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NMR Stereochemical analysis of chiral alkylsulfoxides with α-methoxyaryl acetic acids

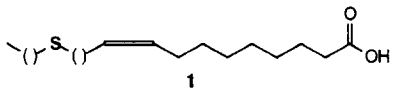
Nicolas Gautier, Nicolas Noiret,* Caroline Nugier-Chauvin and Henri Patin

Laboratoire de Chimie Organique et des Substances Naturelles, associé CNRS, UPRES-A 6052, Ecole Nationale Supérieure de Chimie de Rennes, Av du Gal Leclerc, 35700 Rennes Beaulieu, France

Abstract: (S)-α-methoxyphenyl and (S)-α-methoxy-2-naphthyl acetic acids (MPA and 2-NMA) were used as NMR chiral shift reagents for the stereochemical analysis of alkylsulfoxides. It was shown that the use of C_6D_6 as NMR solvent increased the magnitude of the observed effects for both ^{1}H- and ^{13}C-NMR spectra. Moreover, 2-NMA led to a much longer range effect on the chain but lowered the signal splitting of the α-methylene groups. © 1997 Elsevier Science Ltd. All rights reserved.

Chiral NMR shift reagents are powerful tools for the stereochemical analysis of optically active compounds. Among the shift reagents, some substituted acetic acids designed from the well known Mosher acid[1] have been widely used to elucidate the absolute configuration of secondary alcohols and primary amines. Recently, new α-methoxypolyaryl acetic acids such as naphthyl or anthryl derivatives, have been proposed and successfully used in the determination of the absolute configuration of natural long chain aliphatic alcohols[2] after esterification. Buist *et al.* have suggested the use of (S)-α-methoxyphenyl acetic acid (MPA)[3] for analysing the stereochemistry of dialkylsulfoxides with complex spin systems[4].

In connection with work on the mechanism of the *in vivo* desaturation of oleic acid[5], we reported the synthesis of thia oleic acids[6] **1** using a sulfur atom as probe of oxidation along the C12–C16 part of the chain.



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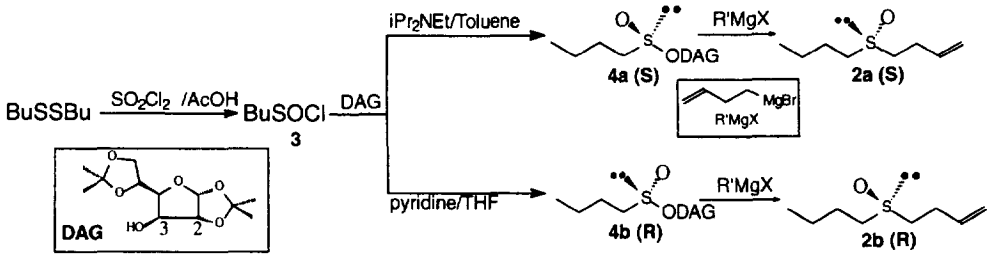
During the *in vivo* experiments[7] with the green algae *Chlorella sorokiniana*, the effects of exogenous acids **1** on the desaturation of [1-^{14}C] oleic acid were evaluated. We showed that the highest effect was obtained when sulfur was at the C-13 position[6]. Moreover, in this case, sulfoxidation occurred and the SO-13 oleic acid was detected by GLC and GLC/MS[8]. In this paper, we describe some results from the stereochemical analysis of these 'bio-oxidized' acids using NMR shift reagents.

First, the new chiral sulfoxide **2** which mimics the homoallylic position of sulfur in the S_{13} oleic acid, was synthesized as a model in order to determine the best conditions for NMR analysis. Both epimers at sulfur were obtained using the 'DAG methodology' [9](Scheme 1).

Butyl disulfide was oxidized to the corresponding sulfinyl chloride **3** with SO_2Cl_2 in AcOH[10]. Then, the treatment of DAG with **3** in the presence of iPr_2NEt gave the sulfinate **4a** (**S**) while the same reaction performed with pyridine as a base led to the opposite stereoisomer **4b** (**R**)[9]. After purification by column chromatography (SiO_2; ethyl ether/petroleum ether, 3/7, v/v), the two butanesulfinates **4** were treated with the Grignard reagent from 4-bromo-1-butene in toluene at 0°C. As the reaction is known to proceed with total configuration inversion[9], the two epimeric sulfoxides were obtained in good yields and a good enantiomeric excess (Table 1).

* Corresponding author. Email: noiret@univ-rennes1.fr



Scheme 1.

Table 1. Synthesis of optically active sulfoxides models **2**[11]

Entry	yield (%)	$[\alpha]_D$	configuration at sulfur.	ee % from NMR spectra[a)]
4a	45	-0.25 (20°C/EtOH/c 0.50)	S	75.2% (72.0%)
4b	80	+0.05 (20°C/EtOH/c 0.50)	R	84.0% (84.5%)
2a	76	+3.16 (20°C/EtOH/c 0.51)	S	-
2b	75	-3.71 (20°C/EtOH/c 0.62)	R	-

a) $CDCl_3$; ^{1}H-NMR (^{13}C-NMR)[11]

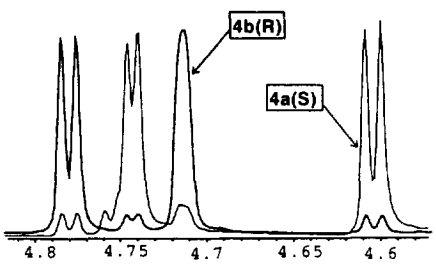


Figure 1. Partial ^{1}H-NMR spectra ($CDCl_3$) of **4** (H_2 and H_3).

The configuration at sulfur for **2** was deduced from those of the corresponding DAG-sulfinates **4**[9]. In the ^{1}H-NMR spectra, the differences in chemical shifts allow the determination of the ratio of sulfinates **4a** and **4b**: the signals of the H-2 and H-3 protons of DAG moiety[12] (Figure 1).

The symmetry around sulfur allows complex spin systems in the ^{1}H-NMR spectra (Figure 2a). Buist *et al.* resolved this problem by the use of S-MPA in $CDCl_3$ and the parallel synthesis of some partially deuterated models[4]. In our case these techniques were not useful, since the overlapping of the methylene signals makes them impossible to analyse (Figure 2b). Moreover, deuterated models are difficult to obtain, especially in the case of thia oleic acids due to the required multistep synthesis[6]. However, during this study, we observed that the use of C_6D_6 as NMR solvent caused a much larger splitting of the signals than $CDCl_3$. In our opinion, this effect, coupled with the use of MPA, could be of interest. As expected, we observed a strong effect on the chemical shifts of CH_2 in the ^{1}H-NMR spectra (Figure 2c). Moreover, in the case of ^{13}C-NMR spectra, all the signals appeared resolved (Table 2).

Some polyaryl acetic acid derivatives have recently been used as NMR shift reagents to determine the absolute configuration of quasi-symmetrical secondary alcohols[2]. As a preliminary work, we chose

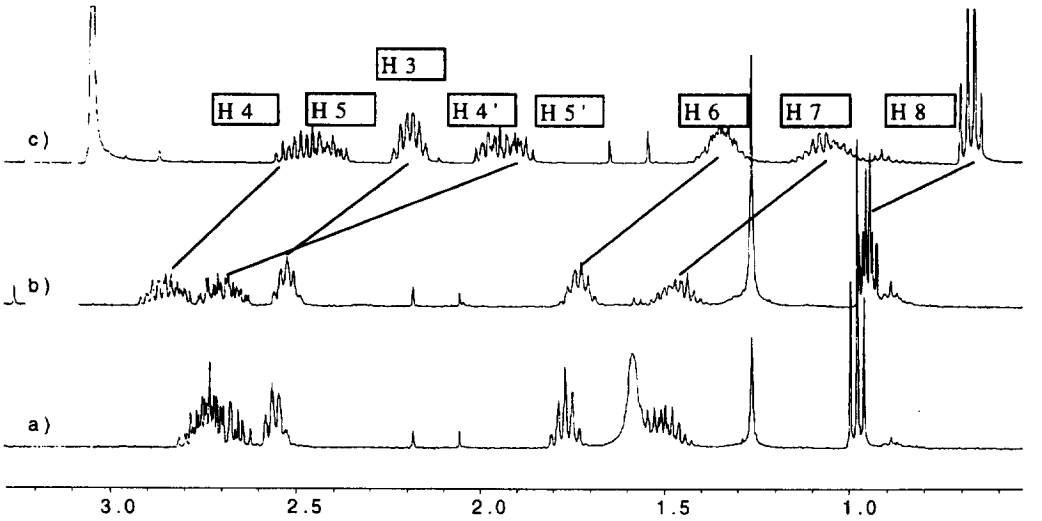
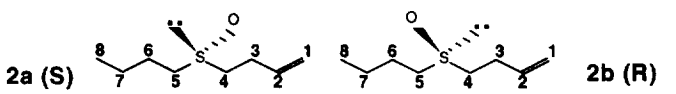


Figure 2. NMR shift experiments on racemic **2** a) without MPA ($CDCl_3$); b) with 3eq of MPA ($CDCl_3$); c) with 3eq of MPA (C_6D_6).

Table 2. Additive effect of C_6D_6 as NMR solvent and MPA on the magnitude of the nonequivalence in ^{1}H- and ^{13}C-NMR spectra for **2** with MPA as shift reagent



Position	^{1}H-NMR		^{13}C-NMR			
	δ(**2a**) - δ(**2b**)[a]		δ(**2a**) - δ(**2b**)[a]		δ(C_6D_6) - δ($CDCl_3$)[a]	
solvent	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	**2a**	**2b**
1	-0.009	-0.015	0	-0.0152	-0.3592	-0.3744
	-0.006	-0.022				
2	0.011	+0.026	-0.0069	-0.0228	+0.4825	-0.0938
3	n.m.[b]	+0.034	-0.0146	-0.0342	+0.2020	+0.1526
4	n.m.[b]	+0.032	-0.0162	-0.0266	-0.4654	-0.5071
		+0.022				
5	n.m[b]	+0.037	+0.0255	+0.0265	+0.5525	-0.5488
		+0.022				
6	n.m[b]	n.m.[b]	+0.0074	+0.0152	+0.1185	+0.1261
7	n.m.[b]	n.m.[b]	+0.0073	+0.0227	+0.0275	+0.0426
8	+0.011	+0.018	+0.0076	+0.0076	+0.0010	+0.0010

a) in ppm; b) n.m.: not measurable due to overlapping signals.

the α-methoxy-2-naphthyl acetic acids (2-NMA) in order to evaluate the interest of these reagents in our case. 2-NMA was obtained as follows: the commercial 2-naphtaldehyde was treated with $CHCl_3$ and NaH in methanol[13] to afford the racemic α-methoxy-2-naphthyl acetic acid. After esterification with (−)-menthol, the diastereoisomeric esters were separated by preparative chromatography (SiO_2, PE/AcOEt; 99/1). Each isomer was recovered by hydrolysis (12N HCl/dioxane, 1/3; 3h, 110°C) of the corresponding ester[13,14]. In the same conditions, we observed, as expected, a higher effect on Δδ (i.e. CH_3 signal, Figure 3). However, the signals relative to the two α-CH_2 (H_4 and H_5) are less split than with MPA. In this case, the versatility of MPA can be attributed to the low number of carbon atoms of the models studied. But, preliminary experiments conducted on our real target (sulfoxides

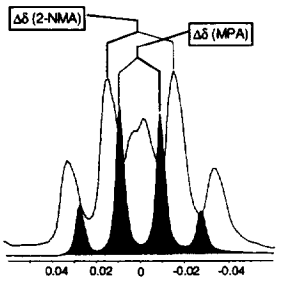
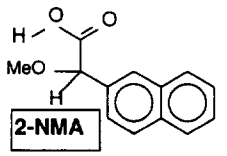


Figure 3. Splitting of the ^{1}H-NMR CH_3 signal with added shift reagent.

from thia oleic acids) demonstrate the very interesting behaviour of 2-NMA in the measurement of ee%, especially when the sulfur is far from the double bond (i.e. SO_{16}–oleic acid).



In conclusion, the new chiral sulfoxide **2** was prepared in both enantiomeric forms and the enantiomeric excess was measured using NMR spectroscopy by taking advantage of (i) the stereoselective interaction between the sulfoxide group and the acidic NMR shift reagent NMA and (ii) a solvent effect. Complete stereochemical determination of a series of thia oleic acids sulfoxides is under way and will be reported soon.

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11. NMR spectra were recorded with a ARX-400 Brucker spectrometer. The correct assignments were established using routine COSY and HMQC experiments. All the samples were prepared as

follows: to 1mg of the sulfoxide in 0.5mL of the solvent was added 3 eq of the desired NMR shift reagent. All the spectra were recorded at 298 K.

12. ^{1}H-NMR ($CDCl_3$): **4a**, δ=4.742 (J=2.6 Hz, H2), 4.604 (J=3.6 Hz, H3); **4b**, δ=4.786 (J=3.6 Hz, H2), 4.719 (H3).
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14. $[\alpha]_D$=+118.9 (20°C/EtOH/0.222g /100mL) lit.[9a]: +120 (25°C/EtOH/0.30g/100mL).

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