JOC Article

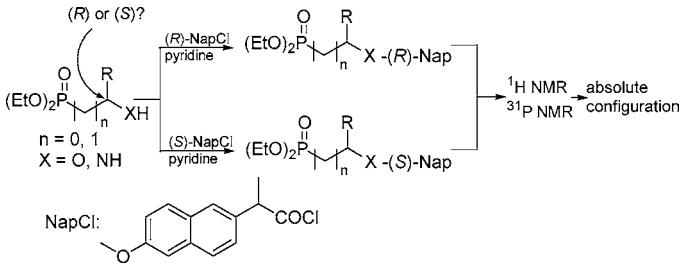
The Assignment of the Absolute Configuration of Diethyl Hydroxy- and Aminophosphonates by ^{1}H and ^{31}P NMR Using Naproxen as a Reliable Chiral Derivatizing Agent

Katarzyna Błażewska,[†] Piotr Paneth,[‡] and Tadeusz Gajda*,[†]

The Faculty of Chemistry, Technical University of Lodz (Politechnika), Żeromskiego St. 116, 90-924 Lodz, Poland

tmgajda@p.lodz.pl

Received October 10, 2006



The assignment of the absolute configuration of hydroxy- and aminophosphonates by their double derivatization with commercially available naproxen is presented. The correlation between the spatial arrangement around the stereogenic carbon center and the signs of the $\Delta\delta^{RS}$ allows determination of the absolute configuration of hydroxy- and aminophosphonates by simple comparison of the ^{1}H and ^{31}P NMR spectra of the (*R*)- and (*S*)-naproxen ester or amide derivatives. Extensive conformational analysis (theoretical calculations, low-temperature experiments) supported by the NMR studies of structurally diverse naproxen esters and amides of hydroxy- and aminophosphonates proved that a simplified model can be successfully used.

Introduction

NMR spectroscopy is one of the most widely used techniques for the assignment of enantiomeric purity and absolute configuration of different classes of compounds.[1−4] Since enantiomers cannot be distinguished in the achiral environment, to make every enantiomer visible in the NMR spectra, there is a need for the introduction of a chiral auxiliary. Besides chiral solvating agents (CSAs)[5−7] and chiral lanthanide shift reagents (CLSRs),[2,8−10] chiral derivatizing agents (CDAs)[1] seem to be the most popular reagents for this purpose. The credible CDA needs to have such structural features as the anisotropic substituent and the functional group providing linkage to the substrate. Moreover, the existence of the conformational preference must be maintained in the two diastereomeric derivatives, irrespective of the configuration and structure of the derivatized compound.

According to the methodology set by Mosher et al.,[3] Trost et al.,[4] and Riguera et al.,[1] application of CDA requires derivatization of the substrate of unknown configuration with two, (*R*) and (*S*), enantiomers of the derivatizing agent (double derivatization).[11] Subsequently, spectra of both diastereomeric derivatives must be recorded separately. Then, the configuration (of the investigated compound) is assigned[1] by subtraction of their chemical shifts δ, expressed by the $\Delta\delta^{RS} = \delta^{R} - \delta^{S}$ (the

[†] Institute of Organic Chemistry.
[‡] Institute of Applied Radiation Chemistry.

(1) (a) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17. (b) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915. (c) Lallana, E.; Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Org. Lett.* **2006**, *8*, 4449.

(2) Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; John Wiley: Chichester, U.K. 2001; p 16.

(3) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(4) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370.

(5) Weisman, G. R. W. In *Asymmetric Synthesis;* Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, p 153.

(6) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263.

(7) Pazos, Y.; Leiro, V.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2004**, *15*, 1825.

(8) Sullivan, G. R. *Top. Stereochem.* **1979**, *10*, 287.

(9) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.

(10) Omata, K.; Aoyagi, S.; Kabuto, K. *Tetrahedron: Asymmetry* **2004**, *15*, 2351.

(11) In the case of single derivatization, which is not the subject of this paper, the substrate needs to be derivatized with one enantiomer of CDA.

10.1021/jo062097z CCC: $37.00
Published on Web 01/10/2007

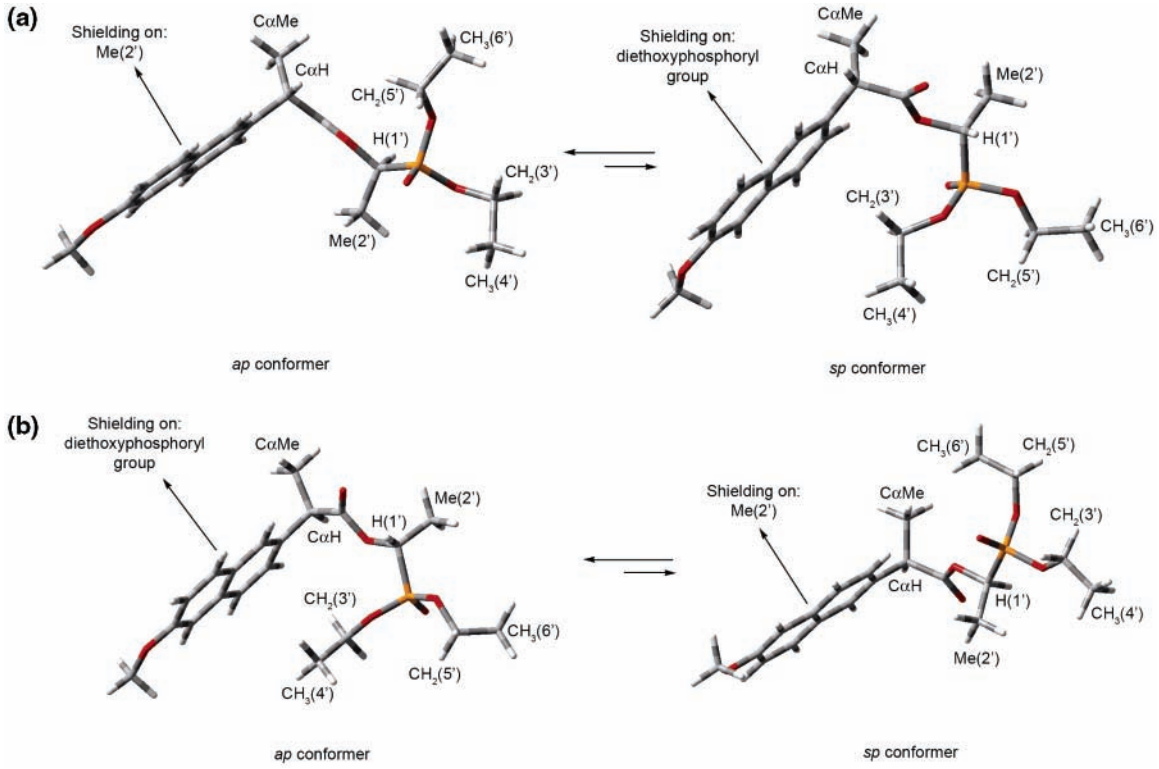


FIGURE 1. Geometries for the antiperiplanar (*ap*) and synperiplanar (*sp*) conformations of the (a) (*S*)- and (b) (*R*)-naproxen esters of diethyl (*S*)-1-hydroxyethylphosphonate.

TABLE 1. HF and B3LYP Relative Energies[a] (in kcal/mol), Relative Populations[b] Calculated for the Lowest-Energy Conformers of the Esters of (*R*)- and (*S*)-Naproxen and Diethyl (*S*)-1-Hydroxyethylphosphonate (Data for the Predominant *ap* Conformer are Given in Bold)

		ΔE[a]		
NapOH	conformer	HF[c] (%)[b]	B3LYP//HF[d]	SCRF1[e]
(*S*)	***ap***	**0.54 (84.6)**	**0**	**0.51**
(*S*)	*sp*	0.85 (15.4)	0.42	1.06
(R)	**ap**	**0 (90.80)**	**0.04**	**0**
(*R*)	*sp*	1.99 (9.20)	1.66	1.58

[a] All of the calculations were performed with the 6-31G(d) basis set. [b] Values in parentheses were calculated from the Boltzmann distribution at 298.15 K. [c] Optimization at the HF level. [d] Single-point calculations at the HF-optimized geometries. [e] C-PCM/HF/6-31G(d).

difference between the chemical shifts representing the groups connected with the stereogenic center in the investigated compound in the (*R*)-CDA derivative minus that in the (*S*)-CDA derivative).

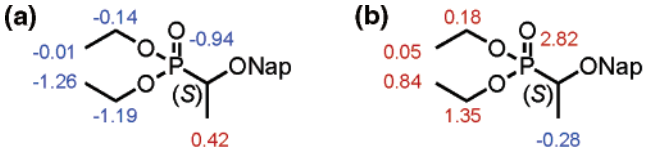


FIGURE 2. Calculated shielding increments for the principal conformers (a) *ap* and (b) *sp* of the (*R*)- and (*S*)-Nap esters of diethyl (*S*)-1-hydroxyethylphosphonate.

Amino-[12] and hydroxyphosphonates[13,14] constitute a class of amino acid and hydroxy acid mimics in which a planar carboxylic group is replaced by a tetrahedral phosphonic moiety. For the close resemblance to the transition state of ester and amide hydrolysis, inhibitors of such enzymes as human rennin,[15] HIV protease and polymerase,[16] leucine aminopeptidase,[17] and serine proteases[18] are known among the hydroxy- and aminophosphonates. They were also exploited as haptens for catalytic antibody research.[19] In addition, phosphonates display a broad spectrum of activities as herbicides,[20] antibiotics,[21] antiviral[22] and anticancer agents, and neuromodulators.[12]

(12) (a) Kafarski, P.; Mastalerz, P. *Aminophosphonates: Natural Occurence, Biochemistry and Biological Properties*; Beiträge zur Wirkstoffforschung: Berlin, Germany, 1984; p 21. (b) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193. (c) Seto, H.; Kazuyama, T. *Nat. Prod. Rep.* **1999**, *16*, 589. (d) *Aminophosphonic and Aminophosphinic Acids Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley: Chichester, U.K., 2000. (e) Moonen, K.; Laureyn, I.; Stevens, Ch. V. *Chem. Rev.* **2004**, *104*, 6177. (f) Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899. (g) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Soloshonok, V. A., Eds; John Wiley: Hoboken, NJ, 2005.

(13) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **2005**, *16*, 3295.

(14) (a) *The Role of Phosphonates in Living Systems*; Hildebrand, R. L., Ed.; CRC Press: Boca Raton, FL, 1983. (b) Engel, R. *Chem. Rev.* **1977**, *77*, 349. (c) Wiemer, D. F. *Tetrahedron* **1997**, *53*, 16609. (d) Gröger, H.; Hammer, B. *Chem.—Eur. J.* **2000**, *6*, 943.

(15) Tao, M.; Bihovsky, R.; Wells, G. J.; Mallamo, J. P. *J. Med. Chem.* **1998**, *41*, 3912.

(16) (a) Stowasser, B.; Budt, K.-H.; Li, J.-Q.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625. (b) Ikeda, J. A.; Ashley, J. A.; Wirsching, P.; Janda, K. D. *J. Am. Chem. Soc.* **1992**, *114*, 7604.

(17) Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603.

(18) Oleksyszyn, J.; Powers, J. C. *Methods in Enzymology*; Academic Press: New York, 1994; Vol. 244, p 423.

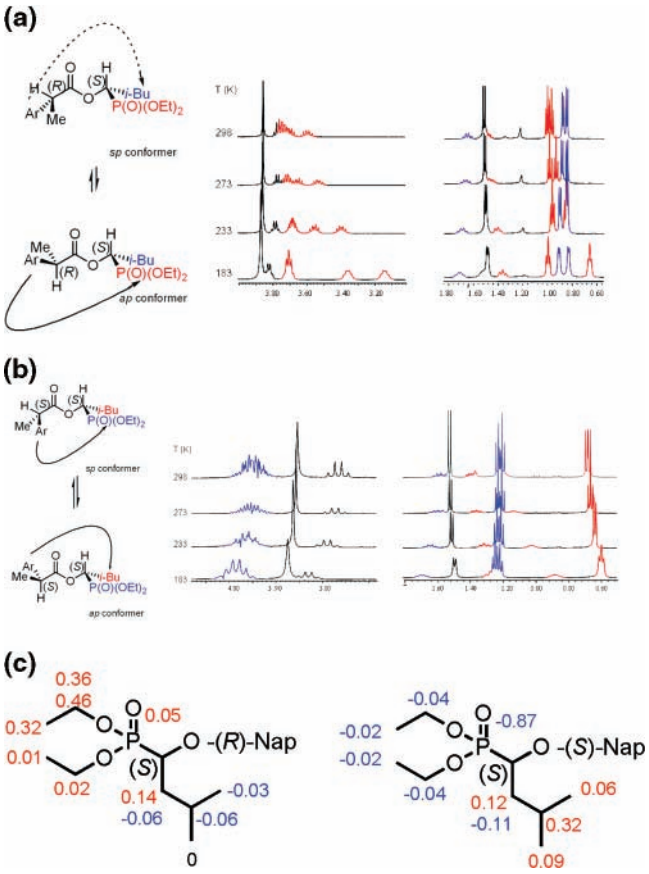


FIGURE 3. Evolution of the ^{1}H NMR spectra of the (a) (*R*)- and (b) (*S*)-naproxen esters of diethyl (*S*)-1-hydroxy-3-methylbutylphosphonate with temperature. (c) Values of the $\Delta\delta^{T_1T_2}$ (T_1 = 298 K, T_2 = 183 K) for both diastereomers of the naproxen esters of diethyl (*S*)-1-hydroxy-3-methylbutylphosphonate (data for positive values of $\Delta\delta^{T_1T_2}$ are given in red, whereas negative values of $\Delta\delta^{T_1T_2}$ are given in blue).

There is, therefore, a demand for the asymmetric synthesis of hydroxy- and aminophosphonates, which has to be accompanied by the methods of enantiomeric purity (ee) determination and absolute configuration assignment. The most widely used CDAs for 1-hydroxyphosphonates' configuration

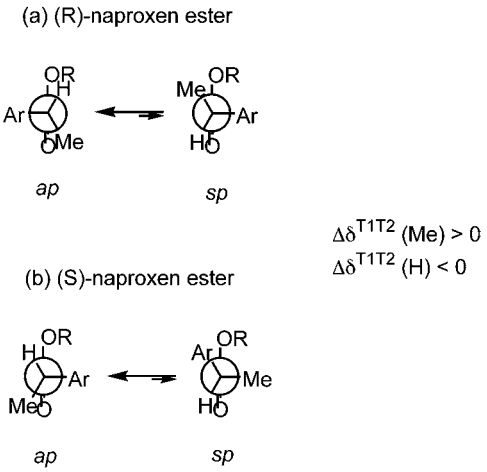


FIGURE 4. Effect of the shielding cone of the carbonyl group on the C_α−H and C_α−Me groups of the (a) (*R*)-naproxen ester and the (b) (*S*)-naproxen ester of diethyl (*S*)-1-hydroxy-3-methylbutylphosphonate observed with the decrease of temperature.

determination are methoxytrifluoromethylphenylacetic acid (MTPA)[23] and methoxyphenylacetic acid (MPA).[24] To the best of our knowledge, the published correlations between $\Delta\delta^{RS}$ of the MPA or MTPA esters of the hydroxyphosphonates and their configuration are empirical only, and no conformational studies have been carried out to confirm those models. Furthermore, there are scarcely any examples of applying NMR methods for the determination of the absolute configuration of the aminophosphonates.[25,26] Hence, there is a demand for the reagents which could be used as CDAs for the absolute configuration assignment of this class of compounds.

Therefore, encouraged by our previous studies on the application of (*S*)-naproxen and (*S*)-ibuprofen, nonsteroidal anti-inflammatory drugs (NSAID), commercially available in the

(19) (a) Lerner, R. A. *Acc. Chem. Res.* **1993**, *26*, 391. (b) Hirschmann, R.; Smith, A. B., III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234. (c) Smithrud, D. B.; Benkovic, P. A.; Benkovic, S. J.; Taylor, C. M.; Yager, K. M.; Witherington, J.; Phillpis, B. W.; Sprengler, P. A.; Smith, A. B., III; Hirschmann, R. *J. Am. Chem. Soc.* **1997**, *119*, 278.

(20) Diddens, H.; Zähner, H.; Kraas, E.; Göhring, W.; Jung, W. G. *Eur. J. Biochem.* **1976**, *66*, 11.

(21) (a) Glamowski, E. J.; Gal, G.; Purick, R.; Davidson, A. J.; Sletzinger, M. *J. Org. Chem.* **1970**, *35*, 3510. (b) Giordano, C.; Castaldi, G. *J. Org. Chem.* **1989**, *54*, 1470.

(22) Guan, H.-P.; Qiu, Y.-L.; Ksebati, M. B.; Kern, E. R.; Zemlicka, J. *Tetrahedron* **2002**, *58*, 6047.

(23) (a) Hammerschmidt, F.; Li, Y.-F. *Tetrahedron* **1994**, *50*, 10253. (b) Hammerschmidt, F.; Wuggenig, F. *Tetrahedron: Asymmetry* **1999**, *10*, 1709. (c) Drescher, M.; Li, Y.-F.; Hammerschmidt, F. *Tetrahedron* **1995**, *51*, 4933. (d) Drescher, M.; Hammerschmidt, F.; Kählig, H. *Synthesis* **1995**, 1267. (e) Eidenhammer, G.; Hammerschmidt, F. *Synthesis* **1996**, 748. (f) Woschek, A.; Lindner, W.; Hammerschmidt, F. *Adv. Synth. Catal.* **2003**, *345*, 1287. (g) Gajda, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1965. (h) Zhang, Y.; Li, J.; Yuan, Ch. *Tetrahedron* **2003**, *59*, 473. (i) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931. (j) Kitamura, M.; Tokunaga, M.; Pham, T.; Lubell, W. D.; Noyori, R. *Tetrahedron Lett.* **1995**, *36*, 5769. (k) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1527. (l) Meier, C.; Laux, W. H. G.; Bats, J. W. *Liebigs Ann. Chem.* **1995**, 1963.

(24) (a) Kozlowski, J. K.; Rath, N. P.; Spilling, Ch. D. *Tetrahedron* **1995**, *51*, 6385. (b) Cermak, D. M.; Du, Y.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 388. (c) Chen, X.; Wiemer, A. J.; Hohl, R. J.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 9331. (d) Jung, K.-Y.; Hohl, R. J.; Wiemer, A. J.; Wiemer, D. F. *Bioorg. Med. Chem.* **2000**, *8*, 2501. (e) Skropeta, D.; Schmidt, R. R. *Tetrahedron: Asymmetry* **2003**, *14*, 265. (f) Wróblewski, A. E.; Piotrowska, D. G. *Tetrahedron: Asymmetry* **1999**, *10*, 2037. (g) Wróblewski, A. E.; Piotrowska, D. G. *Tetrahedron: Asymmetry* **2000**, *11*, 2615. (h) Wróblewski, A. E.; Balcerzak, K. B. *Tetrahedron: Asymmetry* **2001**, *12*, 427. (i) Drąg, M.; Latajka, R.; Gumienna-Kontecka, E.; Kozłowski, H.; Kafarski, P. *Tetrahedron: Asymmetry* **2003**, *14*, 1837. (j) Ordóñez, M.; Gonzáles-Morales, A.; Ruíz, C.; De la Cruz-Cordero, R.; Fernández-Zertuche, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1775. (k) Gonzáles-Morales, A.; Díaz-Coutiño, D.; Fernández-Zertuche, M.; García-Barradas, O.; Ordóñez, M. *Tetrahedron: Asymmetry* **2004**, *15*, 457. (l) Ordóñez, M.; Gonzáles-Morales, A.; Salazar-Fernández, H. *Tetrahedron: Asymmetry* **2004**, *15*, 2719.

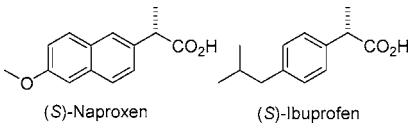
(25) Fadel, A.; Tesson, N. *Eur. J. Org. Chem.* **2000**, 2153.

(26) Skropeta, D.; Schwörer, R.; Schmidt, R. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3351.

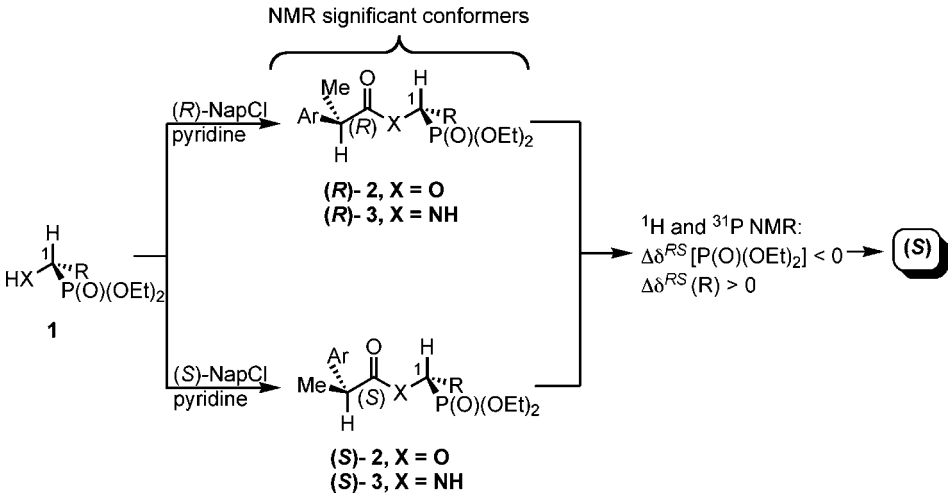
(27) Hulst, R.; Kellog, R. M.; Feringa, B. L. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 115.

(28) Błażewska, K.; Gajda, T. *Tetrahedron: Asymmetry* **2002**, *13*, 671.

(29) Although (*S*)-naproxen as well as (*S*)-ibuprofen have structural features required from CDA (carboxyl group and anisotropic aromatic ring), ibuprofen is less convenient due to the presence of an isobutyl group which can blur the diagnostic area of the ^{1}H NMR spectra and hamper the identification of the appropriate signals.



SCHEME 1. Double Derivatization of 1-Hydroxy and 1-Aminophosphonates by (*R*)- and (*S*)-Naproxen Chlorides



optically pure form, for the determination of the ee of hydroxy- and aminophosphonates,[28] we widened the scope of implementation of naproxen (NapOH) for the absolute configuration assignment of this class of compounds using double derivatization.[29] As has been already mentioned, for double derivatization, both enantiomers of CDA are required. (*S*)-Naproxen is cheap as a popular NSAID. (*R*)-Naproxen is also commercially available, but it can also be easily obtained with 60% enantiomeric purity by fractional crystallization of racemic naproxen with cinchonidine.[30]

In this work, we will demonstrate that a correlation between the absolute configuration of hydroxy- and aminophosphonates and the ^{1}H and ^{31}P NMR spectra of their diastereomeric esters and amides of naproxen exists. To provide detailed explanation and rationalization of the observed NMR effects, theoretical (HF and DFT) calculations and NMR studies were carried out. For the clarity of the presentation, we discussed the results concerning assignment of configuration of hydroxy- and aminophosphonates separately.

Results and Discussion

Naproxen Esters of the Hydroxyphosphonates. Our study on the conformational preference of naproxen esters began with the theoretical calculations on (*S*)- and (*R*)-naproxen esters of model diethyl (*S*)-1-hydroxyethylphosphonate. According to the theoretical considerations of Riguera et al.,[31,32] the main conformers were generated by the rotation around the $C_\alpha-C(O)$ and $C_\alpha-Ph$ bonds in the naproxen moiety.

The theoretical calculations performed at the Hartree−Fock (HF) (optimization of the geometry) and density functional theory (DFT) (calculation of energy) levels of theory proved that, in the gas phase as well as in the chloroform solution for the naproxen esters of the hydroxyphosphonates, the main rotational process involves the rotation around the $C_\alpha-CO$ bond, giving the *ap* conformer when the $C_\alpha-H$ and C═O bonds are in the antiperiplanar disposition ($H-C_\alpha-C{=}O$ 143.5−152.6°) and the *sp* conformer when these two bonds are in the synperiplanar disposition ($H-C_\alpha-C{=}O$ 9.4−15.0°). In both low-energy conformers, the naphthyl ring is coplanar with the $C_\alpha-H$ bond.

Irrespective of the method used, the *ap* conformer was proved to be more stable than the *sp* conformer. The results of the calculations are presented in Table 1 and illustrated by Figure 1.

According to the model studies, in the ester of (*S*)-naproxen and (*S*)-hydroxyphosphonate, the R substituent (R = Me) is shielded by the naphthyl ring in the more stable *ap* conformer, whereas the diethoxyphosphoryl group is shielded in the less stable *sp* conformer. The opposite is observed for the (*R*)-naproxen esters of the (*S*)-hydroxyphosphonates, where the diethoxyphosphoryl group is shielded by the naphthyl ring in the more stable *ap* conformer, while the R substituent is influenced by the aryl group in the *sp* conformer.

In order to confirm the validity of the evaluated model, the shielding effect calculations were carried out. When $\Delta\delta^{RS}$ values were calculated for the *ap* and *sp* conformers (from the respective δ^R and δ^S chemical shifts), the resulting signs of $\Delta\delta^{RS}$ were consistent with the predicted ones only in the case of the *ap* conformers (Figure 2a). A distribution of signs of $\Delta\delta^{RS}$, inconsistent with calculation, has been obtained for the *sp* conformers (Figure 2b).

The results of the theoretical studies on model esters of naproxen and hydroxyphosphonate were confirmed by the low-temperature experiments. The NMR spectra of both diastereomeric esters of (*R*)- and (*S*)-naproxen and diethyl (*S*)-1-hydroxy-3-methylbutylphosphonate were taken in the range of 183−298 K.

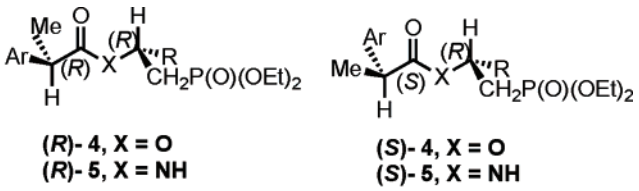


FIGURE 5. The conformational models for the (*R*)- and (*S*)-naproxen esters and amides of the 2-hydroxy- and 2-aminoalkylphosphonates.

(30) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203.
(31) Ferreiro, M. J.; Latypov, S. K.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2000**, *65*, 2658.
(32) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 504.

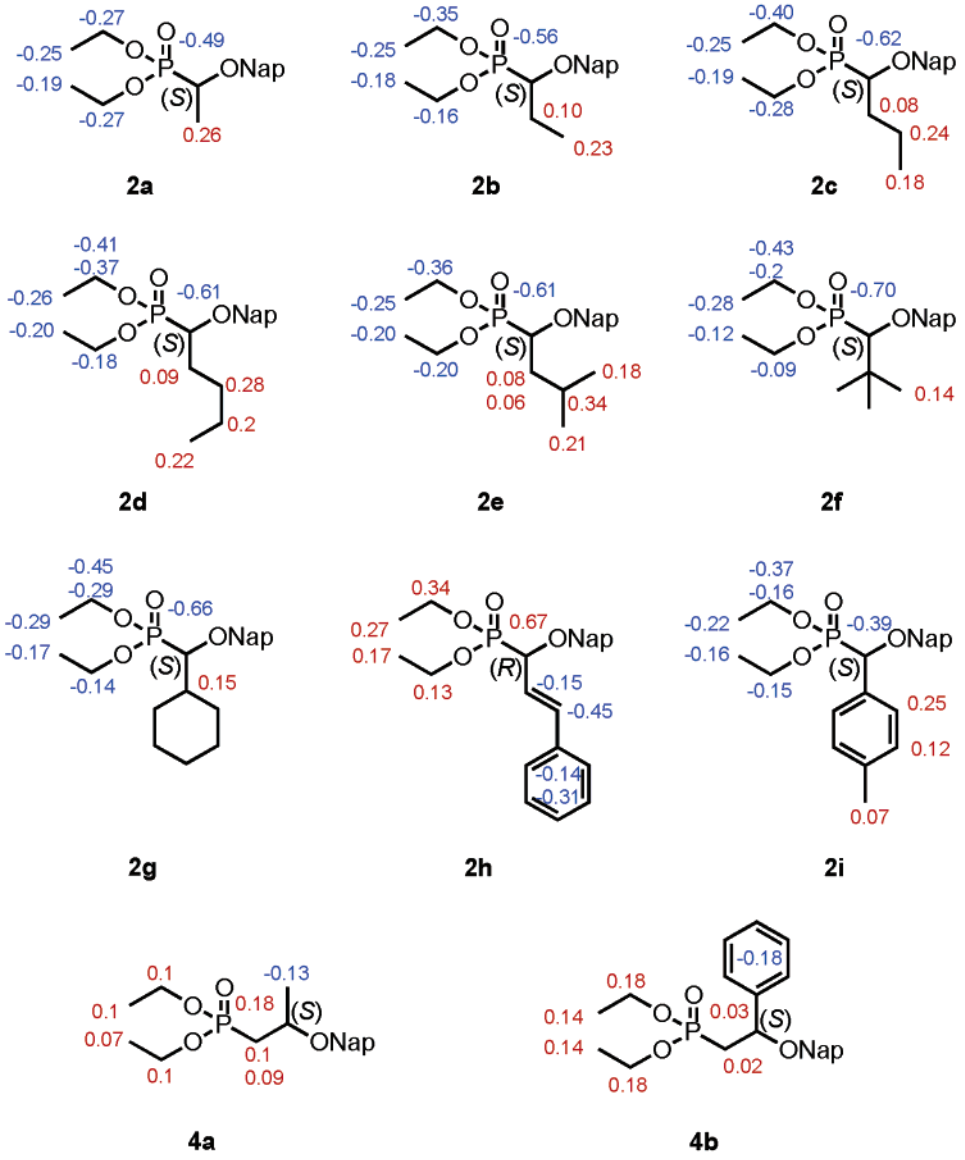


FIGURE 6. $\Delta\delta^{RS}$ values for the (*R*)- and (*S*)-naproxen esters of the diethyl 1- and 2-hydroxyphosphonates.

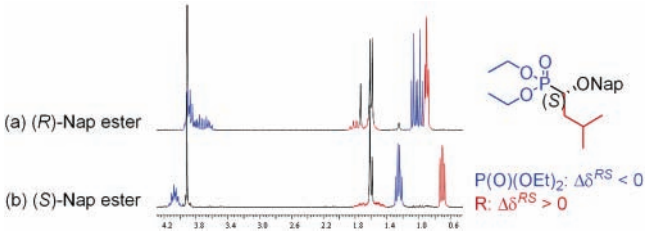


FIGURE 7. Partial ^{1}H NMR spectra of the (*R*)- and (*S*)-naproxen esters of diethyl (*S*)-1-hydroxy-3-methylbutylphosphonate.

Thus, according to the theoretical considerations, reducing the temperature of the NMR probe should lead to an increase of the population of the most stable *ap* conformer, whereas that of the less stable *sp* conformer should be decreased. The average ^{1}H and ^{31}P NMR spectra should reflect these changes (Figure 3).

The NMR spectra taken at different temperatures show that, for the (*R*)-naproxen ester of (*S*)-1-hydroxyphosphonate at a lower temperature, the signals of the diethoxyphosphoryl group are shifted upfield, while the peaks of the isobutyl group are moved downfield (Figure 3a). The opposite was observed in

TABLE 2. HF and B3LYP Relative Energies[a] (in kcal/mol), Relative Populations[b] Calculated for the Lowest-Energy Conformers of Amides of (*R*)- and (*S*)-Nap and Diethyl (*R*)-1-Aminoethylphosphonate (Data for the Predominant *ap* Conformer are Given in Bold)

		ΔE^a		
NapOH	conformer	HF[c] (%)[b]	B3LYP//HF[d]	SCRF1[e]
(*S*)	***ap***	**0.12 (98.32)**	**0**	**0.17**
(*S*)	*sp*	1.30 (1.68)	6.66	3.16
(*R*)	***ap***	**0 (98.79)**	**0.21**	**0**
(*R*)	*sp*	1.16 (1.20)	6.79	3.47

[a] All of the calculations were performed with the 6-31G(d) basis set. [b] Values in parentheses were calculated from the Boltzmann distribution at 298.15 K. [c] Optimization at the HF level. [d] Single-point calculations at the HF-optimized geometries. [e] C-PCM/HF/6-31G(d).

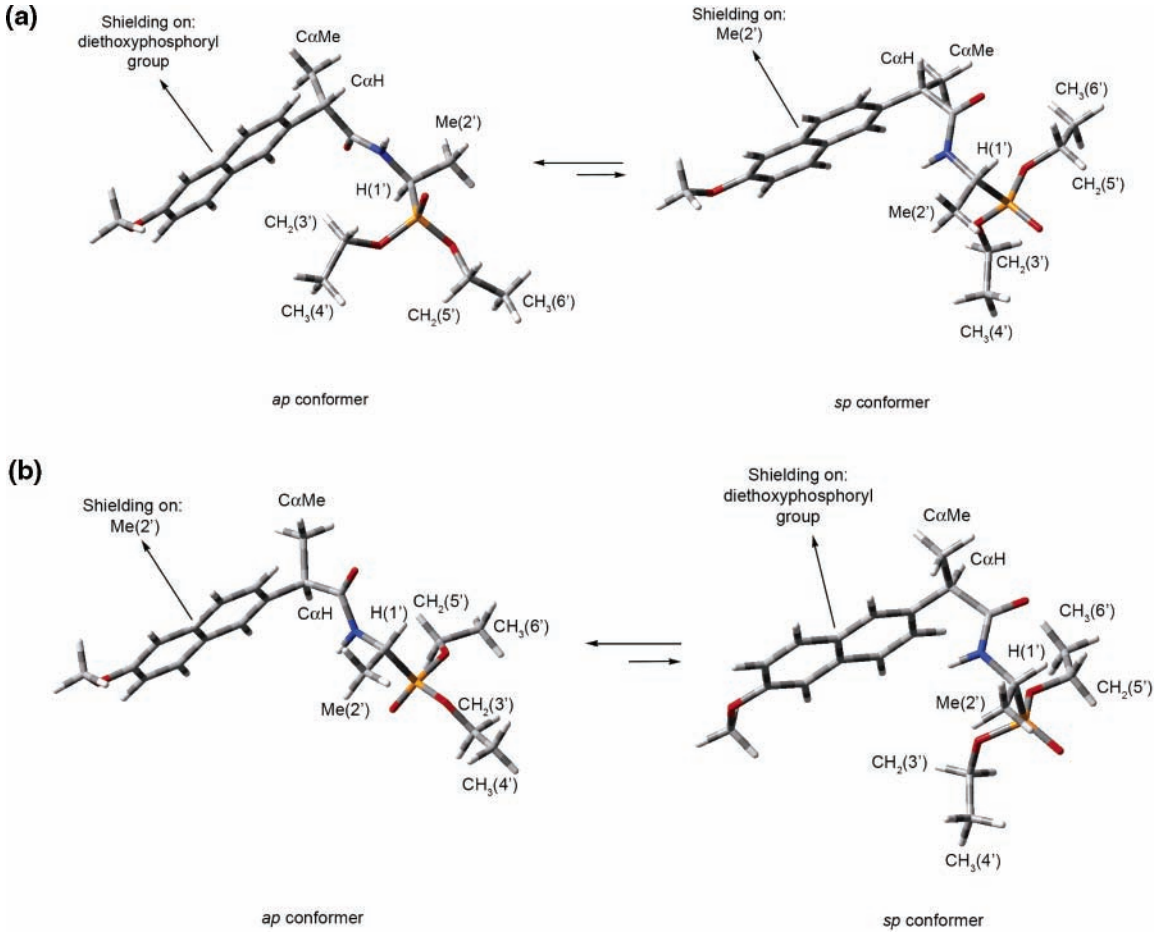


FIGURE 8. Geometries for the antiperiplanar and synperiplanar conformations of the (a) (*S*)- and (b) (*R*)-naproxen amides of (*R*)-1-aminoethylphosphonate diethyl ester.

FIGURE 9. Calculated shielding increments for the principal (a) *ap* and (b) *sp* conformers of the (*R*)- and (*S*)-naproxen amides of diethyl (*R*)-1-aminoethylphosphonate.

the case of the (*S*)-naproxen ester of (*S*)-1-hydroxyphosphonate, where the signals of the diethoxyphosphoryl group are shifted downfield, whereas protons of the isobutyl group are moved upfield (Figure 3b). Therefore, the differences in chemical shifts measured as $\Delta\delta^{T_1T_2}$ (the chemical shift at higher temperature T_1 minus that at the lower temperature T_2) for the diethoxyphosphoryl moiety are positive for (*R*)-naproxen esters and negative for (*S*)-naproxen esters. The opposite is valid for the protons of the R substituent (R = *i*-Bu), where $\Delta\delta^{T_1T_2}$ values are negative for the esters of (*R*)-naproxen and positive for the esters of (*S*)-naproxen.[33]

Additionally, we found that, irrespective of the configuration, lowering the temperature shifted the signal corresponding to the C_α−H of the naproxen residue downfield ($\Delta\delta^{T_1T_2} < 0$), contrary to the methyl group, C_α−Me, of the naproxen part, which is moved upfield ($\Delta\delta^{T_1T_2} > 0$). The explanation of this phenomenon can be found in the equilibrium of the conformers, where the methyl group moves inside the shielding cone of the carbonyl group and the methine proton is shifted outside of the shielding cone of the carbonyl group, as shown in Figure 4.

We assumed that, from a practical point of view, in order to assign the absolute configuration of the hydroxyphosphonates, only the most representative *ap* conformer and its shielding effects could be considered.[1] By using such a simplified model, the absolute configuration of the hydroxyphosphonates can be assigned from the signs (plus or minus) of the chemical shift differences, $\Delta\delta^{RS}$.

Experimental verification of the above assumptions was performed by the NMR analysis of the naproxen esters of structurally diverse diethyl 1- as well as the 2-hydroxyphosphonates of known configuration. Hydroxyphosphonates were doubly derivatized, according to our previously described procedure,[28] with (*R*)- and (*S*)-naproxen chlorides in the presence of pyridine. Next, ^{1}H and ^{31}P NMR spectra of both diastereomers were analyzed, assuming the preference of the *ap* conformation (Scheme 1).

As it is shown in Scheme 1 for the esters of (*R*)-naproxen and the diethyl (*S*)-1-hydroxyphosphonates, **(*R*)-2**, the diethoxyphosphoryl group is more shielded by the aryl ring than in the **(*S*)-2** ester ($\Delta\delta^{RS}$[P(O)(OEt)$_2$] < 0), whereas the R substituent is more shielded in the (*S*)-naproxen in comparison with the **(*R*)-2** ester ($\Delta\delta^{RS}$(R) > 0). The opposite is valid for the esters

(33) In both of the diastereomers, the signs of the $\Delta\delta^{RS}$ of two methylene protons are opposite to each other.

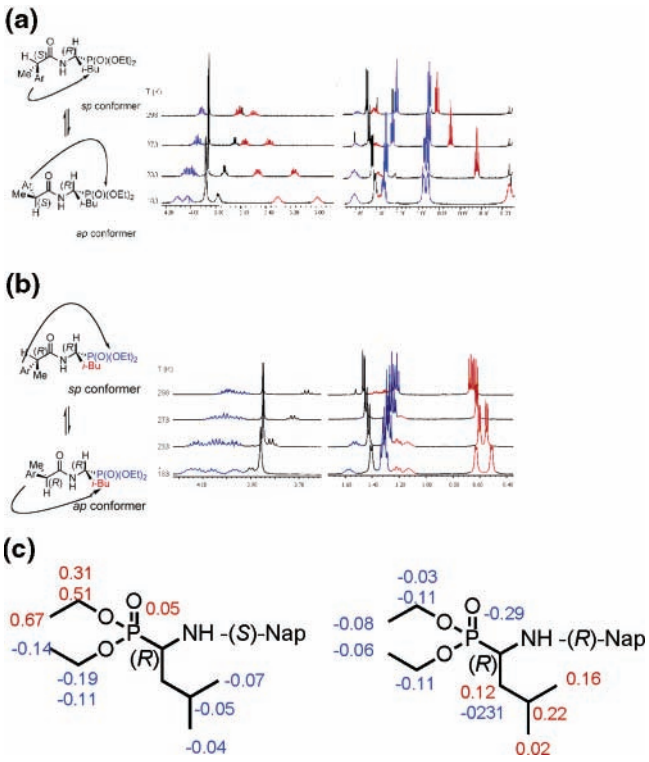


FIGURE 10. Evolution of the ^{1}H NMR spectra of the (a) (*R*)- and (b) (*S*)-naproxen amides of diethyl (*R*)-1-amino-3-methylbutylphosphonate with decreasing temperature. (c) Values of the $\Delta\delta^{T_1T_2}$ (T_1 = 298 K, T_2 = 183 K) for both diastereomers of the naproxen amides of diethyl (*R*)-1-amino-3-methylbutylphosphonate. Data for positive values of $\Delta\delta^{T_1T_2}$ are given in red, whereas negative values of $\Delta\delta^{T_1T_2}$ are given in blue.

of the (*R*)-1-hydroxyphosphonates (not shown in Scheme 1). The diethoxyphosphoryl group is more shielded in the (*S*)-naproxen derivatives than in the **(*R*)-2** esters ($\Delta\delta^{RS}$[P(O)(OEt)$_2$] > 0), while the reverse is true for the R substituent that is more shielded in the **(*R*)-2** than in the **(*S*)-2** esters ($\Delta\delta^{RS}$(R) < 0).

It should be stressed here that the same model is valid for the 2-hydroxyalkylphosphonates. The opposite sign pattern of $\Delta\delta^{RS}$ (in comparison with the 1-hydroxyalkylphosphonates) stems from the change of the substituent priority sequence at the carbon stereogenic center in the 2-hydroxyalkylphosphonates (Figure 5).

Therefore, for the (*R*)-naproxen esters of the (*R*)-2-hydroxyphosphonates, **(*R*)-4**, the diethoxyphosphorylmethyl group is shielded ($\Delta\delta^{RS}$ < 0), while in the **(*S*)-4** esters, it is the R group which is under the influence of the naphthyl ring ($\Delta\delta^{RS}$ > 0) (Figure 5). However, for the esters of the (*S*)-2-hydroxyphosphonates and (*R*)-naproxen, the R group is shielded ($\Delta\delta^{RS}$ < 0), and in the (*S*)-naproxen esters, the diethoxyphosphoryl group is shielded by the naphthyl ring ($\Delta\delta^{RS}$ > 0).

Several hydroxyphosphonates of known absolute configuration have been used to demonstrate the general applicability of this phenomenon. In all of the examples examined, the distribution of the signs of the $\Delta\delta^{RS}$ corresponds perfectly with the model discussed above (Figure 6).

This detailed analysis proved that every proton and phosphorus of the diethoxyphosphoryl (in the case of the 1-hydroxyphosphonates) or the diethoxyphosphorylmethyl (for the 2-hydroxyphosphonates) group are characterized by the same sign of the $\Delta\delta^{RS}$, and simultaneously, it is opposite to the signs of $\Delta\delta^{RS}$ determined for the signals of the second substituent R connected with the carbon stereogenic center. An example of the ^{1}H NMR spectra of two diastereomeric (*R*)- and (*S*)-naproxen esters of diethyl (*S*)-1-hydroxy-3-methylbutylphosphonate is presented in Figure 7.

The methodology presented here can be additionally simplified to the sole usage of the ^{31}P NMR since, for the diethoxyphosphoryl group in ^{1}H as well as in ^{31}P NMR, the signs of $\Delta\delta^{RS}$ are the same. In the case of the naproxen esters of the (*S*)-1-hydroxyphosphonates, the chemical shift difference, $\Delta\delta^{RS}$, in the ^{31}P NMR is negative, whereas the positive sign of $\Delta\delta^{RS}$ confirms the (*R*) configuration of the carbon stereogenic center. The reverse is true for the diethyl (*S*)-2-hydroxypropylphosphonate. For the reasons given earlier, the $\Delta\delta^{RS}$ in the ^{31}P NMR of the naproxen esters of the (*S*)-2-hydroxyphosphonate is positive, whereas for the diethyl (*R*)-2-hydroxyphosphonate, it should be less than zero. Such simplified methodology for assignment of absolute configuration of the hydroxyphosphonates was also proposed for MTPA[23a−d,g] and MPA[24a,e,h] esters of the hydroxyphosphonates.

Naproxen Amides of the Aminophosphonates. In the second part of our studies, we directed our efforts to the absolute configuration assignment of the aminophosphonates. As for the hydroxyphosphonates, the theoretical studies on the conformational preference of (*S*)- and (*R*)-naproxen amides of the model diethyl (*R*)-1-aminoethylphosphonate were done. The main conformers were generated by the rotation of the naproxen moiety around the bonds C$_\alpha$−C(O), C$_\alpha$−Ph, and C(O)NH, analogously to the amides of MTPA and MPA.[34−36] The theoretical calculations performed as before on the Hartree−Fock (optimization of the geometry) and DFT (calculation of energy) levels of theory proved that, in the gas phase as well as in the chloroform solution, naproxen amides of the aminophosphonates consist of two main conformers in equilibrium. The main process involves the rotation around the C$_\alpha$−CO bond, giving the *ap* conformer when the C$_\alpha$−H and C═O bonds are in the antiperiplanar disposition (H−C$_\alpha$−C═O 146.1−162.5°) and the *sp* conformer when these two bonds are in the synperiplanar disposition (H−C$_\alpha$−C═O 32.2−37.4°). In the main conformers, the naphthyl ring is coplanar or under 45° to the C$_\alpha$−H bond, and the (*Z*) arrangement of the C(O)−NH bond is predominant.

Also here, analogously to the results obtained for the esters of naproxen, the *ap* conformer was proved to be predominant, irrespective of the method used. The results of the calculations are presented in Table 2 and illustrated by Figure 8.According to presented results, in the predominant *ap* conformer, the R substituent is shielded by the naphthyl ring in the (*R*)-naproxen amide of (*R*)-aminophosphonate **(*R*)-3** ($\Delta\delta^{RS}$(R) < 0), whereas the diethoxyphosphoryl group is under the influence of the aryl ring in the amide of the (*S*)-naproxen of (*R*)-aminophosphonate **(*S*)-3** ($\Delta\delta^{RS}$[P(O)(OEt)$_2$] > 0).

In order to confirm the validity of the evaluated model, the shielding effect calculations were carried out. When $\Delta\delta^{RS}$ values were calculated for the *ap* and *sp* conformers (from the respective calculated δ^R and δ^S chemical shifts), the resulting signs of $\Delta\delta^{RS}$ were consistent with the predicted ones only in the case of the *ap* conformers (Figure 9a). Nonhomogeneous

(34) Seco, J. M.; Latypov, S. K.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1997**, *62*, 7569.
(35) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 1538.
(36) Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 4669.

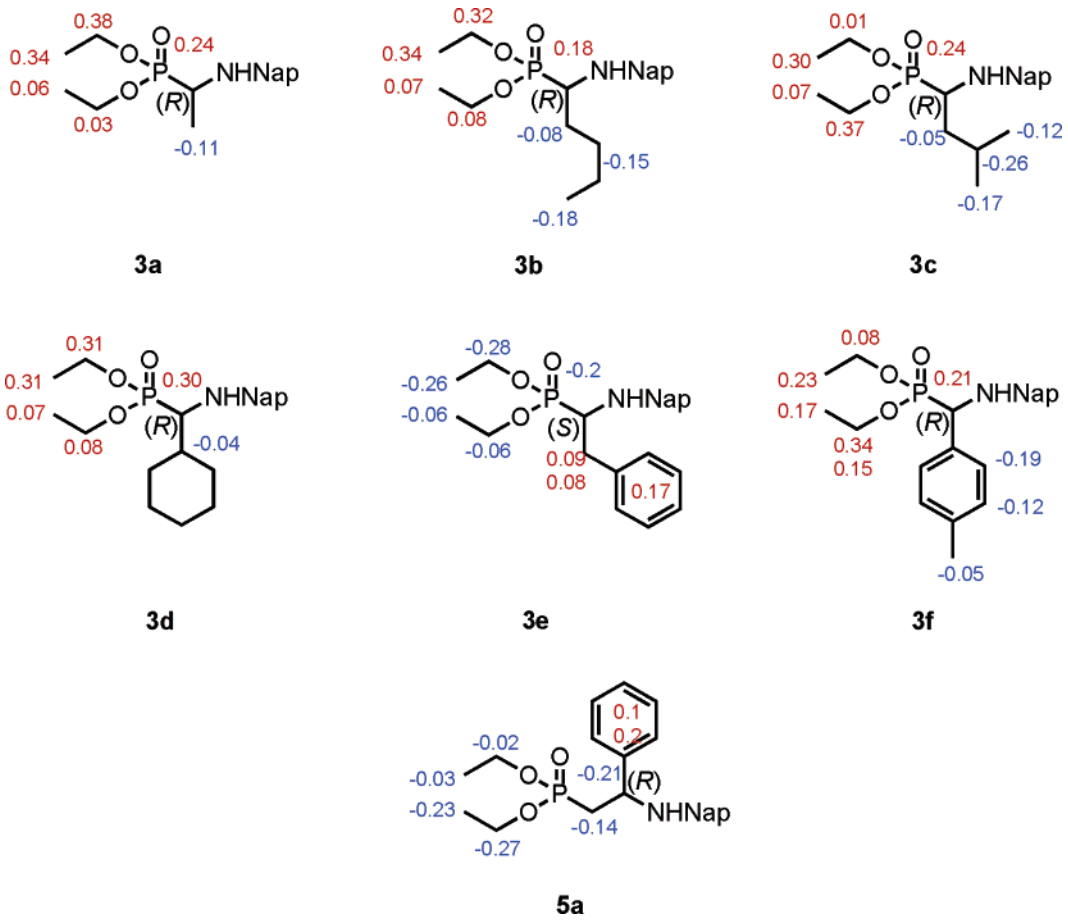


FIGURE 11. $\Delta\delta^{RS}$ values for the (*R*)- and (*S*)-naproxen amides of the diethyl 1- and 2-aminophosphonates.

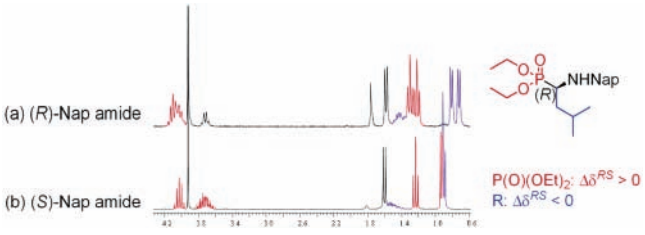


FIGURE 12. Partial ^{1}H NMR spectra of the (*R*)- and (*S*)-naproxen esters of diethyl (*R*)-1-amino-3-methylbutylphosphonate (positive values of $\Delta\delta^{RS}$ are given in red, and negative values are in blue).

distributions of signs of $\Delta\delta^{RS}$ have been obtained for the *sp* conformers (Figure 9b).

Again, the results of the theoretical studies were confirmed by the low-temperature NMR experiments. The spectra of model diastereomeric amides of (*R*)- and (*S*)-naproxen and diethyl (*R*)-1-amino-3-methylbutylphosphonate were taken in the range of 183−298 K.

The observed trend corresponds well with the proposed model (Figure 10a). In the (*S*)-naproxen amide of diethyl (*R*)-1-amino-3-methylbutylphosphonate, decreasing the temperature shifts the conformational equilibrium toward the *ap* conformer, which is manifested by the negative signs of the chemical shift differences, $\Delta\delta^{T_1T_2}$, for the protons of the R substituent ($\Delta\delta^{T_1T_2} < 0$) and by the positive signs for the protons of one ethoxy group in the phosphoryl moiety ($\Delta\delta^{T_1T_2} > 0$). In turn, the second ethoxy group at the phosphorus is characterized by the negative value of the $\Delta\delta^{T_1T_2}$, which can result from the steric bulkiness of the diethoxyphosphoryl group.[37]

For the (*R*)-naproxen amide of (*R*)-1-amino-3-methylbutylphosphonate, the trend is opposite (Figure 10b). Decreasing the temperature shifts the protons of the R substituent upfield and all of the signals of the diethoxyphosphoryl moiety downfield.

As for the esters of naproxen and the hydroxyphosphonates, we found that, irrespective of the configuration, lowering the temperature shifted the signal corresponding to the C_α−H of the naproxen residue downfield ($\Delta\delta^{T_1T_2} < 0$), contrary to the methyl group, C_α−Me, of the naproxen part, which is moved upfield ($\Delta\delta^{T_1T_2} > 0$) (compare with Figure 3).

For the verification of the proposed model, naproxen amides of the structurally diverse aminophosphonates of known configuration were analyzed. As for the hydroxyphosphonates, the aminophosphonates were derivatized with both enantiomers of naproxen. Next, ^{1}H and ^{31}P NMR spectra of both diastereomeric amides were analyzed, considering only the most representative *ap* conformer, and the absolute configuration of the aminophosphonate was assigned only from the signs of the chemical shift differences, $\Delta\delta^{RS}$ (Scheme 1).

As it is clearly seen from Figure 11 (compare with Scheme 1) for the (*R*)-naproxen amides of the (*R*)-1-aminophosphonates, **(*R*)-3**, the R substituent is shielded by the naphthyl ring, whereas the diethoxyphosphoryl group is shielded in the amides of (*S*)-

(37) It seems that, in this case, two ethoxy groups are under different shielding effect of the naphthyl ring.

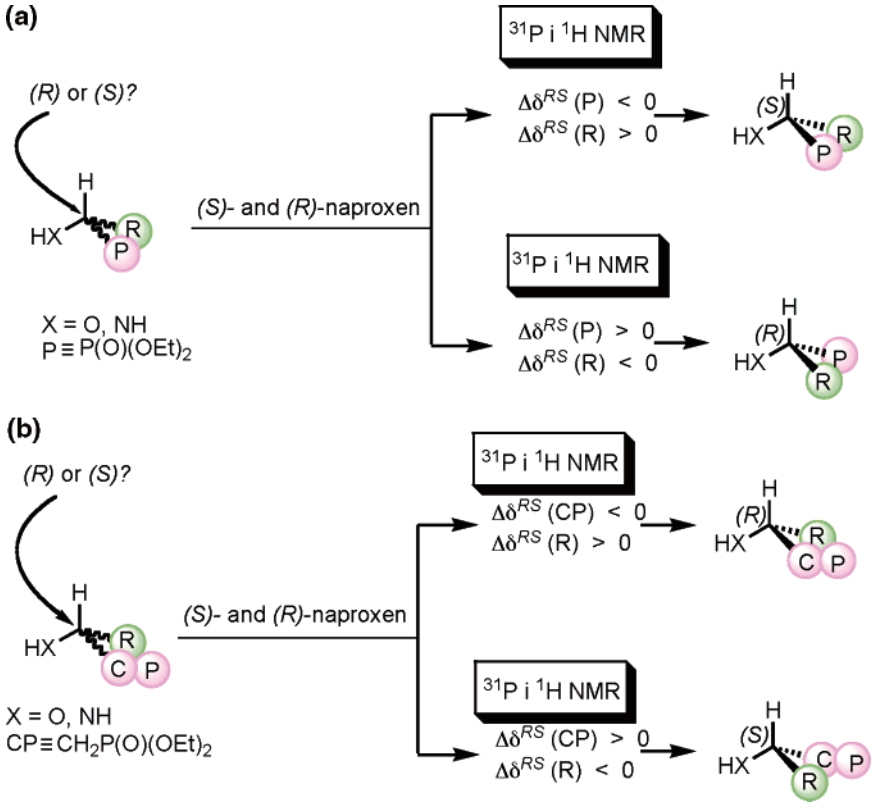


FIGURE 13. Diagram to deduce the absolute configuration of the (a) 1-hydroxy- or 1-aminophosphonates and the (b) 2-hydroxy- or 2-aminophosphonates from the $\Delta\delta^{RS}$ of its (*R*)- and (*S*)-naproxen esters or amides.

naproxen **(*S*)-3**. The opposite was observed for the amides of the (*S*)-1-aminophosphonates. In the (*S*)-naproxen amides of the (*S*)-aminophosphonates, the R substituent was shielded, whereas the diethoxyphosphoryl group is shielded in the (*R*)-naproxen amides of the (*S*)-aminophosphonate.

Opposite $\Delta\delta^{RS}$ signs are observed for the diethyl 2-amino-2-phenylethylphosphonate, owing to the change of the substituent priority sequence at the carbon stereogenic center in this aminophosphonate (Figure 11, compare with the Figure 6).

Example ^{1}H NMR spectra of two diastereomeric naproxen amides of diethyl (*R*)-1-amino-3-methylbutylphosphonate are presented in Figure 12.

As for the esters, the methodology presented here can be additionally simplified to the sole usage of the ^{31}P NMR since, for the diethoxyphosphoryl group in ^{1}H as well as ^{31}P NMR, the signs of $\Delta\delta^{RS}$ are the same. For the naproxen amides of the (*R*)-1-aminophosphonates, the chemical shift difference, $\Delta\delta^{RS}$, in the ^{31}P NMR is positive, whereas the negative sign of $\Delta\delta^{RS}$ confirms the (*S*) configuration of the carbon stereogenic center. The reverse is true for the diethyl (*R*)-2-amino-2-phenylethylphosphonate. For the reasons given earlier, the $\Delta\delta^{RS}$ in the ^{31}P NMR is negative.

As a graphical guide to the reader interested in applying double derivatization of the 1- and 2-hydroxy- together with the 1- and 2-aminophosphonates by means of naproxen, we present here a summary of the described procedure for the assignment of absolute configuration (Figure 13). Thus, the sample of the compound of unknown configuration is doubly derivatized with (*R*)- and (*S*)-naproxen. Next, both obtained diastereomers are analyzed by ^{1}H and ^{31}P NMR, and the $\Delta\delta^{RS}$ values are calculated. The configuration is assigned, depending on the signs of $\Delta\delta^{RS}$, according to the models presented in Figure 13.

Conclusions

It has been demonstrated in this work that naproxen is a convenient, reliable chiral derivatizing agent for the absolute configuration assignment of the 1- and 2-hydroxy- as well as the 1- and 2-aminophosphonates.

The presence of the naphthyl ring in the naproxen residue causes the chemical shifts of the substituents connected with the carbon stereogenic center to depend on their proximity to the shielding cone of the aromatic functionality. Theoretical calculations together with the NMR studies enabled us to propose a conformational model that explains the correlation between the absolute configuration of hydroxy- and aminophosphonates and $\Delta\delta^{RS}$ observed in the NMR spectra of their esters and amides of (*R*)- and (*S*)-naproxen. The model is the same for both hydroxy- and aminophosphonates.

High values and homogeneous signs of the $\Delta\delta^{RS}$, the same for the protons and phosphorus in one substituent and opposite to the signs determined for the signals of the second substituent connected with the carbon stereogenic center, proved reliability of the naproxen as a CDA. Extensive investigation of a wide range of hydroxy- and aminophosphonates of known absolute configuration proved that ^{31}P NMR spectroscopy is also a reliable tool for the absolute configuration assignment of this class of compounds.

Additionally, simple graphical models that allow the absolute configuration assignment of hydroxy- and aminophosphonates

by comparison of ^{1}H or ^{31}P NMR spectra of their naproxen derivatives were presented.

Experimental Section

General Procedures. The optically active hydroxyphosphonates of known absolute configuration were prepared according to the oxazaborolidine-catalyzed reduction of the ketophosphonates.[38] Diethyl (*S*)-2-hydroxypropylphosphonate was prepared via baker's yeast reduction of the diethyl 2-oxopropylphosphonate, according to the described procedure.[39] The aminophosphonates were prepared by the Mitsunobu azidation[23g] of the hydroxyphosphonates and the subsequent hydrolysis of the iminophosphoranes prepared by the Staudinger reaction from azidophosphonates.[23g] The esters or amides were prepared by treatment of the hydroxyphosphonate or the aminophosphonate (0.3 mmol) with the naproxen chloride (1.5 equiv) in the presence of pyridine (5 equiv) in CH_2Cl_2.[28] The reaction was stirred at room temperature for 0.5 h. The solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (20 mL) and washed with water (1 × 1 mL), 5% HCl (3 × 1 mL), brine (1 × 1 mL), 5% K_2CO_3 (2 × 1 mL), brine (2 × 1 mL), then dried ($MgSO_4$) and concentrated under reduced pressure to obtain the ester or amide. Final purification was achieved by column chromatography (hexane−ethyl acetate). All compounds were characterized by NMR, IR, MS, and elemental analysis. Enantiomeric purity of the (*R*)-naproxen derivatives was lower due to application of (*R*)-naproxen of ee = 60%.

NMR Spectroscopy. ^{1}H, ^{13}C, and ^{31}P NMR spectra of samples in $CDCl_3$ were recorded at 500 and 250 MHz. Chemical shifts (ppm) are internally referenced to the TMS signal (0 ppm) or externally to the H_3PO_4. *J* values are recorded in hertz.

Computational Methods. Ab initio-restricted Hartree−Fock (HF) and density functional theory (DFT) calculations were performed to elucidate conformational preferences of the naproxen esters and amides of the hydroxy- and aminophosphonates and to calculate shielding increments for their conformers. Optimization of the geometries was carried out using the standard 6-31G(d) basis set.[40] Gas and condensed phases were considered. The latter was included using the implicit polarized continuum model with COSMO electrostatics (CPCM)[41] and parameters corresponding to those of chloroform. After an initial conformational search at the semiempirical level, torsional configurations around the C(O)−C_α(H) angle were analyzed. For the optimal C(O)−C_α(H) angles, additionally, two dihedral angles for the hydroxy-(P(O)−C_1(H) and C_{ar}−C_α(H)) and three for the aminophosphonates (P(O)−C_1(H), C_{ar}−C_α(H), and C(O)−N(H)) were investigated at the HF level. Energy calculations were performed at the DFT level using the B3LYP functional,[42] 6-31G(d) basis set. Vibrational analysis was performed for the optimized gas-phase HF structures to confirm that they represent stationary points on the potential energy surfaces ($3n - 6$ real normal modes of vibration) and to calculate the Gibbs free energies that were subsequently used in the conformer population analysis. Chemical shifts were calculated at the HF level using the 6-311+G(2d,p) basis set.[43] All calculations were performed using the Gaussian suite of programs.[44]

Acknowledgment. Financial support by a grant 3T 09B 009 26 (2004−2006) from the Polish State Committee for Scientific Research is gratefully acknowledged. We thank Pharmaceutical Works Polfa in Pabianice (Poland) for a generous gift of naproxen and (±)-naproxen. We thank Professor Ricardo Riguera for helpful discussion and the possibility of taking 500 and 400 MHz spectra at the University of Santiago de Compostela. We also thank Miss Agata Jagiełło for her technical assistance. Access to the supercomputer facilities at PCSS, Poznan (Poland), is gratefully acknowledged.

Supporting Information Available: Experimental data (NMR, MS, etc.) of esters **2**, **4** and amides **3**, **5** of (*S*)- and (*R*)-naproxen and the hydroxy- and aminophosphonates. The level of theory, specific program, basis set, matrixes or Cartesian coordinates, and computed total energies of optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062097Z

(38) Meier, C.; Laux, W. H. G.; Bats, J. W. *Liebigs Ann. Chem.* **1995**, 1963.

(39) Żymańczyk-Duda, E.; Klimek-Ochab, M.; Kafarski, P.; Lejczak, B. *J. Organomet. Chem.* **2005**, *690*, 2593.

(40) (a) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213. (b) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654.

(41) (a) Baronel, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995. (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comp. Chem.* **2003**, *24*, 669.

(42) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Truong, T. N.; Duncan, W. T.; Bell, R. L. In *Chemical Applications of Density Functional Theory;* Laird, B., Ross, R., Ziegler, T., Eds.; ACS Symposium Series 629; American Chemical Society: Washington, DC, 1996, p 85. (c) Stephens, P. J.; Devlin, F. J.; Ashvar, C. S.; Bak, K. L.; Talyor, P. R.; Frisch, M. J. In *Chemical Applications of Density Functional Theory;* Laird, B., Ross, R., Ziegler, T., Eds.; ACS Symposium Series 629; American Chemical Society: Washington, DC, 1996, p 105. (d) Baker, J.; Muir, M.; Andzelm, J.; Scheiner, A. In *Chemical Applications of Density Functional Theory;* Laird, B., Ross, R., Ziegler, T., Eds.; ACS Symposium Series 629; American Chemical Society: Washington, DC, 1996, p 342.

(43) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.

(44) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.