ASSIGNMENT OF ABSOLUTE CONFIGURATION OF

SULFOXIDES BY NMR. A SOLVATION MODEL.

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We have previously pointed out that use of chiral solvent $\underline{1}$ causes the nmr spectra
of the enantiomers of a number of methyl alkyl or methyl aryl sulfoxides to be nonidentical,
and that this spectral nonequivalence allows direct determination of enantiomeric purities
and empirical assignment of absolute configuration.[1] We are concerned with the details of
the solvent-solute interactions giving rise to these effects and herein describe a
solvation model which accounts for the observed enantiomeric spectral nonequivalence and
which appears to be useful in assigning absolute configurations to configurationally unknown
sulfoxides.

Sulfoxides form 1:1 solvates with alcohols, it being generally accepted that this occurs
via hydrogen bonding to the sulfinyl oxygen. Infrared measurements show that the acidic
(pK_a 12.4) hydroxyl of $\underline{1}$ bonds strongly to sulfoxides; so strongly that, at the usual nmr
concentrations, a 2-3 fold excess of $\underline{1}$ ensures that essentially all sulfoxide is hydrogen
bonded. Figure 1 shows that little additional nonequivalence is obtained beyond a 3-fold
excess of $\underline{1}$ and that _differential_ degrees of hydrogen bonding of the sulfoxide enantiomers
cannot be essential for nonequivalence, since there is no diminishment of nonequivalence at
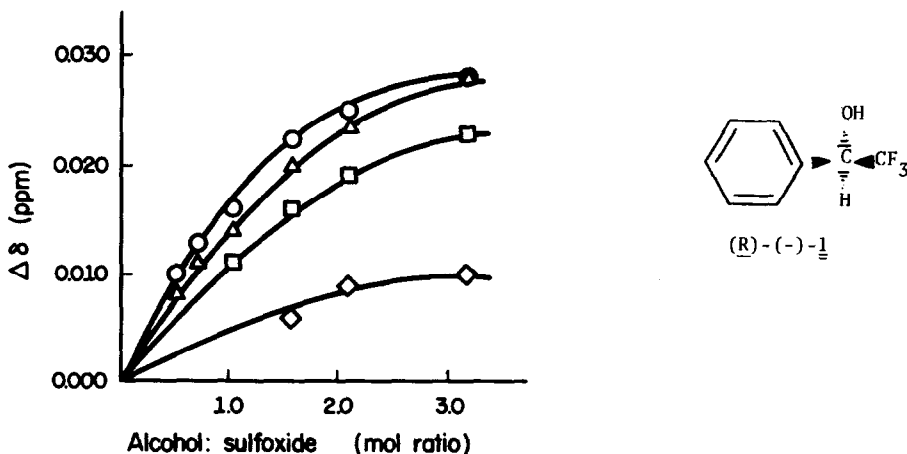high carbinol concentrations.

FIGURE 1. Plots of the chemical shift differences between enantiomers of
1.25 $\underline{M}$ methyl isopropyl sulfoxide in the presence of chiral alcohol $\underline{1}$ at 28°
in CCl_4. Each of the four proton sets show nonequivalence: O $SC\underline{H}_3$,
△ $CC\underline{H}_3$, (low field), ◇ $CC\underline{H}_3$ (high field), □ $C\underline{H}$.

While there can be no question concerning the formation of short-lived, rapidly exchanging
diastereomeric solvates, we suggest that the bulk of the observed nonequivalence stems from the
solvates assuming rather specific (and transient) conformations owing to the existence of weak
intramolecular interactions between the lone electron pair of sulfur and the carbinyl hydrogen
of 1. The inductive effects of the proximate electron withdrawing groups (trifluoromethyl,
hydroxyl, phenyl) serve to render the carbinyl hydrogen somewhat acidic and will direct an
electric dipole roughly along the C-H bond axis. Sulfur atoms in sulfoxides are known to be
basic and nucleophilic. In effect then, alcohol 1 is postulated to chelate about the sulfoxide
to afford conformations 2 and 3 shown for the solvates derived from (R)-1 and the enantiomers
of methyl i-propyl sulfoxide.
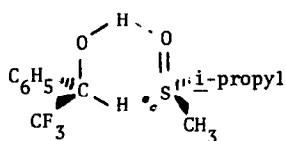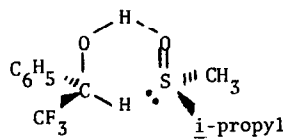
(R,R)-Solvate 2   (R,S)-Solvate 3

In the conformations shown, note that i-propyl is cis to the phenyl in the (R,R)
diastereomer 2, and trans in the (R,S) diastereomer, 3. The opposite situation holds for the
sulfinyl methyls. Because of shielding by the phenyl, one expects the i-propyl resonances to
occur at higher field for the (R,R) solvate than for the (R,S) solvate. The converse is ex-
pected for the sulfinyl methyl resonance. Since solvation is a fast exchange reaction,
these time averaged chemical shift differences are observed in chiral 1 but not racemic 1.

This model is consistent with the data reported[1] earlier for ten partially resolved
methyl alkyl and methyl aryl sulfoxides of known configuration. In addition, a number of
partially resolved configurationally known p-tolyl alkyl (and alkenyl) sulfoxides have since
been similarly examined.[2] All give results consistent with this model. In every instance,
the senses of nonequivalence of the two groups on either side of sulfur are (when dis-
cernable) opposite, the senses correlate with known configurations, and the senses of
nonequivalence for all protons within a given group are (when discernable) always the same.
Understandably, the magnitude of nonequivalence diminishes with increasing distance from
sulfur.

As expected on the basis of this model, no difference in size or nature of the sulfoxide
substituents is required; the methyls of DMSO and the ethyls of DESO are perceptably diastereo-
topic in the presence of chiral 1. Substitution of a group of lesser magnetic anisotropy
(i.e., cyclohexyl) for phenyl in chiral 1 spoils its ability to promote nonequivalence in

sulfoxide spectra whereas replacement of phenyl with α-naphthyl, 3-pyrenyl, or 9-anthryl, groups of greater shielding ability, affords chiral solvents[3] giving 2-5 fold nonequivalence enhancement of the appropriate senses. Several of these newly prepared alcohols give pre-liminary indication of being even more useful than 1.

Further circumstantial support for the model may be advanced. Figure 2 shows the temperature dependence of the nmr nonequivalence of the four enantiomeric sets of protons in methyl i-propyl sulfoxide in chiral 1. The magnitudes of the Δδ's for all sets increase by approximately the same factor (2.1 ± .25 from least square lines) over the range 70° to -30°. This is understandable provided essentially all nonequivalence stems from one type of conformation and the effect of diminished temperature is simply to cause this type of stabilized conformation to be more heavily populated.[4] If a variety of conformations made dissimilar contributions toward the nonequivalence of the four proton sets, one would not necessarily expect the Δδ's for all sets to change in the same proportion as the temperature is varied.
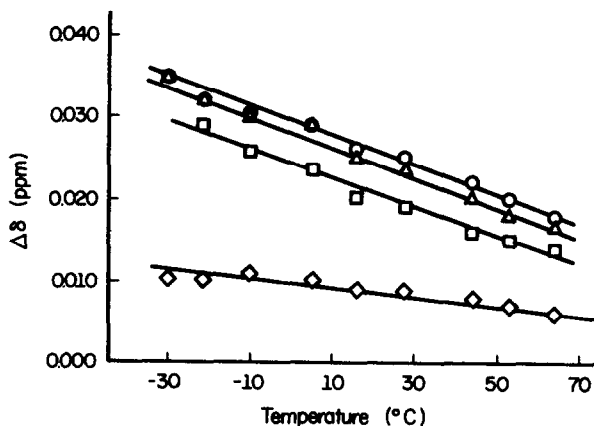

FIGURE 2. Effect of temperature upon the magnitude of the chemical shift difference between methyl isopropyryl sulfoxide enantiomers in the presence of chiral alcohol 1 in CCl_4. Alcohol-sulfoxide-solvent mol ratio is 2:1:5. Symbols are as in Figure 1.

It should also be noted that sulfoxides can additionally form weak 1:2 complexes with alcohols[5] and with chloroform[6]. While the structures of these 1:2 complexes are unknown, the existence of a 1:2 sulfoxide-chloroform complex encourages the view that an acidic C-H can interact with the lone pair of sulfur electrons, especially since, in the postulated chelate, the interaction is <u>intramolecular</u> and apt to contribute more importantly than if intermolecular.

Finally, it should be pointed out that interactions between sulfur and the π-electrons of alcohol <u>1</u> analagous to the collision complexes depicted by Ledaal[7], do not seemingly suffice to account for the observed spectral nonequivalence. Such interactions may well occur but simply be "wasted" so far as nonequivalence is concerned.

REFERENCES

1. W. H. Pirkle and S. D. Beare, <u>J. Amer. Chem. Soc.</u>, <u>90</u>, 6250 (1968).

2. R. L. Muntz, PhD Thesis, University of Illinois, Urbana, Illinois (1972).

3. Since some of these compounds are solid, the term "chiral additive" is more accurate. The preparation and resolution of these compounds is being reported elsewhere.

4. Temperature reduction cannot substantially increase the extent of the primary hydrogen bonding interactions since this equilibrium lies far to the right even at 30^0.

5. S. Zmant, <u>Spectrochim Acta</u>, <u>22</u>, 1107 (1966).

6. A. L. McClellan, S. W. Nicksic, and J. C. Guffy, <u>J. Mol. Spectrosc.</u>, <u>11</u>, 340 (1963).

7. T. Ledaal, <u>Tetrahedron Lett.</u>, 1683 (1968).