Aberrant Rotatory Dispersion Curves of α-Hydroxy- and α-Methoxy-α-trifluoromethylphenylacetic Acids

Sir:

Numerous optical rotatory dispersion studies have indicated that the ultraviolet absorption band of carboxylic acids at about 210 mμ is optically active, and the sign of the resulting Cotton effect has been found to correlate well with the absolute configuration of amino acids,[1,2] α-substituted succinic acids,[3] and α-hydroxy acids.[4,5] 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.

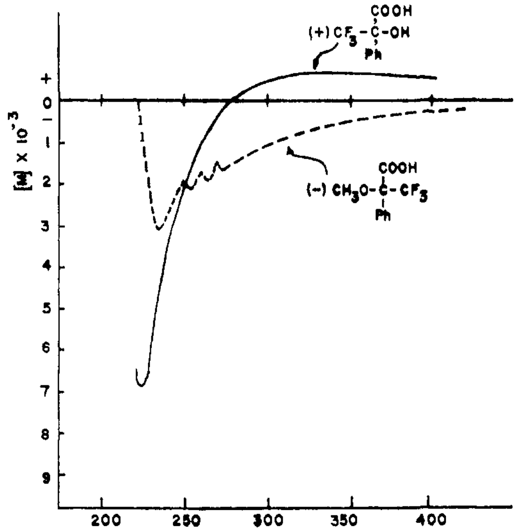

Figure 1. ORD curve (—) in methanol for (+)-α-hydroxy-α-trifluoromethylphenylacetic acid, $[\alpha]^{20}_D$ +31.1° (*c* 2.7, H_2O); note that in chloroform this isomer has α^{20}_D −22.5°. ORD curve (- -) in methanol for enantiomerically related (−)-α-methoxy-α-trifluoromethylphenylacetic acid prepared from the parent acid, $[\alpha]^{22}_D$ +8.8° ($CHCl_3$). 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.*

α-Hydroxy-α-trifluoromethylphenylacetic acid, mp 111–113°, was prepared in 64% yield from 2,2,2-trifluoroacetophenone by the cyanohydrin procedure[6] followed by hydrolysis with concentrated hydrochloric acid at 110°. Resolution with (+)-α-(1-naphthyl)-ethylamine from 6:1 benzene–absolute ethanol gave acid I, mp 123–124°, $[\alpha]^{20}D$ −22.5° (*c* 2.7, $CHCl_3$), $[\alpha]^{20}D$ +31.1° (*c* 2.7, H_2O). A sample of the partially resolved *enantiomorph* with $[\alpha]^{22}D$ +8.8° ($CHCl_3$) was converted in 90% yield into the levo methyl ester (II), $\alpha^{20}D$ −48.64° (neat, *l* = 1), bp 82–84° (2 mm). Basic hydrolysis gave (−)-α-methoxy-α-trifluoromethylphenylacetic acid (III), $[\alpha]^{18}D$ −36.5° (*c* 1.7, CH_3OH), bath temperature 100° (0.5 mm).[7] The ORD curves for 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.*[3,4] This lack of internal consistency with reference to the configurational standard, mandelic acid, means that the relative configuration of α-hydroxy-α-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[4] that the sign of the Cotton effect can be used to determine the configuration of α-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 α-trifluoromethylphenylacetic acid and its derivatives.[8]

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.

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(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).

(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.

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D. L. Dull, Harry S. Mosher
Department of Chemistry, Stanford University
Stanford, California 94305

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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.[1] Although there are a relatively large number of stable, resolvable complex ions of tervalent 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

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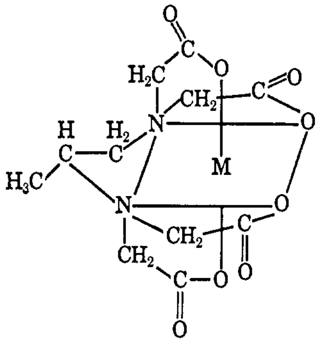
(1) A. W. Adamson and S. Spees, *Discussions Faraday Soc.*, **29**, 121 (1960), attempted to demonstrate such a difference in reactivity by searching for optical activity in the product of the reaction of excess *dl*-$Cr(bipy)_3^{2+}$ with *l*-$Co(en)_3^{3+}$. They recognized, however, that the negative result might arise from racemization of $Cr(bipy)_3^{3+}$, and this certainly would occur *via* the lability of $Cr(bipy)_3^{2+}$ and the now known (R. Farina and R. G. Wilkins, unpublished) rapid electron transfer between the tris(bipyridine)chromium(II) and -(III) ions.

Table I. Kinetic Data at 25° for Certain Redox Reactions Involving Optically Active Complex Ions ($I = 0.5\ M$, pH ~4.5)

Reaction	Reductant[a]	Oxidant[b]	Rate constant,[c] $M^{-1}\ \mathrm{sec}^{-1}$	ΔH^*,[c] kcal mole^{-1}	ΔS^*, eu
1	L-$[\mathrm{Co}(-)\mathrm{PDTA}]^{2-}$	DL-$\mathrm{Fe(bipy)_3}^{3+}$	8.1×10^4[d]	5.7	−17
2	L-$[\mathrm{Fe}(-)\mathrm{PDTA}]^{2-}$	D-$[\mathrm{Co(EDTA)}]^-$	12.5	6.7	−32
		L-$[\mathrm{Co(EDTA)}]^-$	13.0	7.5	−29
3	L-$[\mathrm{Fe}(-)\mathrm{PDTA}]^{2-}$	DL-*cis*-$[\mathrm{Co(en)_2(NH_3)Cl}]^{2+}$	2.0×10^2[d]	10.9	−12
4	L-$[\mathrm{Fe}(-)\mathrm{PDTA}]^{2-}$	D-$[\mathrm{Co(EDTA)Cl}]^{2-}$	3.9×10^2	6.3	−26
		L-$[\mathrm{Co(EDTA)Cl}]^{2-}$	3.9×10^2	6.5	−25
5	L-$[\mathrm{Fe}(-)\mathrm{PDTA}]^{2-}$	DL-$\mathrm{Co(oxal)_3}^{3-}$	2.2×10^2[d]	3.0	−37
6	DL-$[\mathrm{Fe(PDTA)}]^{2-}$	$\mathrm{Co(NH_3)_5Cl}^{2+}$	2.2×10^3	9.2	−13
		$\mathrm{Co(NH_3)_5Br}^{2+}$	1.8×10^3	10.9	−7
		$\mathrm{Co(NH_3)_5N_3}^{2+}$	7.0×10^3	8.6	−12
		$\mathrm{Co(NH_3)_5NCS}^{2+}$	2.7×10^{-1}[e]	...	...

[a] Excess, $\sim 10^{-2}\ M$ except in reaction 1, $10^{-4}\ M$. [b] Deficiency, $\sim 10^{-3}\ M$ except in reaction 1, $10^{-5}\ M$. [c] Rate constant ±10%, ΔH^* ± 1 kcal mole^{-1}. [d] No deviation from linearity of first-order kinetic plots for three to four half-lives. Experiments with artificial mixtures convince us that ≥15% differences in half-lives of components of oxidant would have yielded curved plots. [e] Values at 30.0°.

the resolved forms of 1,2-propylenediaminetetraacetate (PDTA^{4-}) impose an absolute configuration on their bivalent metal complexes, which although labile are nevertheless optically stable.[2] We have measured by the stopped-flow method the rates of oxidation of L-$[\mathrm{Fe}(-)\mathrm{PDTA}]^{2-}$ and in one case L-$[\mathrm{Co}(-)\mathrm{PDTA}]^{2-}$ (I)[3] by the enantiomorphs of several complex ions, including examples of both outer-sphere and inner-sphere oxidation. In some cases the two optical forms of oxidant have been used in separate experiments. Otherwise we have employed racemic oxidant and searched for deviation from linearity of pseudo-first-order plots (reductant in excess) which would be associated with different reactivity of the two nonlabile forms of the racemic mixture. The second-order rate constants and attendant Arrhenius parameters are shown in Table I. We conclude from the work that the kinetic behavior of the D or L form of the oxidant toward the optically active form of reductant is disappointingly similar.



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The inertness and nature of the oxidant in reaction 1 and the bulkiness of the reactants in (2) (Table I) label these, we believe, as outer-sphere reactions in which no interpenetration of ligands occurs. Stereospecific effects might be expected to be less important in these than in the inner-sphere type of redox process, an example of which occurs with reaction 3. The inner-sphere nature of this reaction is suggested by a comparison of the rate of oxidation of $\mathrm{Fe(PDTA)}^{2-}$ by $\mathrm{Co(NH_3)_5N_3}^{2+}$ and $\mathrm{Co(NH_3)_5NCS}^{2+}$ (reactions 6). The ratio, $k_{\mathrm{N_3^-}}/k_{\mathrm{NCS^-}} = 2.6 \times 10^4$, is considered a most reliable criterion for an inner-sphere redox process.[4] The characterization of reactions 4 and 5 is uncertain. The corresponding reactions with ferrous ion reductant are unambiguously inner sphere,[5] and this may apply to our reactions also. On the other hand, the energies and entropies of activation belong more to the outer-sphere redox grouping in Table I. We have not as yet searched for any mixed Fe(III)-PDTA-chloro or -oxalate intermediates, the observation of which would establish the inner-sphere mechanism.[6]

We can calculate expected rate constants for the cross-reactions 1, 2, and 5 on the basis of the Marcus theory.[7] The values obtained, $\geqslant 10^5$, 13, and $1.0 \times 10^3\ M^{-1}\ \mathrm{sec}^{-1}$ at 25°, compare well with the experimental values and give some support to their formulation as outer-sphere reactions.

Observations pertinent to this problem appear sparse in the literature. Pronounced differences in the rate of oxidation of (+)- and (−)-altrose by alkaline copper(II) (+)-tartrate solutions have been reported,[8] but the mechanism is complex and the point (substitution or redox) at which the stereoselectivity enters is uncertain. The rates of electron transfer between the radical anion of 1-(α-naphthyl)-1-phenylethane and the neutral molecule have been measured in dimethoxyethane recently by an esr method.[9] Small differences, almost within experimental error, were observed in the rate constants using only the *d* enantiomer and with racemic mixtures. Our results show that certainly with the types of redox processes we have investigated no difference exists in the reactivity of enantiomers toward an optically pure reductant. We propose searching for medium effects (optically active solvents and salts) in these reactions.

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(2) D. H. Busch and D. W. Cooke, *J. Inorg. Nucl. Chem.*, **23**, 145 (1961); F. P. Dwyer and F. L. Garvan, *J. Am. Chem. Soc.*, **83**, 2610 (1961); Y. A. Im and D. H. Busch, *ibid.*, **83**, 3362 (1961).

(3) This formulation is not meant to presume sexadentate character for PDTA, which may be coordinated only at five centers, with $\mathrm{H_2O}$ completing the octahedron.

(4) J. H. Espenson, *Inorg. Chem.*, 4, 121 (1965).

(5) A. Haim and N. Sutin, *J. Am. Chem. Soc.*, **88**, 5343 (1966).

(6) The participation of $[\mathrm{Co(EDTA)}]^{2-}$ in a chlorine-bridged inner-sphere reaction has been demonstrated in its reduction of $[\mathrm{Co(py)_4Cl_2}]^+$, when $[\mathrm{Co(EDTA)Cl}]^{2-}$ is formed: R. G. Wilkins and R. Yelin, unpublished.

(7) R. A. Marcus, *Ann. Rev. Phys. Chem.*, **15**, 155 (1964). The required rate constants and redox potentials are available in the literature except for the second-order rate constant for the $\mathrm{Fe(PDTA)}^{2-}$–$\mathrm{Fe(PDTA)}^-$ couple which we have determined as $\sim 4 \times 10^4\ M^{-1}\ \mathrm{sec}^{-1}$: R. G. Wilkins and R. Yelin, unpublished.

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Bernard Grossman, R. G. Wilkins
Department of Chemistry, State University of New York at Buffalo
Buffalo, New York 14214

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Hydrogenolysis of Thymine Dimer to Cyclobutanes by Sodium Borohydride

Sir:

Stable thymine dimers are formed by ultraviolet irradiation of frozen solutions of thymine[1] as well as of liquid solutions of DNA[2] in a reversible process.[3] Recent interest has been focused on the dimerization of the pyrimidine bases of nucleic acids and the role of these photoproducts in biological systems with respect to photoreactivation,[4] photoreversal,[5] and repair processes.[6,7]

Scheme I

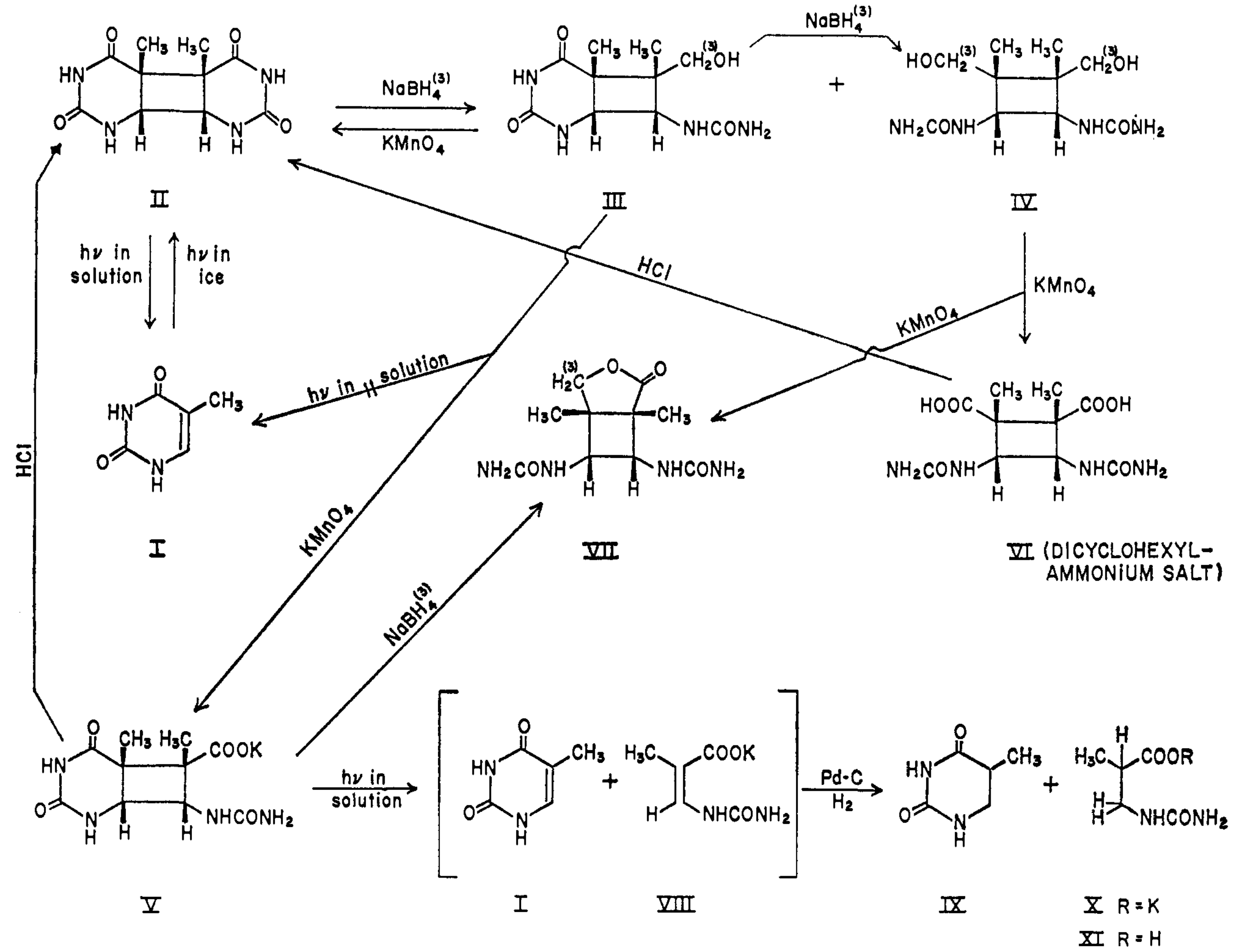

Table I. Hydrogenolysis of Thymine Dimer (II) to the Monoalcohol III and the Dialcohol IV as a Function of Time and Amount of Reducing Agent

Moles of NaBH$_4$/mole of dimer	Time (temp, °C)	Monoalcohol III, %	Dialcohol IV, %
4	5 hr (20)	74	11
10	20 hr (20)	18	61.4
2	4 days (20)	59[a]	3.7[a]
8	19 hr (reflux)	Trace	

[a] In this experiment 25% of dimer II was recovered; the corrected yields for III and IV are then 79 and 4.8%, respectively.

So far there is scant information on the chemical degradation of thymine dimers[8] which would be mild and selective enough to permit the investigation of irradiated polynucleotides

In this communication we wish to report the smooth conversion of thymine dimer (II) to aminocyclobutane derivatives by stepwise hydrogenolysis with sodium borohydride and the oxidation and photochemistry of these novel compounds (see Scheme I). Thymine

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