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(*S*)-Naproxen® and (*S*)-Ibuprofen® chlorides—convenient chemical derivatizing agents for the determination of the enantiomeric excess of hydroxy and aminophosphonates by ^{31}P NMR

Katarzyna Błażewska and Tadeusz Gajda*

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

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Abstract—The acid chlorides of (*S*)-Naproxen® and (*S*)-Ibuprofen® are shown to be convenient chiral derivatizing agents for determination of the enantiomeric purity of diethyl 1-hydroxy- and 2-hydroxyalkylphosphonates as well as their aminoalkylphosphonate analogues by means of ^{31}P NMR spectroscopy. Correlation between the phosphorus chemical shift and the absolute configuration of the 1-hydroxyalkylphosphonate is also discussed. © 2002 Elsevier Science Ltd. All rights reserved.

^{31}P NMR spectroscopy is a very convenient tool for the determination of enantiomeric purity because of the large chemical dispersion and the simplicity of the broad-band ^{1}H decoupled spectra.[1,2] Determination of the enantiomeric excess using chiral derivatizing agents (CDAs) is the most widely used NMR technique, as the discrete diastereomers show chemical shift non-equivalences, $\Delta\delta$, that are usually higher than for related chiral solvating agents.[2]

Enantiomerically pure (*S*)-(+)-Naproxen® [2-(6-methoxynaphthalen-2-yl)propionic acid] and (*S*)-(+)-Ibuprofen® [2-(4-isobutylphenyl)propionic acid] are the most frequently prescribed members of the non-steroidal anti-inflammatory drugs (NSAID). Therefore, they are relatively cheap in comparison with other structurally similar, commercially available chiral derivatizing agents. Recently, (*S*)-Naproxen® and (*S*)-Ibuprofen® derivatives have been applied as chiral derivatizing reagents to assess the e.e. of chiral sulfoxides[3] by ^{1}H NMR and (*S*)-Naproxen® derivatives were also used for the determination of enantiomeric purity of amino derivatives[4] and cyanohydrins[5] by means of HPLC. In turn, the enantiomeric purity of these NSAID drugs can be easily assessed by ^{31}P NMR spectroscopy prior to derivatization with organophosphorus CDAs.[6] However, to the best of our knowledge (*S*)-Naproxen® and (*S*)-Ibuprofen® derivatives have not been applied for the e.e. determination of chiral phosphonates.

1-Hydroxyalkylphosphonate[7] and 1-aminoalkylphosphonate[8] derivatives have received considerable attention in bioorganic and medicinal chemistry due to their unique biological activities. Several methods of derivatization using numerous CDAs and various techniques (^{1}H, ^{19}F, ^{31}P NMR and HPLC) have been employed for the e.e. determination of dialkyl hydroxyalkylphosphonates. These methods include: (i) the formation of diastereomeric esters by coupling with (*R*)- or (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl),[9] (ii) esterification with O-methylmandelic acid[10,11] or camphanic chloride,[9i–l,12] (iii) formation of the phosphonodepsipeptides[13] and diazaphospholidine[14] derivatives. The determination of enantiomeric purity of aminophosphonates was also assayed via amidation with MTPA chloride and ^{1}H, ^{19}F or ^{31}P NMR spectroscopy.[9g,15]

Herein, we communicate our preliminary studies on the use of (*S*)-Naproxen® and (*S*)-Ibuprofen® chlorides as CDAs for a simple and fast ^{31}P NMR e.e. determination of hydroxy and aminoalkylphosphonates.

The above-mentioned chlorides were quantitatively obtained by heating (*S*)-(+)-Naproxen® or (*S*)-(+)-Ibuprofen® with oxalyl chloride in methylene chlo-

* Corresponding author. Tel.: +48-42-631-31-46; fax: +48-42-636-5530; e-mail: tmgajda@ck-sg.p.lodz.pl

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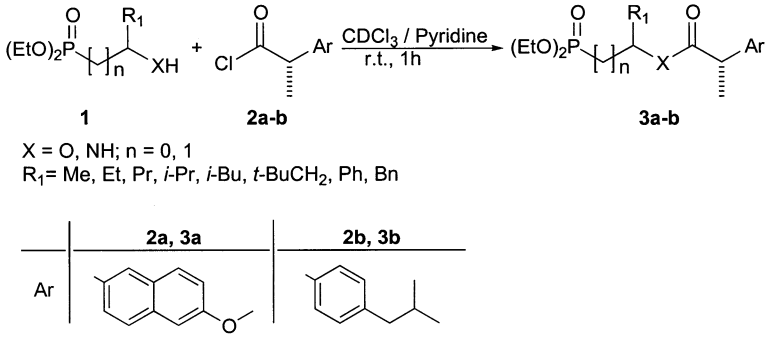
ride.[16] Racemic 1-hydroxy- and 2-hydroxyalkylphosphonates as well as their amino analogues were prepared according to the literature procedures.[17–19] Samples of chiral non-racemic 1-hydroxy and 1-aminoalkylphosphonates were obtained from previous studies on the asymmetric reduction of diethyl 1-oxoalkylphosphonates.[9g] The entire derivatization reactions were performed in an NMR tube using anhydrous $CDCl_3$ and pyridine as base,[20] according to Scheme 1.

A series of racemic and non-racemic diethyl 1-hydroxy- and 2-hydroxyalkylphosphonates and corresponding aminoalkylphosphonates and/or their oxalates were investigated. A comparison of ^{31}P NMR chemical shifts and chemical shifts differences ($\Delta\delta$) are collected in Table 1. Esterification and amidation under these conditions proceeds quantitatively within 1 h, and is not accompanied by racemization or the formation of any side products. We found however, that replacing pyridine with triethylamine causes racemization[21] to some extent.

The results given in Table 1 (entries 1–8) clearly indicate that both CDAs gave well resolved signals and most of the chemical shift non-equivalences ($\Delta\delta$) observed for the (*S*)-Naproxen® **3a** and (*S*)-Ibuprofen® esters **3b** are in a range comparable with those reported for the MTPA[9a,f–n] or O-methylmandelate[10a,c] esters. As far as diethyl 1-aminoalkylphosphonate amides are concerned, the diastereomeric anisochronicity is larger ($\Delta\delta = 0.11$–0.34 ppm), in comparison to those obtained for MTPA–amides.[9g,15a] ($\Delta\delta = 0.05$–0.07 ppm). Even when the stereogenic center is in the β-position to the phosphoryl moiety, as for 2-hydroxy and 2-aminoalkylphosphonates, the diastereomeric anisochronicity is sufficiently large to accurately assay the enantiomeric excess ($\Delta\delta = 0.11$–0.17 ppm, Table 1, entries 9–11 and 16).



Scheme 1.

Table 1. ^{31}P NMR chemical shifts δ (ppm) and chemical shift differences $\Delta\delta$ (ppm) of Naproxen® **3a** and Ibuprofen® **3b** derivatives of the diethyl hydroxy and aminoalkylphosphonates **1**

Entry	Compound **1**		Naproxen® derivatives **3a**[a]				Ibuprofen® derivatives **3b**[a]			
	X, *n*	R_1 (e.e. (config.)[b]	δ_1	δ_2	$\Delta\delta$ (δ_1–δ_2)	D.e. (%)	δ_1	δ_2	$\Delta\delta$ (δ_1–δ_2)	D.e. (%)
1	O, 0	Me	21.17	20.69	0.48	–	21.15	20.71	0.44	–
2		Et [74 (*R*)]	20.63	**20.09**[c]	0.54	72	20.59	**20.07**[c]	0.52	74
3		Et [70 (*S*)]	**20.60**[c]	20.06	0.54	68	**20.71**[c]	20.18	0.53	70
4		*i*-Pr	20.07	19.48	0.59	–	20.30	19.71	0.59	–
5		*i*-Bu [82 (*R*)]	21.23	**20.62**[c]	0.61	82	21.08	**20.48**[c]	0.60	82
6		*i*-Bu [81 (*S*)]	**21.24**[c]	20.62	0.62	79	**21.40**[c]	20.79	0.61	80
7		Ph [43 (*S*)]	**17.35**[c]	17.01	0.34	42	**17.36**[c]	17.07	0.29	41
8		Bn	19.91	19.46	0.45	–	19.76	19.35	0.41	–
9	O, 1	Pr	26.68	26.51	0.17	–	26.46	26.33	0.13	–
10		*i*-Bu	26.79	26.63	0.16	–	26.97	26.83	0.14	–
11		*t*-$BuCH_2$	26.21	26.04	0.17	–	26.28	26.16	0.12	–
12	NH, 0	Me	25.72	25.61	0.11	–	25.96	25.70	0.26	–
13		Et [75 (*R*)]	25.10	**24.89**[c]	0.21[d]	73	25.25	**24.97**[c]	0.28[d]	73
14		Et [74 (*S*)]	**25.26**[c]	24.95	0.31[d]	72	**25.27**[c]	24.97	0.30[d]	74
15		*i*-Bu [78 (*R*)]	25.99	**25.65**[c]	0.34[d]	77	25.56	**25.18**[c]	0.38[d]	80
16	NH, 1	*i*-Bu	29.10	28.99	0.11	–	29.40	29.25	0.15	–

[a] Derivatives **3a** and **3b**, after isolation and purification were fully characterized by MS, IR and ^1H NMR.

[b] The e.e. values and absolute configurations given in parentheses refer to the ones of the (*R*)-MTPA esters or amides obtained by derivatization with (*S*)-MTPA-Cl of the corresponding non-racemic diethyl 1-hydroxy or 1-aminoalkylphosphonates. For details see Ref. 9g.

[c] Major diastereomer is given in bold.

[d] The same $\Delta\delta$ values were obtained when the appropriate oxalate was used instead of the free aminophosphonate.

Finally, the method presented here may also be useful for the tentative determination of the absolute configurations of chiral 1-hydroxyalkylphosphonates. The phosphorus chemical shifts were consistent for a given diastereomer. Comparing the chemical shifts of chiral non-racemic 1-hydroxyalkylphosphonates of known configurations we found the phosphorus signal of diastereomeric (*S*)-Naproxen® and (*S*)-Ibuprofen® esters related to (*S*)-1-hydroxyalkylphosphonate consequently shifted downfield (δ_1) in relation to the signal (δ_2) of its (*R*)-enantiomer (Table 1, entries 2, 3, 5 and 6). Such assumptions are consistent with the conformational model of Naproxen® and Ibuprofen® esters presented recently by Riguera[22] and co-workers. In the preferred conformation[22] the hydrogen atom and the carbonyl group in the acid residue are anti-periplanar and the carbinyl hydrogen is eclipsed with the carbonyl oxygen. According to this model, the phosphorus atom in these (*S*)-Naproxen® and (*S*)-Ibuprofen® esters will be shielded by the aromatic ring when the 1-hydroxyalkylphosphonate has (*R*)-configuration at C(1) relative to the hydroxyphosphonate having (*S*)-configuration. The correlation of absolute configuration of chiral 1-hydroxyalkylphosphonates with phosphorus chemical shift were reported earlier for (*R*)-MTPA[9f–h,j,m,n] and (*S*)- or (*R*)-O-methylmandelic[10b,c] esters of 1-hydroxyalkylphosphonates.

It is suggested that the presented method can also be applied to 1-aminoalkylphosphonates (Table 1, entries 13–15) but to securely assign their absolute configuration more detailed analysis should be done.

In conclusion, (*S*)-Naproxen® chloride and (*S*)-Ibuprofen® chloride have been proved to be convenient CDAs for the determination of enantiomeric purity of diethyl 1-hydroxy- and 2-hydroxyalkylphosphonates as well as their aminoalkylphosphonate analogues by means of ^{31}P NMR. It is also suggested that the ^{31}P NMR shifts of diastereomeric (*S*)-Naproxen® and (*S*)-Ibuprofen® esters are diagnostic for the determination of absolute configuration of 1-hydroxyalkylphosphonates. However, for configurational assignment of a single enantiomer of hydroxy and aminoalkylphosphonates, both enantiomers of the auxiliary reagent are needed for derivatization.[23] This may be a limitation of the presented method to some extent, because only one enantiomer of Naproxen® and Ibuprofen®, as yet, are commercially available. Further investigation on the application of (*S*)-Naproxen® and (*S*)-Ibuprofen® derivatives, as CDAs are currently underway and will be reported in due course.

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20. To a cooled solution of the appropriate hydroxy- or aminoalkylphosphonate, or aminoalkylphosphonate oxalate (0.05–0.07 mmol) in dry $CDCl_3$, was added anhydrous pyridine (0.1–0.2 mL, 20–40 equiv.), followed by the addition of Naproxen® or Ibuprofen® chloride (2.5 equiv.) in dry $CDCl_3$. The tube was sealed and shaken well by hand. After 1 h the $^{31}P\{^1H\}$ NMR spectrum (101.3 MHz) was collected on a Bruker AVANCE DPX 250 spectrometer (spectrum decoupled during aquisition only; pulse 90° and repetition 7 s were set).
21. Such racemization was observed during esterification of (*S*)-(+)-Naproxen® using Et_3N/BOP system. For details, see: Araźny, Z.; Czarnocki, K.; Wojtasiewicz, K.; Maurin, J. K. *Tetrahedron: Asymmetry* **2000**, *11*, 1623–1628.
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