

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY IN OPTICALLY ACTIVE SOLVENTS. V.
THE DETERMINATION OF THE ABSOLUTE CONFIGURATION OF (+)- α -HYDROXY- α -
TRIFLUOROMETHYLPHENYLACETIC ACID

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Mosher has pointed out (1) that although the optical rotatory dispersion spectra of optically active α -hydroxy acids and their configurationally similar methyl ethers generally have identically signed Cotton effects, optically active α -hydroxy- α -trifluoromethylphenylacetic acid, 1, and its configurationally similar methyl ether have oppositely signed Cotton effects. This anomaly presently precludes confident assignment of absolute configuration to 1 by means of ORD.

It has recently been shown (2) that the use of an appropriate optically active solvent causes the nmr spectra of diastereomerically solvated enantiomers to differ and that the sense of nmr nonequivalence* may be used to assign absolute configurations of both enantiomers. This method has been employed to determine the absolute configuration of (+)-1.

Dextrorotatory α -(1-naphthyl)ethylamine, used as solvent throughout this nmr study, causes the carbomethoxy resonances of the enantiomers of partially resolved methyl α -hydroxy- α -trifluoromethylphenyl acetate, 2, to have observably different chemical shifts (see Table I and Figure I) at 39°C and 60 MHz, the levorotatory enantiomer having its carbomethoxy resonance at higher field than the dextrorotatory enantiomer. Similarly, the carbomethoxy resonances of the levorotatory enantiomers of methyl mandelate, 3, and methyl atrolactate, 4, and the dextrorotatory enantiomer of methyl α -hydroxy- α -trichloromethylphenyl acetate, 5, occur at higher field (see Table I) than do those of their mirror images.

*The term "sense of nonequivalence," used for the sake of brevity, refers to the field position of a resonance of an enantiomer relative to that of its enantiomorph (in a given optically active solvent). If the solute is partially resolved, the larger of the two sets of unequally intense resonances will arise from the predominant enantiomer whose sign of rotation may be determined polarimetrically.

Table I

Chemical Shift Differences ($\Delta\delta$) Between the Carbomethoxy Resonances of the Enantiomers of Partially Resolved Methyl α -Hydroxyphenyl Acetates

Ester	$\Delta\delta$ (Hz) ^a	Specific Rotation	% Optical Purity	Relative Field Position of Largest Carbomethoxy Resonance
<u>2</u>	0.5	$\alpha^{25D} +5.52^\circ$ (neat, $\underline{1} = 1$)	37 ^b	Low
<u>3</u>	1.9	$[\alpha]^{25D} -167^\circ$ (\underline{c} 1.02, CHCl ₃)	95 ^c	High
<u>4</u>	0.9	$[\alpha]^{25D} -7.95^\circ$ (\underline{c} 4.4, EtOH)	21 ^a	High
<u>5</u>	0.4	$[\alpha]^{25D} -32.0^\circ$ (\underline{c} 10.7, EtOH)	58 ^e	Low

^aSpectra were taken on either Varian A56/60A or A-60A nmr spectrometers at 39°C. The samples were composed of amine: ester: CFCl₃ in 2:1:3 mole ratios.

^b(+)-2 was methylated (MeI, Ag₂O) to the corresponding (-)-methyl α -methoxy- α -trifluoromethyl-phenyl acetate, $\alpha^{25D} -46.33^\circ$ (neat, $\underline{1} = 1$), which Mosher reports as the methyl ester (1), $\alpha^{25D} -48.64^\circ$ (neat, $\underline{1} = 1$) for a sample of 39% optical purity.

^cReported [W. A. Bonner, *J. Am. Chem. Soc.*, **73**, 3126 (1951)] $[\alpha]^{25D} -174.2^\circ$ (\underline{c} 0.58, CHCl₃) for the optically pure enantiomer.

^dThis rotation is given for the acid rather than the ester. Reported [W. A. Bonner, J. A. Zgeric, and G. A. Casaletto, *J. Am. Chem. Soc.*, **74**, 5086 (1952)] $[\alpha]^{25D} +37.7^\circ$ (\underline{c} 3.5, EtOH) for the optically pure acid; $[\alpha]^{25D} +5.0^\circ$ (\underline{c} 4.9, EtOH) for the corresponding ester 4.

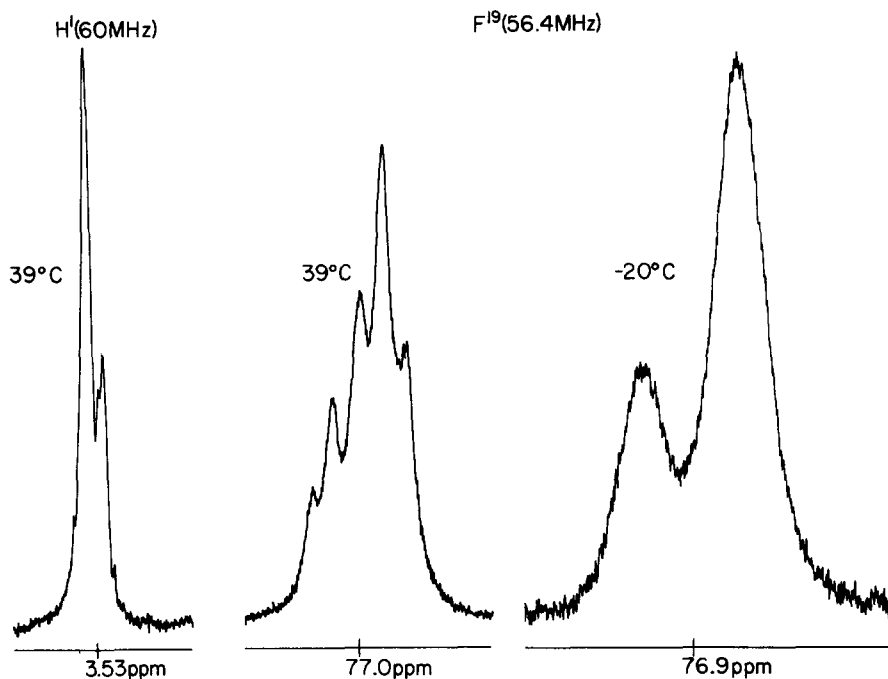
^ePartially resolved atrolactic acid, $[\alpha]^{25D} +21.9^\circ$ (\underline{c} 5.3, EtOH), of 58% optical purity (see preceding footnote) is easily chlorinated in refluxing CCl₄ to the (-)-trichloro acid, $[\alpha]^{25D} -20.8^\circ$ (\underline{c} 10.3, EtOH), which leads to (-)-5 upon diazomethane esterification. Chlorination of racemic atrolactic acid leads to the unreported racemic α -hydroxy- α -trichloromethylphenylacetic acid, mp 135.5-6°, having an elemental composition, infrared and nmr spectra in accord with the assigned structure.

Lavorotatory 3 and 4 are known (3,4) to have the R configuration as shown, while (+)-5 must have the R configuration depicted since it is derived from (-)-atrolactic acid via free radical chlorination and diazomethane esterification. Clearly, substitution of either a methyl group or a trichloromethyl group for the carbonyl proton of 3 has not altered the observed sense of carbomethoxy nonequivalence. From the assumption that substitution of a trifluoromethyl group for either the carbonyl proton of 3, the C-methyl group of 4 or the trichloromethyl group of 5 will also fail to change the observed sense of carbomethoxy nonequivalence, it follows that (-)-2 is configurationally similar to (-)-3, (-)-4 and (+)-5 since all these stereoisomers exhibit the same sense of carbomethoxy nonequivalence. Accordingly, the levorotatory trifluoromethyl substituted acetate is assigned the R configuration as shown in 2.

In a similar fashion, one may correlate the sense of the F¹⁹ nmr nonequivalence of (-)-enriched acetate 2 with that of (+)-enriched 2,2,2-trifluorophenylethanol, 6. Both predominant enantiomers have their F¹⁹ resonances at lower field than do the minor enantiomers ($\Delta\delta = 1.9$ Hz

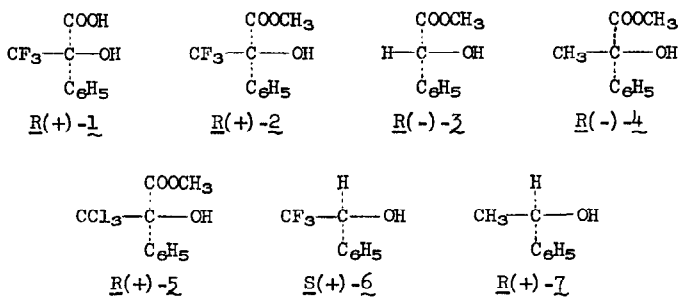
Figure I

Portions of the Nmr Spectra of Partially Resolved 2
 (see Table I) in $\underline{\alpha}$ -(1-naphthyl)ethylamine^{a, b}



^aThe carbomethoxy resonances are downfield from tetramethylsilane while those of the trifluoromethyl group are upfield from fluorotrichloromethane.

^bWhen racemic α -(1-naphthyl)ethylamine is employed as solvent at 39°, the trifluoromethyl group of 2 appears as a triplet ($|J|_{\text{HF}} = 0.8 \text{ Hz}$), presumably arising from long-range coupling with the ortho aromatic protons.



and 3.3 Hz, respectively at 56.4 MHz). Since (+)-6 is known (5) to have the S configuration shown, it follows that (-)-acetate 2 has the R configuration, a finding in agreement with the pmr stereochemical correlation. By including the previously reported (2) nmr configurational correlation between carbinol 6 and R(+)- α -phenylethanol, 7, the correlation sequence 2 \rightarrow 4 \rightarrow 7 \rightarrow 6 \rightarrow 2 clearly constitutes an internally consistent loop of configurational assignments.*

Significantly, the carbomethoxy and trifluoromethyl resonances of (-)-2 exhibit opposite senses of nonequivalence, just as do the carbinyl protons and trifluoromethyl groups of partially resolved aryltrifluoromethylcarbinols (2). Moreover, the presently observed senses of nonequivalence can be explained by the conformational hypothesis previously advanced to rationalize the senses of nonequivalence exhibited by enantiomeric alkylarylcarbinols under similar conditions (2). These observations, plus the fact that configurational correlation of 2 with either 3, 4 and 5 or 6 leads to the same stereochemical result, are taken as strong circumstantial evidence supporting the presently made stereochemical assignments.

Having assigned the absolute configuration of (-)-acetate 2, it is a simple matter to assign the stereochemistry of the corresponding acid, 1. Fischer esterification of that stereoisomer of 1 which is dextrorotatory in water while levorotatory in chloroform (1) leads to (-)-acetate 2.

It is of interest to note that acid 1 of the R(+) configuration has (in methanol) a negative Cotton effect (1) as do R(-)-mandelic and R(-)-atrolactic acids (6). Apparently then, it is the methyl ether of 1 which has the anomalously signed Cotton effect rather than 1 itself.

*To correlate 4 with 7 it must be assumed that the sense of nonequivalence of the carbomethoxy resonance can be compared with that of the carbinyl proton of 7.

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