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DIASTEREOMERIC INTERACTIONS IN SOLUTION [*]

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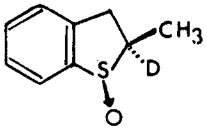
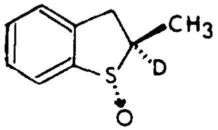
Recently it has been reported[1,2,3,4,5] that enantiomeric molecules show different nmr spectra (chemical shifts) when dissolved in an optically active solvent. For simple enantiomeric molecules, the differential proton chemical shifts at room temperature have been quite small[2,3], of the order of 0.03 ppm, although more complex molecules (with many asymmetric centers) apparently show a larger effect[5]. The present study illustrates the conditions necessary for the observation of diastereomeric interactions of two components as solutes in an optically inactive solvent.


(+)I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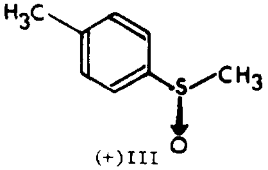
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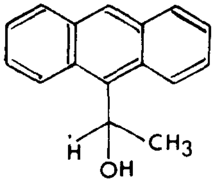
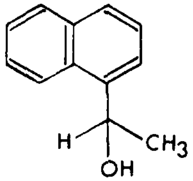

(±)IV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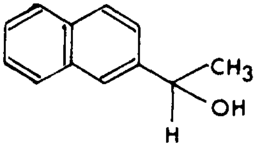
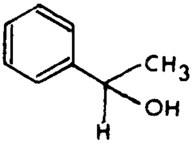

(±)VI


(±)VII

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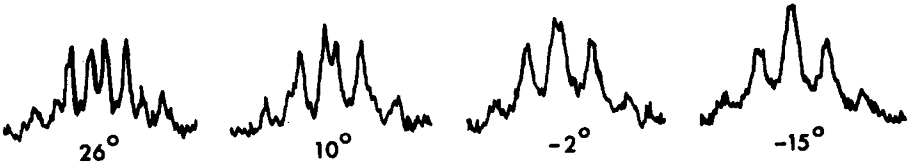
The diastereomeric sulfoxides (+)I, (-)II and sulfoxide (+)III were available in optically active form from another investigation[6]. Spectra were taken of solutions 0.3 M in (+)I, (-)II, or (+)III, together with an approximately equimolar concentration of the carbinols (±)IV, (±)V, (±)VI, or (±)VII, in CCl_4 or $CDCl_3$. For all combinations of carbinol and sulfoxide, except those involving (+)III and the combinations ((-)II, (±)VI) and ((-)II, (±)VII) (see Table I), the methine protons were two overlapping chemically shifted quartets[7] (see Figure I), one for each of the enantiomers. Spectra at 100 MHz confirmed this interpretation. Only one chemical shift was observed for the methyl band of the carbinol in these systems; the aromatic protons gave very complex bands which were not amenable to the detection of diastereomeric interactions.

The chemical shift difference between the carbinol enantiomers would be expected to depend on the nature of the interactions between the molecules in the system, as well as on the magnetic properties of these molecules. The alcohols are hydrogen-bonded at the concentrations used, at least in part to the sulfoxide, as shown by infrared and nmr (chemical shift) studies on pure alcohol and alcohol-sulfoxide mixtures. Others[8] have estimated $OH \cdots O \leftarrow S$ bonds to be about the same strength or slightly weaker than $OH \cdots OH$ bonds. Addition of dimethyl sulfoxide (DMSO) to a solution of alcohol and sulfoxide reduced the chemical shift difference, presumably because the DMSO displaced the less basic aromatic sulfoxide from the hydrogen-bonded complex. About two equivalents of DMSO removed the effect completely. Addition of benzyl alcohol had a similar, but smaller, effect. Chloroform as a solvent decreased the shift differences, presumably because of its dipolar and hydrogen-bonding interactions with the solutes. Thus, in our systems, hydrogen-bonding is necessary for the observation of diastereomeric chemical shift differences.

FIGURE I

NMR Spectra of Alcohol Methine Proton at Various Temperatures, (±)IV, (+)I



Increasing the sulfoxide:alcohol ratio increased the shift difference, although the change became small beyond 2:1 mole ratio. An increase in concentration of the components at constant mole ratio also caused an increased shift difference which tapered off at high concentrations. The shift differences were temperature-dependent (Figure I, Table I), decreasing with increasing temperature. The hydroxyl proton, shifted downfield in the presence of sulfoxide, was shifted further with decreasing temperature, while most non-aromatic protons were shifted upfield. These shift variations are consistent with equilibrium formation of hydrogen-bonded complexes.

TABLE I

Shift Difference Between Methine Protons of Enantiomeric Aryl Methyl Carbinols in Mixtures of Carbinols and Optically Active Sulfoxides

Sulfoxide	Shift Difference (Hz)[a]								
	Anthryl Methyl Carbinol, (±)IV[b]								
	CCl$_4$			CDCl$_3$					
	-25°	0°	25°	-50°	-25°	0°	25°		
(+)I	7.2	5.0	3.9 (7)[c]	4.0	3.1	2.1	1.2		
(-)II	6.3	4.2	3.1 (6)[c]	-	-	-	-		
(+)III	-	~ 0	~ 0	-	-	-	~ 0		
	Naphthyl Methyl Carbinols in CCl$_4$[d]						Phenyl Methyl Carbinol, (±)VII, in CCl$_4$[e]		
	α-isomer, (±)V			β-isomer, (±)VI					
	-25°	0°	25°	-25°	0°	25°	-25°	0°	25°
(+)I	4.5	3.6	-	2.2	1.9	-	1.6	1.2	0.8
(-)II	3.8	3.0	2.1	~ 0	~ 0	~ 0	~ 0	~ 0	~ 0

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a. Spectra taken on a Varian A-60 spectrometer. The shift differences are graphical interpolations from spectra taken at 15° intervals; each point on the graph was an average of several scans, average deviation ~ 0.3 cps.

b. 0.28 M in alcohol and sulfoxide.

c. Chemical shift differences (±1 Hz) at ambient temperature and at 100 MHz. We are grateful to Dr. K. L. Servis of the University of Southern California for taking these spectra.

d. ~ 0.27 M alcohol, ~ 0.34 M sulfoxide.

e. 0.3 M in alcohol and sulfoxide. (+)III showed no effect with V, VI, or VII.

The importance of π-π interaction in determining the geometry of the hydrogen-bonded complex is uncertain. The uv spectrum of the mixture of (+)I and (±)IV, with IV one-fifth the usual (nmr) concentration, was simply the sum of those of the pure compounds. However, the fact that anthryl > naphthyl > phenyl in shift differences, suggests that more extensive aromatic systems result in increased interaction or at least in larger differences in magnetic environment for the diastereomeric methine protons. Other influences such as steric effects should be identical for the β-naphthyl and phenyl compounds but the differential shift is greater for the π-electron-rich β-naphthyl compound. Steric effects are nevertheless important and must be at least in part responsible for the difference between the α- and β-naphthyl carbinols and between (+)I (*cis*) and (-)II (*trans*)[9]. For the carbinols, this difference may be due to some restriction of rotation in the α-isomer by the *peri*-hydrogen. This effect would be even greater in the anthryl carbinol but absent in the β-naphthyl and phenyl carbinols. The least rigid sulfoxides and alcohols, (+)III, (±)VI, and (±)VII, result in the smallest shift differences, presumably because the differential effect is partly averaged by contributions from many rotamers.

Therefore, in our systems, the chemical shift difference of the methine proton becomes larger as the hydrogen-bonded sulfoxide-carbinol complex becomes geometrically more constrained.

Acknowledgments

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4. W. H. Pirkle and T. G. Burlingame, *Tetrahedron Letters*, 4039 (1967).
5. J. C. Jochims, G. Taigel and A. Seeliger, *Tetrahedron Letters*, 1901 (1967). This study was carried out using the same enantiomer of the solute in each of the enantiomeric phenyl methyl carbinols.
6. The sulfones corresponding to I and II (D. J. Cram and T. A. Whitney, *J. Am. Chem. Soc.*, **89**, 4651 (1967)) were reduced with lithium aluminum hydride and reoxidized at 0° with hydrogen peroxide in acetic acid. The diastereomeric sulfoxides I and II were separated by chromatography on silica gel, and gave satisfactory carbon and hydrogen analyses (undeuterated I and II). Sulfoxide III: J. Day and D. J. Cram, *J. Am. Chem. Soc.*, **87**, 4398 (1965). Carbinol (±)IV was prepared by F. Wudl in connection with other work.
7. Spectra were taken under conditions where the OH proton resonance was a single line because of intermolecular OH proton exchange. Thus the methine proton was effectively decoupled from the OH Proton.
8. C. P. Rader, *J. Am. Chem. Soc.*, **88**, 1713 (1966), and references cited therein.
9. Evidence for the configurations indicated: The ORD of (-)I (with H instead of D) shows a typical sulfoxide Cotton effect curve, with a negative rotation at long wavelengths, followed by positive rotation at shorter wavelengths, indicating the S-configuration at sulfur (K. Mislow, M. M. Green, P. Laur, J. T. Mellillo, T. Simmons, and A. L. Ternay, Jr., *J. Am. Chem. Soc.*, **87**, 1958 (1965)). Compound (+)II (H) is similar to a typical R-sulfoxide, but the wavelength separation between the major Cotton effects is greater. Compounds (-)I and (+)II have the same configuration at carbon and opposite at sulfur[6]. *Cis* and *trans* isomers were assigned on the basis of their retention times on silica gel.