

Nonequivalence of the Nuclear Magnetic Resonance Spectra
of Enantiomers in Optically Active Solvents III

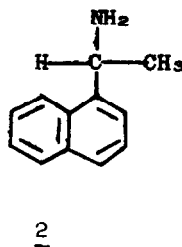
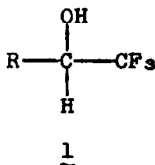
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We wish to point out that our previous report (1,2) of the use of an optically active solvent to cause nonequivalence of the F^{19} nmr spectra of the enantiomers of 2,2,2-trifluoro-1-phenylethanol, (1 $R-C_6H_5$), is not a unique instance of this phenomenon: the enantiomers of type 1 alcohols typically have dissimilar F^{19} nmr spectra when optically active α -(1-naphthyl) ethylamine, 2 is employed as a solvent.



The trifluoromethyl resonances of the enantiomers of type 1 alcohols are normally coincident and are split into doublets by the carbinyl protons ($J_{HF} = \text{ca. } 7 \text{ Hz}$). Weaker long range hydrogen-fluorine couplings may also

be observed. In the presence of optically active 2, the enantiomeric trifluoromethyl groups have different chemical shifts and two sets of doublets (with possible fine structure) are observed. The relative intensities of the two sets of resonances reflect the relative amounts of the enantiomeric alcohols. Owing to the generality of this method, it is now possible to determine the optical purities of samples of type 1 alcohols by nmr spectroscopy. Owing to the fast exchange of solvent between solute-solvent aggregates, variation of the optical purity of the solvent will change the relative chemical shifts but not the relative intensities of resonances originating from enantiomeric solutes. Consequently, such optical purity determinations are absolute and no standard of known optical purity is required.

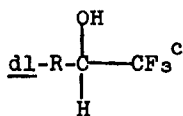
Table I indicates the magnitude of $\Delta\delta$ (the chemical shift difference between the enantiomeric trifluoromethyl resonances) for several enantiomeric type 1 alcohols. The $\Delta\delta$ values reported are not the maximum obtainable but are those observed at 56.4 MHz for samples at 20° having 2.0:1.0:5.0 mole ratios of optically active amine 2, racemic alcohol 1, and fluorotrichloromethane. The chemical shift difference, $\Delta\delta$, is enhanced by increasing the amine concentration, decreasing the temperature at which the spectra are obtained (2,3), or by increasing the optical purity of amine 2. The use of racemic 2 reduces $\Delta\delta$ to zero. The use of an optically inactive diluent to reduce the viscosity of the solutions (and thereby improve spectral resolution) will generally diminish $\Delta\delta$.

These observations are consistent with the hypothesis that the observed enantiomeric spectral nonequivalence arises through rapid reversible formation of diastereomeric solvates in which amine-alcohol hydrogen bonding is the principle mode of interaction. The observation that the racemic methyl ether of 2,2,2-trifluoro-1-phenylethanol shows no detectable spectral nonequivalence

under these conditions lends strong support to this hypothesis, since one would not expect this ether to associate as strongly with amine 2 as would the corresponding alcohol.

TABLE I

Comparison of F^{19} NMR Spectral Nonequivalence of Enantiomeric Type 1 Alcohols.



| R | $F^{19} \Delta\delta (\text{H}_z)$ | $F^{19} \delta^a (\text{H}_z)$ |
|----------------------------------------|------------------------------------|--------------------------------|
| C_6H_5 | $3.3 \pm .1$ | 4373 ± 1 |
| m- $\text{CH}_3\text{-C}_6\text{H}_4$ | 3.1 | 4353 |
| m- $\text{CF}_3\text{-C}_6\text{H}_4$ | 2.6 | 4394 |
| m- $\text{NO}_2\text{-C}_6\text{H}_4$ | 2.2 | 4364 |
| m- $\text{NH}_2\text{-C}_6\text{H}_4$ | 3.5 | 4352 |
| m- $\text{F-C}_6\text{H}_4$ | 2.9 | 4363 |
| o- $\text{F-C}_6\text{H}_4$ | 2.9 | 4385 |
| p- $\text{F-C}_6\text{H}_4$ | 3.4 | 4380 |
| p- $\text{CH}_3\text{O-C}_6\text{H}_4$ | 3.7 | 4389 |
| 2,4-dinitrophenyl | 5.8 | 4347 |
| α -naphthyl | 4.6 | 4277 |
| β -naphthyl | 3.8 | 4326 |
| α -pyridyl | ca. 0.4 ^b | 4326 |
| α -thienyl | 3.0 | 4396 |
| methyl | 1.1 | 4559 |
| cyclohexyl | 2.5 | 4215 |
| t-butyl | ca. 3.5 ^b | 4044 |

- (a) Average chemical shift of the two enantiomeric resonances upfield from internal fluorotrichloromethane.
- (b) Estimated from values obtained at 94 MH_z and 25°.
- (c) Alcohols listed in this table either correspond in physical properties to those previously reported for authentic samples or possess the correct elemental composition. In all cases, infrared and nmr spectra are consistent with the assigned structures.

The variations in the $\Delta\delta$ values listed in Table I are attributed to varying degrees of amine-alcohol interaction and the varying differences in

conformational preferences of the short lived diastereomeric solvates. Note that $\Delta\epsilon$ is unusually small when R= α -pyridyl and unusually large when R=2,4-dinitrophenyl. In the first instance, intramolecular hydrogen bonding between the hydroxyl group and the pyridine nitrogen* can compete with intermolecular hydrogen bonding with amine 2. Only intermolecular association can lead to enantiomeric spectral nonequivalence. In the second case, π complexing of the 2,4-dinitrophenyl group with amine 2 could augment hydrogen bonding as an intermolecular associative interaction and possibly favor conformations important to enantiomeric spectral nonequivalence. On standing, solutions of this dinitrophenyl alcohol and amine 2 deposit crystalline material having an elemental composition and infrared and nmr spectra consistent with those of a 1:1 adduct. Chromatography of the adduct on silica gel regenerates the free alcohol and the amine. The exact structure of this adduct is not yet known.

* Infrared spectra of 0.01M solutions of 2,2,2-trifluoro-1-(α -pyridyl)-ethanol in cyclohexane show the hydroxyl stretching band to be broad and at a frequency (3375 cm^{-1}) indicative of hydrogen bonding. At this concentration, 2,2,2-trifluoro-1-phenylethanol shows a narrow stretching band at 3620 cm^{-1} .

Acknowledgment

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REFERENCES

1. W. H. Pirkle, J. Am. Chem. Soc., 88, 1837 (1966).
2. T. G. Burlingame and W. H. Pirkle, ibid., 88, 4294 (1966).
3. J. C. Jochims, G. Taigel and A. Seeliger, Tetrahedron Letters, 1901 (1967).