Pergamon

Tetrahedron Letters, Vol. 38, No. 45, pp. 7875-7878, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10153-8

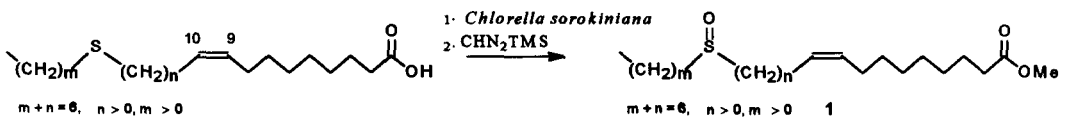
Enantiomeric excess determination of some chiral sulfoxides by NMR: use of (S)-Ibuprofen® and (S)-Naproxen® as shift reagents

Laëtitia Fauconnot, Caroline Nugier-Chauvin*, Nicolas Noiret and Henri Patin

Laboratoire de Chimie Organique et des Substances Naturelles, associé au CNRS,
Ecole Nationale Supérieure de Chimie de Rennes, Av du Gal Leclerc, 35700 Rennes Beaulieu, France

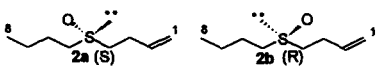
Abstract: The well known drugs (S)-Ibuprofen and (S)-Naproxen were used as NMR shift reagents for the stereochemical analysis of alkylsulfoxides. It was shown that (S)-Naproxen could be worthwhile substituted to (S)-MPA or (S)-2-NMA for the stereochemical analysis of some chiral alkyl sulfoxides . © 1997 Elsevier Science Ltd.

Among the large range of shift reagents used for the stereochemical analysis of optically active compounds, a few were successfully reported for the enantiomeric excess determination of sulfoxides[1]. For instance, the α-methoxyarylacetic acids were very successful as shift reagents for the stereochemical analysis of long-chain aliphatic secondary alcohols or sulfoxides[2]. In the course of our plant oleoyl desaturase investigations, we previously reported the synthesis of thiaoleic acids and demonstrated the inhibitory effect of 13-thiaoleic acid on the desaturase activity[3] . Moreover, these sulfur-containing oleic acid analogues appeared to be converted to the corresponding sulfoxides **1** by the green algae *Chlorella sorokiniana* (Scheme 1). Consequently, we recently reported the use of (S)-α-methoxyphenyl and (S)-α-methoxy-2-naphthyl acetic acids (respectively (S)-MPA and (S)-2-NMA)[4], in C_6D_6 as NMR solvent, for their stereochemical analysis.



Scheme 1: Oxidation of thiaoleic acids by *Chlorella sorokiniana*

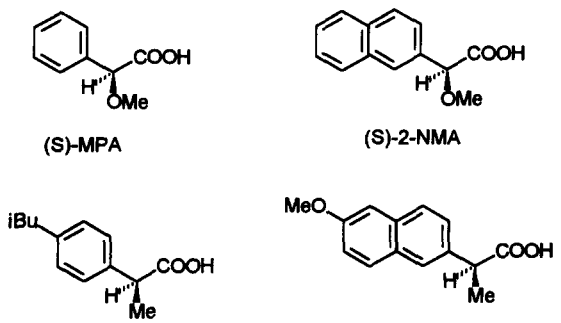
The chemical shift effects of (S)-MPA and (S)-2-NMA both in ^{1}H- and ^{13}C-NMR spectra were evaluated by the use of our chiral sulfoxide models **2a** and **2b**.



* Fax : (33) (0)2 99 87 13 98 E-mail : Caroline.Nugier@univ-rennes1.fr

However, complete configurational determination of the S-oxide thiaoleic acids could not be achieved with (S)-MPA. More interesting results were observed in preliminary experiments conducted with (S)-2-NMA, certainly because of the long range effect on the chemical shifts of CH_2 along the alkyl chain. Thus (S)-2-NMA shift reagent behaviour was characterized by anisotropic effects similar to those of (S)-MPA but the methyl signal was the only one fully differentiated between both enantiomers **2a** and **2b** (Fig. 1). It should be underlined that such optically active compounds (1-NMA, 2-NMA) are difficult to obtain in high optical purity[2] and involve either tremendous enantiomers resolution or chiral phase separation[5].

Among the most commonly prescribed members of non-steroidal anti-inflammatory drugs, the 2-arylpropionic acids, (S)-Naproxen and (S)-Ibuprofen[6] (Scheme 2) are of interest as NMR shift reagents because of, firstly their similar structures and secondly their attractive price compared to the expensive commercial MPA[7]. In this paper, we describe the results of the configurational analysis of our models and target sulfoxides by the use of such optically pure compounds.



Scheme 2: Arylacetic acids used as NMR shift reagents on our sulfoxide model.

In a first experiment, we observed the effect of (S)-Ibuprofen and (S)-Naproxen on the difference of the chemical shifts between enantiomers **2a** and **2b**, in ^{1}H-NMR spectra[8]. The resolution of the signals are not complete in the case of Ibuprofen, but most of the enantiomers signals appear differentiated when Naproxen is used as shift reagent (Table 1).

Table 1: Effect of the shift reagent on the magnitude of the non-equivalence in ^{1}H-NMR spectra of **2a** and **2b**.

	$\lvert \delta(2a) - \delta(2b) \rvert$		
^{1}H Position	**Ibuprofen**	**Naproxen**	**MPA**
1	n.m.	0.016	0.015
	n.m.	0.022	0.022
2	0.017	0.025	0.026
3	n.m.	0.023	0.034
4	n.m.	0.031	0.032
	n.m.	0.010	0.022
5	n.m.	0.025	0.037
	n.m.	0.015	0.022
6	n.m.	n.m.	n.m.
7	n.m.	n.m.	n.m.
8	0.011	0.023	0.018

n.m. : not measurable due to overlapping signals.

In order to better appreciate such effects, figure 1 illustrates the splitting of the methyl signals in ^{1}H-NMR spectra of the racemic butylbutene sulfoxide **2** in C_6D_6 using (S)-Ibuprofen and (S)-Naproxen, compared to the MPA reagent and to the previously studied (S)-2-NMA[3].

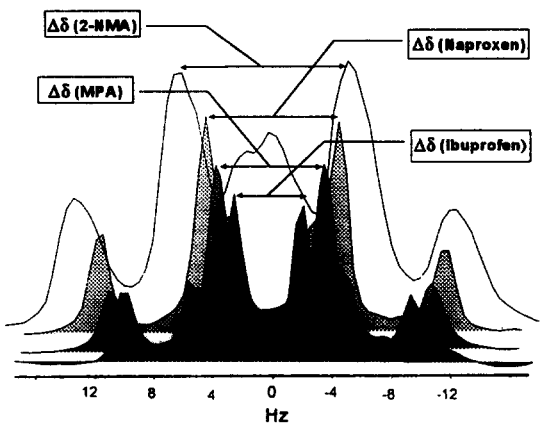


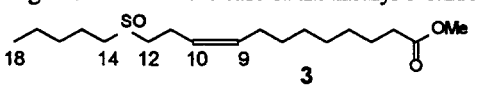
Figure 1 . Splitting of the ^{1}H-NMR CH_3 signal with added shift reagent .

The triplet CH_3 signals appears splitted in both cases but a stronger effect on Δδ is observed with (S)-Naproxen. On our racemic sulfoxide model, (S)-Naproxen could thus be worthwhile substituted to (S)-MPA and with similar success as the efficient (S)-2-NMA. Consequently, we observe the effect of (S)-Ibuprofen and (S)-Naproxen in comparison with MPA and 2-NMA, on the difference of CH_2 chemical shifts between enantiomers **2a** and **2b**, in ^{13}C-NMR (Table 2). Whereas the signals relative to the two α-CH_2 (C_4 and C_5) are less split than with MPA, Naproxen seems to exert a longer distance effect on the alkyl chain. However, it should be noticed that (S)-2-NMA caused an enhanced effect on the Δδ of the distant carbons C_1, C_2, C_7 and C_8.

Table 2: Effect of the shift reagent on the magnitude of the non-equivalence in ^{13}C-NMR spectra of **2a** and **2b** .

	|δ(2a)-δ(2b)| (ppm)			
^{13}C Position	**Ibuprofen**	**Naproxen**	**MPA**	**2-NMA**
1	0.0113	0.0190	0.0152	0.0303
2	0.0113	0.0227	0.0228	0.0265
3	0.0265	0.0265	0.0342	0.0303
4	0.0265	0.0265	0.0266	0.0228
5	0.0227	0.0228	0.0265	0.0227
6	0.0114	0.0152	0.0152	0.0114
7	0.0114	0.0152	0.0227	0.0190
8	0	0.0189	0.0076	0.0227

Consequently, some experiments, conducted on our real targets (sulfoxides from thiaoleic acids) lead to the same observations, as shown on figures 2 and 3 in the case of the methyl S-oxide-13-thiaoleate **3** .



3

(S)-Naproxen appears more efficient than (S)-MPA on the methyl end signal splitting (Figure 2) whereas the differentiation is better achieved on the C_{12} and C_{14} carbons with (S)-MPA (Figure 3). As previously suggested[2d], the naphthyl ring may produce a much wider-range anisotropic effect on the protons and the carbons of the chain than the phenyl ring might do.

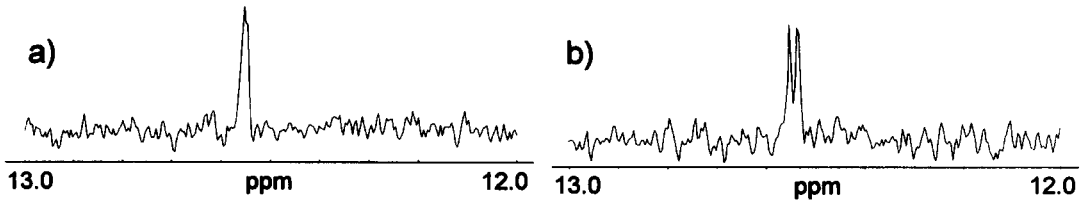


Figure 2 : ^{13}C signal of the CH_3 (C18) with a) MPA or b) Naproxen.

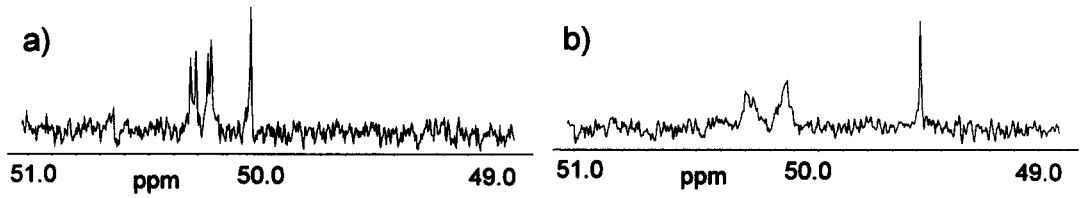


Figure 3 : ^{13}C signals of the CH_2S (C12 and C14) with a) MPA or b) Naproxen.

In conclusion, (S)-Ibuprofen and (S)-Naproxen tested on our sulfoxide model, proved to be valuable NMR shift reagents and (S)-Naproxen was successfully and economically used for the configurational analysis of the dialkylsulfoxides with complex spin systems such as methyl S-oxide 13-thiaoleate .

References and Notes

1. Some relevant papers on the topic : (a) Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519. (b) Deshmukh, M.; Dunach, E.; Juge, S.; Kagan, H.B. *Tetrahedron Lett.* **1984**, *25*, 3467-3470. (c) Drabowicz, J.; Duddek, H. *Sulfur Lett.* **1989**, *10*, 37-40. (d) Drabowicz, J.; Dudzinski, B.; Mikolajczyk, M..*Tetrahedron : Asymmetry* **1992**, *3*, 1231-1234.
2. (a) Buist, P.H.; Marecak, D.M. *J. Am. Chem. Soc.* **1992**, *114*, 5073-5080. (b) *Tetrahedron: Asymmetry* **1995**, *6*, 7-10. (c) Kusumi, T.; Takahashi, H.; Xu, P.; Fukushima, T.; Asakawa, Y.; Hashimoto, T.; Kan, Y.; Inouye, Y. *Tetrahedron Lett.* **1994**, *35*, 4397-4400. (d) Kouda, K.; Kusumi, T.; Xu, P.; Kan, Y.; Hashimoto, T.; Asakawa, Y. *Tetrahedron Lett.* **1996**, *37*, 4541-4544. (e) Kouda, K.; Ooi, T.; Kaya, K.; Kusumi, T. *Tetrahedron Lett.* **1996**, *37*, 6347-6350.
3. Poulain, S.; Noiret, N.; Nugier-Chauvin, C.; Patin, H. *Liebigs Ann./ Recueil* **1997**, 35-40.
4. Gautier, N.; Noiret, N.; Nugier-Chauvin,C.; Patin, H. *Tetrahedron: Asymmetry* **1997**, *8*, 501-505.
5. Latypov, Sh. K.; Seco, J.M.; Quiñoa, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 504-515.
6. See for examples: (a) Bruna, K.; Geisslinger, G.; Menzel-Soglowok, S. *J. Clin. Pharmacol.* **1992**, *32*, 944. (c) Wechter, W.J.; Bigornie, A.E.; Murray, E.D., Jr.; Levine, B.H.; Young, J.W. *Chirality* **1993**, *5*, 492-494.
7. Comparative commercial prices for 1g of shift reagent : (S)-MPA/(S)-Naproxen ~ 465/33.
8. NMR spectra were recorded with a ARX 400 Bruker spectrometer. The correct assignements were established using routine COSY and HMQC experiments. All the samples were prepared as follows : to 1 mg of the sulfoxide in 0.5 mL of solvent was added 3 molar eq. of the desired NMR shift reagent. All the spectra were recorded at 298K.

(*Received in France* 28 *July* 1997; *accepted* 17 *September* 1997)