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(*S*)-α-Methoxyphenyl Acetic Acid : a New NMR Chiral Shift Reagent for the Stereochemical Analysis of Sulfoxides.

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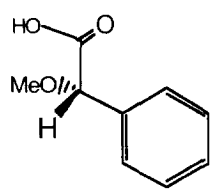
ABSTRACT : The use of (*S*)-α-methoxyphenyl acetic acid (MPAA) as a general chiral ^{1}H NMR shift reagent for the stereochemical analysis of sulfoxides is demonstrated. Using this methodology, both the enantiomeric purity and the absolute configuration of a wide variety of sulfoxides can be determined.

The stereochemical analysis of sulfoxides is becoming increasingly important as new methods for the synthesis [1,2] and biosynthesis[3] of chiral sulfoxides are developed. As part of an investigation into the mechanism of enzymic desaturation,[4] we have recently reported the use of (*S*)-(+)- α-methoxyphenyl acetic acid (MPAA) as a chiral NMR shift reagent to determine the enantiomeric purity and absolute configuration of some fatty acid sulfoxides. It was necessary to invent this reagent because all current NMR methods[5-7] for analyzing the stereochemistry of sulfoxides failed when applied to a dialkyl sulfoxide with complex spin systems. In this paper, we wish to show that the methodology we have developed is broadly applicable to a wide variety of sulfoxides. A number of representative examples (**1** -**12**) are given in Figure 1.



(S) - MPAA

A typical analytical procedure involves recording the ^{1}H NMR signals due to the α-sulfinyl hydrogens of racemic sulfoxide (dilute (ca. 1% w/v) solution in dry, DCl-free $CDCl_3$).[8] Addition of 3 equivalents of (*S*)-(+)-MPAA (Aldrich) will cause these resonances to shift downfield and to split into doublets. The magnitude of the nonequivalence is typically 0.01 - 0.03 ppm and is dependent on sulfoxide structure. (See Figure 1.) Addition of 3 equivalents of (*S*)-(+)-MPAA to a sample of enantiomerically enriched sulfoxide allows one to determine the optical purity of the latter via integration of the appropriate

pairs of signals. To date this shift reagent has been used with a 100 % success rate (ca. 60 cases) using spectrometers operating in the range of 200-500 MHz.

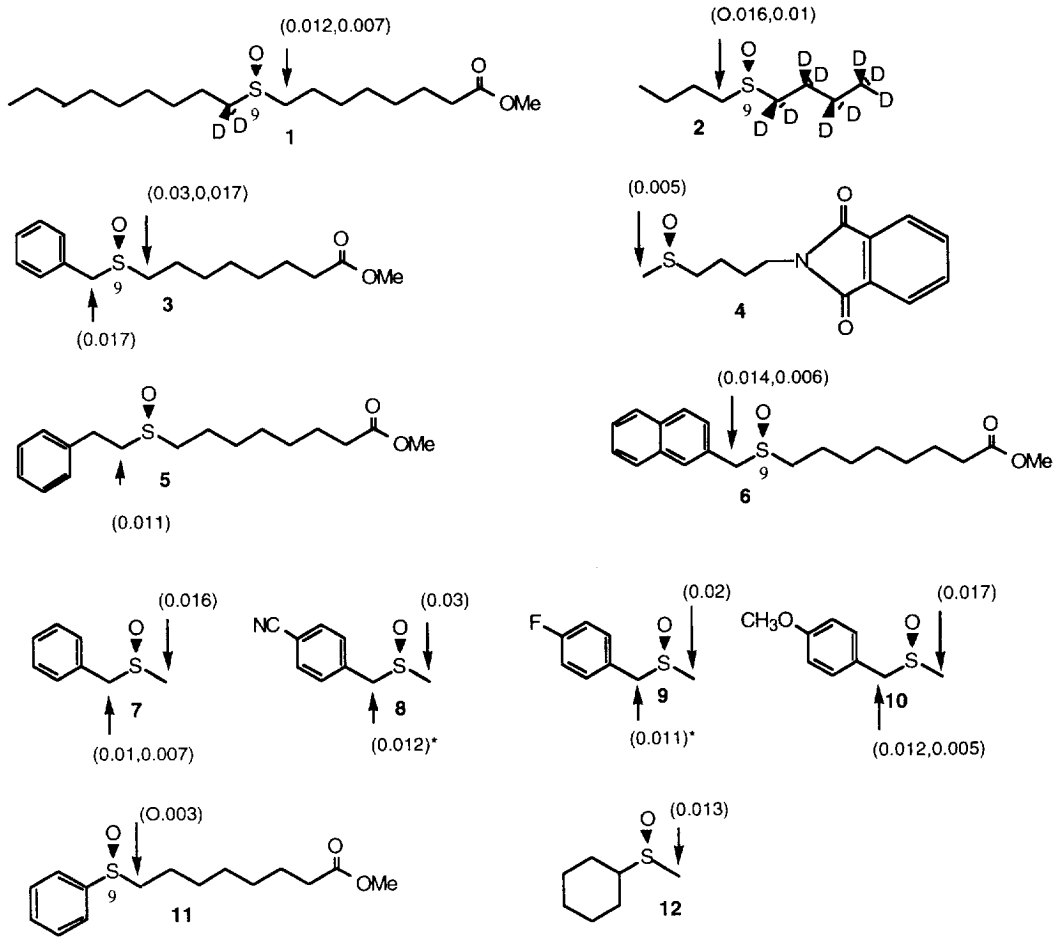


Figure 1. Various sulfoxides which have been analyzed using (*S*)-MPAA. The magnitude of the nonequivalence ($\Delta\delta$, ppm) induced by addition of the shift reagent is given in brackets. In the majority of cases, diastereotopic α-sulfinyl hydrogens have different $\Delta\delta$'s: Both values are given where applicable. *For these sulfoxides, only the upfield half of the AB q was split.

The absolute configuration of the predominant enantiomers can be deduced through the use of a Pirkle-type complexation model[6] (See Figure 2.) The ^{1}H NMR signals due to the " X " α-sulfinyl hydrogens of the (*S*)-sulfoxide depicted in Figure 1 are magnetically shielded by the aromatic ring of (*S*)-(+)-MPAA and are shifted upfield with respect to the " X" α-sulfinyl hydrogens of the (*R*)-sulfoxide. The sense of the nonequivalence is reversed for the signals due to the α-sulfinyl hydrogens on the " Y " group. This provides a convenient internal check on the correctness of the methodology. In addition, it should be

noted that methylene groups as far as 4 carbons away from the sulfinyl moiety can be affected by the shielding cone of the phenyl group. Also, ^{13}C NMR can be used as a probe in order to further validate the assignments.[4]

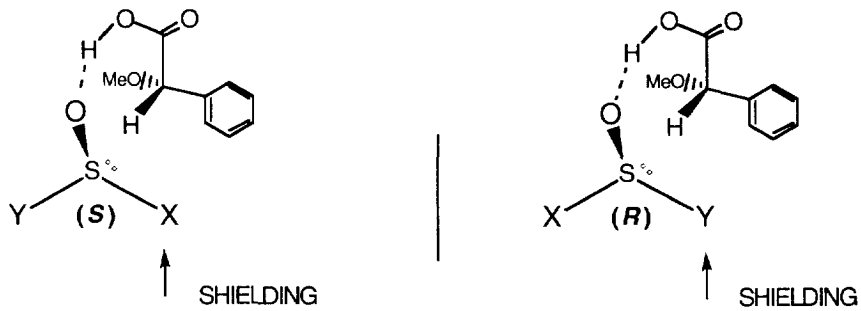


Figure 2. Binding model for the interaction of (*S*)-(+)-α-methoxyphenyl acetic acid (MPAA) with the two enantiomers of a sulfoxide.

The application of the model is illustrated for the case of (*S*)- and (*R*)- benzyl methyl sulfoxide which have been produced by microbial oxidation;[9] the absolute configuration of these sulfoxides had been previously established by synthesis.[10] (See Figure 3.)

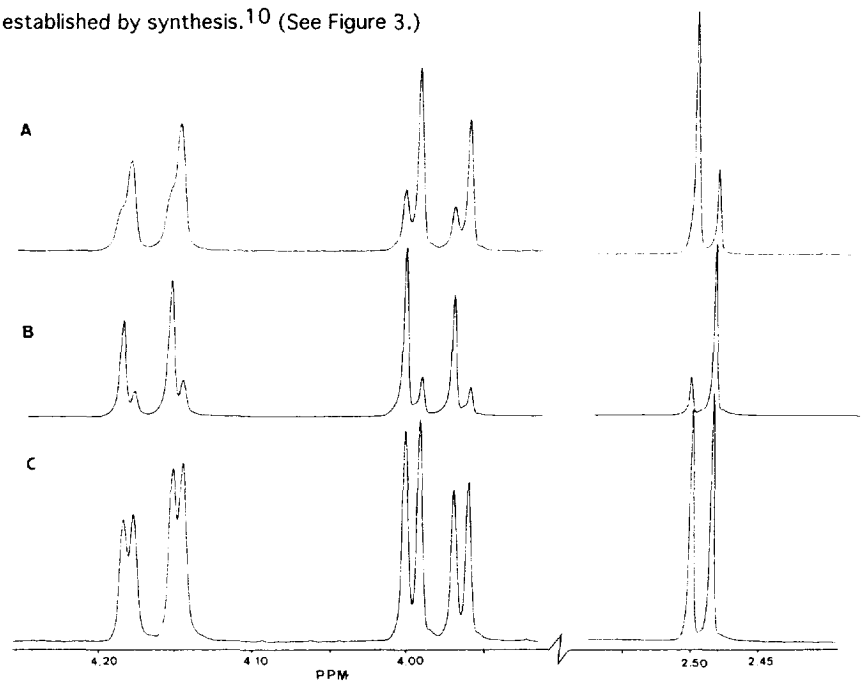


Figure 3. Effect of addition of 3 equiv. of (*S*)-(+)-MPAA on ^{1}H NMR (400 MHz) resonances due to the α-sulfinyl hydrogens of (A) (*R*)-benzylmethyl sulfoxide (48 % ee), (B) (*S*)-benzylmethyl sulfoxide. (62 % ee), (C) (±)- benzylmethyl sulfoxide produced by chemical oxidation of the corresponding sulfide.

At this point, the correctness of our complexation model is based solely on empirical evidence - i.e. we are able to correctly predict the absolute configuration of 14 chiral sulfoxides of known configuration. In addition, the assignment of absolute configuration of some 40 biological chiral sulfoxides using this method agrees with that predicted by optical rotation data. [3]

We attribute the success of our methodology to the fact that MPAA is more acidic than the Pirkle alcohol[6] or the Kagan amide.[7] As a consequence, the complex between MPAA and the sulfoxide forms readily at dilute concentrations through H-bonding to the basic sulfinyl oxygen.

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