminophosphonates, naproxen emerges as a reliable chiral derivatizing agent for configuration assignment. There are many examples for the application of (S_P)-*tert*-butylphenylphosphinothioic acid and quinine as chiral solvating agents (CSAs) for NMR configuration assignment of hydroxyphosphonates. In a few cases quinine was successfully used for dihydroxyphosphonates NMR differentiation. However, the main drawback of applying CSAs for configuration assignment is the difficulty in proposing the conformational model explaining the correlation between the absolute configuration and the chemical shift differences in the NMR spectra.

In some cases NMR configuration assignments were confirmed by other methods such as chemical correlation, X-ray analysis, and specific rotation. There are, however, no reports on systematic

Table 12
Chemical shifts in ^{31}P NMR[h] of quinine and hydroxyphosphonates complexes



Entry	*n*	R^1	R^2	R^3	^{31}P NMR			Ref.
					δ^R	δ^S	$\Delta\delta^{SR}$	
1	0	Et	—	Et	26.66	26.95	0.29	98[a]
2	0	Pr	—	Et	26.93	27.22	0.29	98
3	0	*i*-Bu	—	Et	27.27	27.66	0.39	98[a]
4	0	Bu	—	Et	26.85	27.12	0.27	98[a]
5	0	Allyl-	—	Et	23.91	24.22	0.31	98
6	0	$PhCH(CH_3)$-	—	Et	25.59, 25.34	25.72, 25.50	0.13, 0.16	98
7	0	$PhCH_2CH_2$	—	Et	26.73	26.92	0.19	98
8	0	Ph	—	Me	—	—	—	99[b,c]
9	0	Ph	—	Et	23.07	23.28	0.21	99[b,c], 98[a]
10	0	4-MeC_6H_4	—	Me	—	—	—	99[b,c]
11	0	4-MeC_6H_4	—	Et	—	—	—	99[b,c]
12	0	4-$MeOC_6H_4$	—	Me	—	—	—	99[b,c]
13	0	4-BrC_6H_4	—	Me	—	—	—	99[b,c]
14	0	4-$MeOC_6H_4$	—	Et	23.25	23.35	0.20	99[b,c], 98
15	0	4-ClC_6H_4	—	Et	22.43	22.56	0.13	98
16	0	4-BrC_6H_4	—	Me	—	—	—	99[b,c]
17	0	4-BrC_6H_4	—	Et	—	—	—	99[b,c]
18	0	4-$O_2NC_6H_4$	—	Me	—	—	—	99[b,c]
19	0	4-$O_2NC_6H_4$	—	Et	—	—	—	99[b,c]
20	0	4-$Me_2NC_6H_4$	—	Me	—	—	—	99[b,c]
21	0	2-Furyl	—	Et	21.12	21.45	0.33	98
22	1	Ph	OH	Et	24.12[d]	24.18[e]	0.06	147[f]
23	1	4-MeC_6H_4	OH	Et	24.12[d]	24.25[e]	0.13	147[f]
24	1	2-MeC_6H_4	OH	Et	24.09[d]	24.24[e]	0.15	147[f]
25	1	3-MeC_6H_4	OH	Et	24.11[d]	24.19[e]	0.08	147[f]
26	1	4-BrC_6H_4	OH	Et	23.69[d]	23.80[e]	0.11	147[f]
27	1	4-ClC_6H_4	OH	Et	23.80[d]	23.92[e]	0.12	147[f]
28	1	CF_3	OH	Et	—	—	—	100[c,g]

[a] Absolute configuration confirmed by comparison with the literature values of specific rotations for compounds of the known absolute configuration.[76]
[b] Absolute configuration confirmed by correlation of ^{31}P NMR chemical shifts with the specific rotations values.
[c] No data given.
[d] The chemical shifts of the complex of quinine and *threo*-(1*R*,2*R*)-dihydroksyphosphonate.
[e] The chemical shifts of the complex of quinine and *threo*-(1*S*,2*S*)-dihydroksyphosphonate.
[f] The stereochemistry of *threo*-dihydroxyphosphonates was confirmed by independent dihydroxylation of the corresponding *trans*-vinylphosphonates.[147]
[g] Absolute configuration confirmed by Kazlauskas rule.[118]
[h] δ^R—chemical shift of the complex of (*R*)-hydroxyphosphonate and quinine; δ^S—chemical shift of the complex of (*S*)-hydroxyphosphonate and quinine; $\Delta\delta^{SR} = \delta^S - \delta^R$.

studies on applying CDAs and CSAs for absolute configuration assignments of polyfunctional phosphonates.

In last 15 years there were abundant reports on supporting experimental results with theoretical calculations, defining the conformational model that could explain and predict the absolute configuration based on chemical shift differences. Such systematic studies were performed only for naproxen esters and amides of the corresponding phosphonates. However, of uttermost importance remains broad empirical material, covering a wide range of structurally diverse compounds with known configuration and theoretical calculations should be treated as a good complementary method.

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