

## Aberrant Rotatory Dispersion Curves of $\alpha$ -Hydroxy- and $\alpha$ -Methoxy- $\alpha$ -trifluoromethylphenylacetic Acids

Sir:

Numerous optical rotatory dispersion studies have indicated that the ultraviolet absorption band of carboxylic acids at about 210  $m\mu$  is optically active, and the sign of the resulting Cotton effect has been found to correlate well with the absolute configuration of amino acids,<sup>1,2</sup>  $\alpha$ -substituted succinic acids,<sup>3</sup> and  $\alpha$ -hydroxy acids.<sup>4,5</sup> We wish to report an example which demonstrates that great caution should be exercised in assigning absolute configuration based on the sign of this Cotton effect in conformationally mobile molecules.

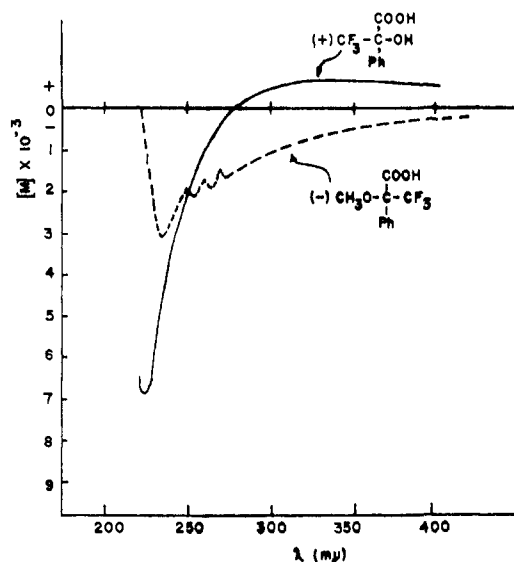


Figure 1. ORD curve (—) in methanol for (+)- $\alpha$ -hydroxy- $\alpha$ -trifluoromethylphenylacetic acid,  $[\alpha]^{20D} +31.1^\circ$  (*c* 2.7,  $H_2O$ ); note that in chloroform this isomer has  $\alpha^{20D} -22.5^\circ$ . ORD curve (---) in methanol for enantiomerically related (–)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetic acid prepared from the parent acid,  $[\alpha]^{22D} +8.8^\circ$  ( $CHCl_3$ ). This curve has been corrected to 100% enantiomeric purity. The formulas in this figure do not necessarily represent the correct absolute configurations of these compounds but do represent the fact that, whatever the absolute configurations, the relative configurations are opposite.

$\alpha$ -Hydroxy- $\alpha$ -trifluoromethylphenylacetic acid, mp 111–113°, was prepared in 64% yield from 2,2,2-trifluoroacetophenone by the cyanohydrin procedure<sup>6</sup> followed by hydrolysis with concentrated hydrochloric acid at 110°. Resolution with (+)- $\alpha$ -(1-naphthyl)ethylamine from 6:1 benzene–absolute ethanol gave acid I, mp 123–124°,  $[\alpha]^{20D} -22.5^\circ$  (*c* 2.7,  $CHCl_3$ ),  $[\alpha]^{20D} +31.1^\circ$  (*c* 2.7,  $H_2O$ ). A sample of the partially resolved enantiomorph with  $[\alpha]^{22D} +8.8^\circ$  ( $CHCl_3$ ) was converted in 90% yield into the levo methyl ester (II),  $\alpha^{20D} -48.64^\circ$  (neat, *l* = 1), bp 82–84° (2 mm). Basic hydrolysis gave (–)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetic acid (III),  $[\alpha]^{18D} -36.5^\circ$  (*c* 1.7,  $CH_3OH$ ), bath temperature 100° (0.5 mm).<sup>7</sup> The ORD curves for

- (1) E. Iizuka and J. T. Yang, *Biochemistry*, **3**, 1519 (1964).
- (2) W. Gaffield, *Chem. Ind.* (London), 1460 (1964).
- (3) A. Fredga, J. P. Jennings, W. Klyne, P. M. Scopes, B. J. Sjöberg, and S. Sjöberg, *J. Chem. Soc.*, 3928 (1965).
- (4) T. R. Emerson, D. F. Ewing, W. Klyne, D. G. Nelson, D. A. V. Peters, L. H. Roach, and R. J. Swan, *ibid.*, 4007 (1965).
- (5) I. D. Dirks and F. L. J. Sixma, *Rec. Trav. Chim.*, **83**, 522 (1964).
- (6) For a previous report of an unsuccessful attempt at this synthesis see J. H. Simons and E. G. Rambler, *J. Am. Chem. Soc.*, **65**, 389 (1943).

the parent acid I and this methyl ether III made from the enantiomorph are given in Figure 1.

These two acids with opposite configurations give comparable negative Cotton effects. This is in direct contrast to mandelic and malic acids and their methyl ethers where the Cotton effects of the configurationally related hydroxy acids and their methyl ethers have the same sign.<sup>3,4</sup> This lack of internal consistency with reference to the configurational standard, mandelic acid, means that the relative configuration of  $\alpha$ -hydroxy- $\alpha$ -trifluoromethylphenylacetic acid cannot be assigned on the basis of these ORD curves. It is of interest to note that if we had not made the methyl ether and taken its ORD curve we would have been unaware of this anomaly and would have assigned the configuration relative to mandelic acid with confidence.

Therefore, the conclusion<sup>4</sup> that the sign of the Cotton effect can be used to determine the configuration of  $\alpha$ -hydroxy acids lacks general validity. Specifically this anomaly makes it impossible to determine the absolute configuration of fluorine-containing compounds of this type by comparison with nonfluorine analogs of known configuration. It should be noted, however, that we did not observe any aberrant optical rotatory behavior in the case of  $\alpha$ -trifluoromethylphenylacetic acid and its derivatives.<sup>8</sup>

We are now exploring the extent of this anomaly in related compounds and are undertaking the establishment of their absolute configuration by other means.

**Acknowledgment.** We gratefully acknowledge support for this investigation by the National Science Foundation (Grant No. GP 6738) and the National Institutes of Health (Grant No. GM 05248). We wish to thank Mrs. Ruth Records for her technical assistance in the ORD determinations.

(7) Since these two derivatives were liquids, no concentration of enantiomorphs was expected during these transformations and the products must have the same enantiomeric purity, namely 39%, as the starting material. All compounds gave compatible spectra and analysis within experimental error.

(8) C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohashi, and H. S. Mosher, *J. Org. Chem.*, in press.

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Received June 12, 1967

## Absence of Stereospecific Effects in Certain Oxidation–Reduction Reactions

Sir:

There appears to have been no systematic study of the influence of enantiomorphic configuration on the rates of redox reactions between pairs of optically active complex ions.<sup>1</sup> Although there are a relatively large number of stable, resolvable complex ions of trivalent metals which can be used as one redox partner, there are few correspondingly stable, easily oxidizable ions of bivalent metals. We have therefore utilized the fact that

- (1) A. W. Adamson and S. Spees, *Discussions Faraday Soc.*, **29**, 121 (1960), attempted to demonstrate such a difference in reactivity by searching for optical activity in the product of the reaction of excess *dl*-Cr(bipy)<sub>3</sub><sup>2+</sup> with *l*-Co(en)<sub>3</sub><sup>3+</sup>. They recognized, however, that the negative result might arise from racemization of Cr(bipy)<sub>3</sub><sup>2+</sup>, and this certainly would occur *via* the lability of Cr(bipy)<sub>3</sub><sup>2+</sup> and the now known (R. Farina and R. G. Wilkins, unpublished) rapid electron transfer between the tris(bipyridine)chromium(II) and -(III) ions.