NMR Spectroscopic Determination of the Absolute Configuration of Chiral Sulfoxides via *N*-(Methoxyphenylacetyl)sulfoximines

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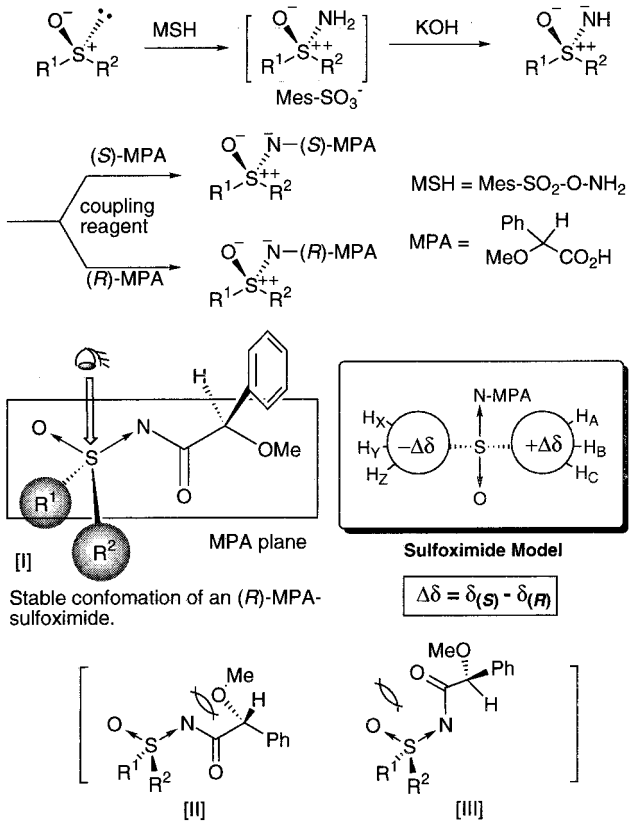
An increasing number of reports is being published on the NMR methods that enable the elucidation of the absolute configuration of chiral secondary alcohols,[1] amines,[2] and carboxylic acids.[3] In respect to chiral sulfoxides, however, there have been very few methods to determine their absolute configuration except for X-ray crystallography, although the sulfinyl moiety is an important functional group that is frequently found in biologically active natural products and synthetic drugs. 9-Anthryl-1,1,1-trifluoroethanol,[4] α-methoxyphenylacetic acid,[5] and (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine[6] have been developed as the NMR reagents for deducing the absolute configuration of sulfoxides. These reagents form complexes by hydrogen bonds between their acidic OH groups and the oxygen atom of the sulfoxide, and because of the instability of the complexes, the chemical shift differences between the diastereomeric complexes are usually very small or in some cases nonsystematic, which makes these methods somewhat uncertain. Difficulty in assuming the stable conformation of the fragile complexes may also be an intrinsic drawback of these methods.

We considered that, if a certain chiral anisotropic reagent[7] could be covalently bonded to the stereogenic sulfur or the sulfoxide oxygen, the anisotropic effect from the aromatic ring of the chiral auxiliary would be more significant than the conventional hydrogen-bonded complexes. Introduction of a chiral anisotropic moiety at the sulfoxide oxygen seems less promising because the Pummerer rearrangement[8] would occur on acylation, and the information on the chirality would thus be lost. Therefore, we focused on amination of sulfoxide with *O*-mesitylsulfonylhydroxylamine[9] which proceeded with complete retention of chirality at the sulfur atom.[10] The strategy of our method is outlined in Scheme 1.

When an amino group is introduced at the stereogenic sulfur atom, (*R*)- and (*S*)-methoxyphenylacetic acids can be introduced specifically at the nitrogen atom. The stable conformation of the resulting *N*-(methoxyphenylacetyl)sulfoximine is easily deduced to be [I],[11] because the alternative conformations [II] and [III] will be destablized by the serious dipole−dipole repulsion between the electronegative atoms. The absolute configurations will be determined by the "Sulfoximine Model" in an analogous way to the modified Mosher's method.[1]

Scheme 1



To see if this strategy works as expected, racemic sulfoxides **1**−**4** were prepared by reaction of methyl alkylsulfinates[12] with Grignard reagents as shown in Scheme 2. The racemic sulfoxides were treated with *O*-mesitylsulfonylhydroxylamine in dichloromethane to give the corresponding sulfoximines **1a**−**4a** in 60−80% yields. Each product was condensed with *rac*-methoxyphenylacetic acid (PyBOP/HOBT),[13] affording the respective *N*-(methoxyphenylacetyl)sulfoximines **1b**−**4b** in 50−80% yields. The enantiomeric pairs of diastereomers were separated by flash chromatography, and the "apparent" Δδ values were calculated by subtracting the proton chemical shifts of the fast-eluting *N*-(methoxyphenylacetyl)sulfoximine from those of the slow-eluting one. The results are shown in Scheme 2. The apparent Δδ values with opposite signs are arranged systematically on both sides of the methoxyphenylacetyl plane (Scheme 2).

This new methodology was applied to chiral sulfoxides **5**−**15**.[14,15] These optically active sulfoxides were prepared by the diacetone-D-glucose method,[16] which can produce the chiral sulfoxides with predictable absolute configurations (Scheme 3). The chiral sulfoxides were aminated with *O*-mesitylsulfonylhy-

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(11) An X-ray analysis of *S*,*S*-dimethyl *N*-(methoxyphenylacetyl)sulfoximine indicated that its methoxyphenylacetyl part existed in the expected conformation whereas the dimethylsulfoximine moiety rotates in 30° from the supposed one. This deviation may have been caused by the stacking effect; a neighboring molecule was found to be located very close to the questioning molecule. The verification of conformation [I] by ab initio MO calculation is in progress.

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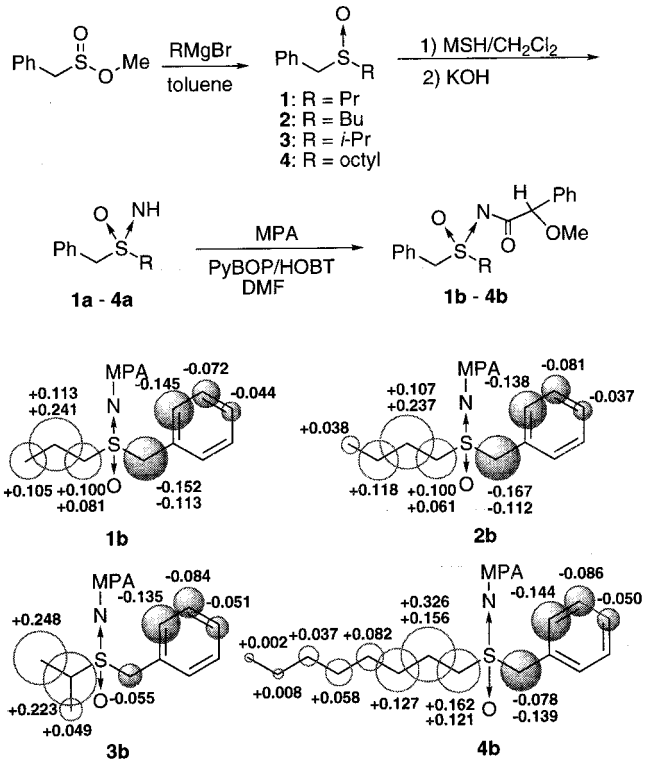
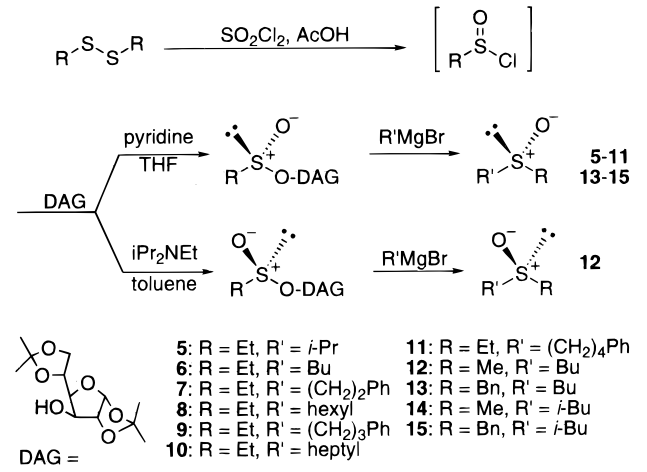
Scheme 2



Scheme 3



droxylamine followed by acylation with (*R*)- and (*S*)-methoxyphenylacetic acids to give a single diastereomer in each case. The $\Delta\delta$ values were calculated according to the equation $\Delta\delta = \delta_{S-\text{amide}} - \delta_{R-\text{amide}}$. The results are shown in structures **5a**−**15a** (Figure 1).

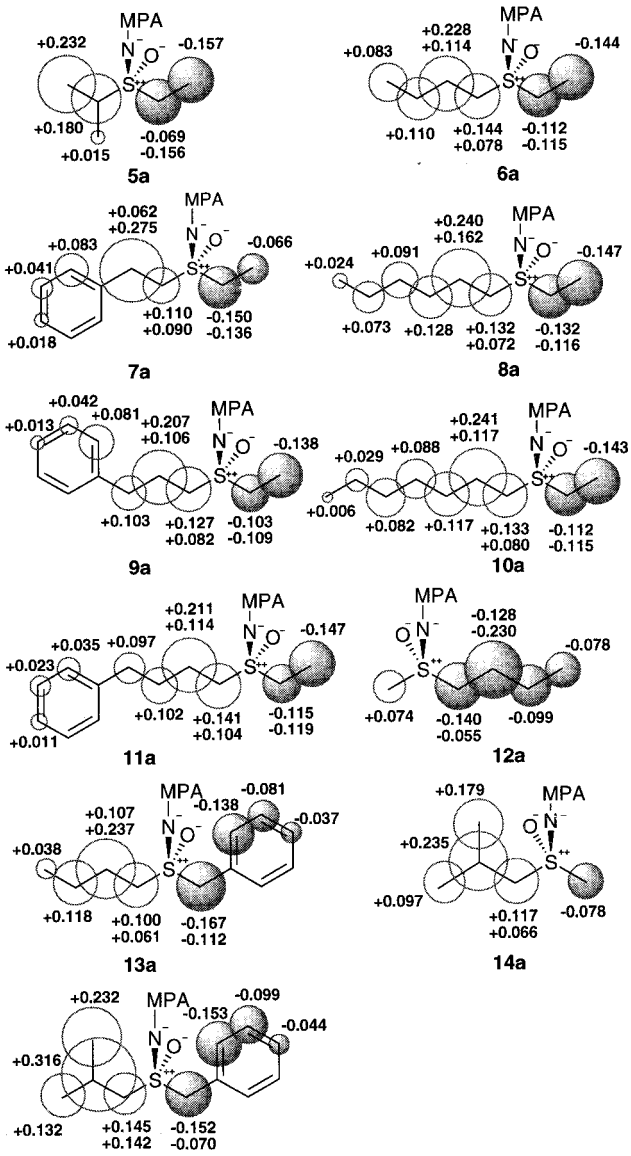


Figure 1. The $\Delta\delta$ values [$\Delta\delta = \delta_{[(S)-\text{amide}]} - \delta_{[(R)-\text{amide}]}$] obtained for *N*-MPA-sulfoximides **5a**−**15a**. The ^{1}H-NMR spectra were recorded at 400 MHz ($CDCl_3$).

The absolute configurations, determined by the present method, of these sulfoxides are in complete accord with those of the known ones (**12**[17] and **14**[17]) and as predicted by the literature (**5**−**11**, **13**).[16] The $\Delta\delta$ values of the protons are much larger than those observed in the conventional methods such as those using methoxytrifluoromethylphenylacetic acid (MTPA) for secondary alcohols, which indicates that the presumed conformation of the *N*-(methoxyphenylacetyl)sulfoximine (Scheme 1) is quite predominant.

We later found that *N*-(methoxyphenylacetyl)sulfoximine (**7a**) was obtained from sulfoxide (**7**) in 61% yield by a one-pot reaction (**7**/*O*-mesitylsulfonylhydroxylamine/CH_2Cl_2 then methoxyphenylacetic acid/PyBOP/HOBT/pyridine), without isolation of the sulfoximine. This finding may greatly contribute to the expediency of the present methodology.

Supporting Information Available: Procedure of the one-pot reaction from (*R*)-(ethyl 2-phenylethyl sulfoxide) to the corresponding (*S*)-*N*-(methoxyphenylacetyl)sulfoximine and the ^{1}H and ^{13}C NMR data of (*R*)- and (*S*)-*N*-(methoxyphenylacetyl)sulfoximines (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The enantiomeric excess (ee) values of the synthesized sulfoxides are as follow: **5**, 99%; **6**, 98%; **7**, 98%; **8**, 94%; **9**, 98%; **10**, 95%; **11**, 94%; **12**, 67%; **13**, 45%; **14**, 96%; **15**, 46%. These ee's were determined by comparing the chiroptical properties with those reported (**12** and **14**), or integration of the proton signals observed for the corresponding *S*,*S*-dimethyl *N*-(methoxyphenylacetyl)sulfoximine diastereomers. Alternation of stereochemistry in the amination reaction of the chiral sulfoxides or the epimerization of the methoxyphenylacetyl moiety did not occur at all, because (i) the ee's observed for **12a** and **14a** were exactly the same as those for **12** and **14** and (ii) the ee's obtained by analyzing the ^{1}H NMR spectra of **5a**−**15a** were identical between their (*R*)- and (*S*)-*N*-(methoxyphenylacetyl) derivatives.

(15) The ^{1}H NMR spectra were recorded at 32 °C for the 6 mM $CDCl_3$ solutions.

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