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OPTICALLY ACTIVE NMR SOLVENTS VI. THE DETERMINATION OF OPTICAL PURITY AND ABSOLUTE CONFIGURATION OF AMINES.

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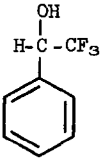
Previous papers in this series (1-5) have shown that the enantiomers of secondary and tertiary alcohols may be caused to have nonequivalent nmr spectra through the use of appropriate optically active amines as solvents. The converse of this phenomenon also obtains; amine enantiomers may have nonequivalent nmr spectra in optically active alcohols. Preliminary investigations indicate that the optical purities and absolute configurations of the amine solutes may be determined in this manner.

For example, in S(+)-2,2,2-trifluorophenylethanol, 1 (α^{25}D +41°; neat, l= 1), R(+)-α-(1-naphthyl)ethylamine, 2, of 16% optical purity, shows its methine resonance as two unequally intense quartets and its methyl resonance as two unequally intense doublets. The chemical shift differences between the similar multiplets, 2.2 Hz and 0.7 Hz respectively at 60 MHz, are dependent not only upon spectrometer frequency but also upon optical purity of the solvent, temperature, and concentration. In the preceding experiment, the methine and methyl resonances of the major amine enantiomer lie to higher and lower fields respectively than do the corresponding resonances of the minor enantiomer. The relative intensities of the two methine quartets (or the two methyl doublets) reflect the optical purity of the amine solute while the senses of nonequivalence (i.e., the relative field positions of the corresponding resonances arising from the major and minor enantiomers) observed for the methyl and methine resonances are indicative (for a solvent of given chirality) of the absolute configurations of the two enantiomers. Table I illustrates the degree and sense of nmr nonequivalence observed for the spectra of nine partially resolved type 3 amines in optically active 1 as solvent.



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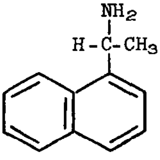

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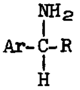


$$\mathrm{Ar}-\overset{\displaystyle \mathrm{NH_2}}{\underset{\displaystyle \mathrm{H}}{\mathrm{C}}}-\mathrm{R}$$

3

TABLE I

NMR Absolute Configurational Correlations for Type **3** Amines in *S*(+)-2,2,2-Trifluorophenylethanol[a] and Related Carbinols

Carbinol Solvent	Ar	R	α^{25}_{D}[b]	% Optical Purity	$\Delta\delta$[g] and Relative Field Position of Largest Enantiomeric Resonance		Configuration of Predominant Enantiomer	
					Carbinyl Proton	R	Known	Predicted
(+)-**1**[a]	β-naphthyl	CH_3	-7.56°[f]	36[d]	3.0, low	----	*S*(6)	
"	α-naphthyl	C_2H_5	$+4.57^{\circ}$	15[e]	2.9,[h] high	----[h]		*R*
"	α-naphthyl	CH_3	+[c]	16[e]	2.2,[h] high	1.2, low	*R*(7-9)	
"	phenyl	CF_3	-8.01°[i]	33[e]	2.7, low	----		*R*
"	phenyl	CH_3	-6.26°	16[d]	1.7, low	----	*S*(10)	
"	*p*-CH_3O-C_6H_4	CH_3	$+21.62^{\circ}$	60[e]	3.0, high	----	*R*(11)	
"	*p*-NO_2-C_6H_4	CH_3	$+3.43^{\circ}$	17[d]	----	----	*R*(12)	
"	α-thienyl	CH_3	$+1.38^{\circ}$	24[e]	1.5, high	1.4, low		*R*
(-)-**5**[j]	α-thienyl	CH_3	$+1.38^{\circ}$	24[e]	2.5, low	3.4, high		*R*
"	α-naphthyl	CH_3	+[c]	16[e]	6.2, low	1.5, high	*R*(7-9)	
"	phenyl	CF_3	-8.01°[i]	33[e]	13.8, high	----		*R*
"	*p*-NO_2-C_6H_4	CH_3	$+3.43^{\circ}$	17[d]	5.8, low	----	*R*(12)	
"	cyclohexyl	CH_3	0	0	----	----	(+)-*S*(13)	
(*R*)-**6**[k]	α-naphthyl	CH_3	+[c]	25[c]	----	----	*R*(7-9)	

[a] Optical purity ≥ 90% (as determined by polarimetry and F^{19} nmr spectrum (+)-**2**).

[b] Rotations are those observed for neat samples, *l*=1, unless otherwise specified.

[c] Prepared from known amounts of the optically pure enantiomers.

[d] Obtained polarimetrically.

[e] Calculated from peak height measurements.

[f] Specific rotation (*c* 23, absolute ethanol).

[g] Chemical shift difference (in Hz) between two enantiomeric resonances at 30°C and 100 MHZ (H^1) or 94.1 MHz (F^{19}) unless otherwise noted. Samples have 2:1:3 mole ratios of carbinol, amine and $CFCl_3$ respectively. A dashed line denotes no observable chemical shift difference under the conditions specified.

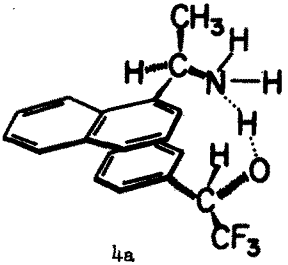
[h] Measured at 40°C and 60 MHz.

[i] Specific rotation (*c* 12.1, absolute ethanol).

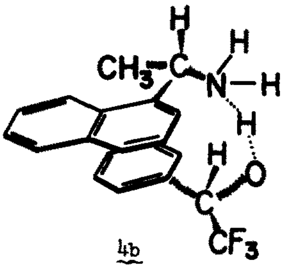
[j] Values obtained using *R*(-)-2,2,2-trifluoro-α-naphthylethanol (**5**) of 65% optical purity and normalized to 100% optical purity. The optical purity and absolute configuration of (-)-**5** was established by F^{19} nmr in (+)-**2** as solvent (4).

[k] Values obtained using (*R*)-2,2,2-trifluorocyclohexylethanol, **6**, as solvent, prepared by stereospecific hydrogenation of optically pure *R*(-)-**1**.

We feel that the relative and absolute senses of nonequivalence observed for the methyl and methine resonances in Table I may be rationalized. Hydrogen bonding leads to the formation of conformationally mobile diastereomeric solvates which are capable of assuming conformations in which secondary π-π interactions between solvent and solute are possible. While conformations similar to 4a may not necessarily predominate, it seems likely that only such conformers contribute appreciably to the observed spectral differences between the diasteromeric solvates. Conformation 4a depicts the solvate diastereomer derived from R-(+)-amine 2 and S-(+)-alcohol 1, both of known stereochemistry (7-9,14). For the analogous conformation, 4b, of the solvate diastereomer derived from S-(-)-amine 2 and S-(+)-alcohol 1, the positions of the methyl group and the methine proton are simply interchanged. While conformations 4a and 4b need not be equally populated, their contributions to the average magnetic environment of the methyl and methine protons of partially resolved amine 2 are such as to shield the methyl protons of (-)-2 and to deshield the methine proton of (-)-2 more than that of (+)-2. Using this model, absolute configurations have been suggested for the configurationally unassigned amines in Table I.



4a



4b

On the basis of the preceding model, one would expect that for comparable optical purities, 2,2,2-trifluoro-α-naphthylethanol, 5, would be superior to carbinol 1 in promoting spectral nonequivalence of type 3 amines while 2,2,2-trifluorocyclohexylethanol, 6, would be expected to be inferior in this regard to 1. This is indeed the case (see Table I); the ability of these solvents to cause nonequivalence of the nmr spectra of the enantiomers of type 3 amines parallels the relative abilities of naphthyl, phenyl and cyclohexyl groups to π-complex and parallels the magnitudes of the magnetic anisotropies associated with these groups.

Despite the success of this model in rationalizing the nonequivalence phenomenon, we wish to emphasize that this model is naive and that it takes no explicit cognizance of steric factors etc. While we expect that the model will be further refined, its present utility is clear. The model is being further tested and is being used to design more efficacious optically active solvents.

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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. W. H. Pirkle and T. G. Burlingame, Tetrahedron Letters, 4039 (1967).
4. W. H. Pirkle and S. D. Beare, J. Am. Chem. Soc., **89**, 5485 (1967).
5. W. H. Pirkle and S. D. Beare, Tetrahedron Letters, 2579 (1968).
6. V. M. Patapov, J. M. Dem'yonovich, and A. P. Terent'ev, Zh. Obshch. Khim., **35**, 1538 (1965).
7. H. Wolf, E. Bunnenberg, and C. Djerassi, Ber., **97**, 533 (1964).
8. M. E. Warren, Jr., and H. E. Smith, J. Am. Chem. Soc., **87**, 1757 (1965).
9. K. Mislow, J. Jacobus, M. G. B. Drew, D. H. Templeton, and A. Zalkin, unpublished work.
10. W. Leithe, Ber., **64**, 2827 (1931).
11. J. H. Brewster and S. F. Osman, J. Am. Chem. Soc., **82**, 5754 (1960).
12. A. P. Terent'ev and V. M. Patapov, Zh. Obshch. Khim., **27**, 1092 (1957).
13. W. Leithe, Ber., **65**, 660 (1932).
14. H. M. Peters, D. M. Feigl, and H. S. Mosher, Abstracts of papers presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Florida, April, 1967.