Optical Rotatory Dispersion Studies. CXVII.[1] Absolute Configurational Assignments of Some α-Substituted Phenylacetic Acids by Circular Dichroism Measurements[2]

Gunter Barth,[3a] Wolfgang Voelter,[3b] Harry S. Mosher, Edward Bunnenberg, and Carl Djerassi

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. *Received May 19, 1969*

Abstract: The solvent- and temperature-dependent circular dichroism spectra of a series of closely related α-substituted phenylacetic acids are reported. It is suggested that the apparently aberrant optical rotatory dispersion and circular dichroism spectra exhibited by several members of this series are due to simplistic correlations based on "atomic asymmetry." The α-substituted phenylacetic acids are regarded as examples of conformationally mobile homoconjugated systems and configurational correlations are made in accordance with the tenets of the extended octant rule. The Cotton effects appearing at lower wavelengths are considered as being primarily associated with the $n \rightarrow \pi^*$ transition of the carboxyl group and only secondarily with a transition of the phenyl group.

In the last decade an evolution in the applications of optical rotatory dispersion (ORD) and circular dichroism (CD) to problems in organic chemistry[4] can be discerned. This evolution, although receiving considerable impetus from theoretical chemists active in several areas, can be attributed to the recent commercial availability of spectropolarimeters and circular dichrometers which are not only more sensitive but which also have a more extended wavelength range. Earlier instrumental limitations imposed rather severe restrictions on the chromophores which could be investigated. For example, in an extensive ORD study of aryl-substituted carboxylic acids Sjöberg[5] observed, with a single exception, only plain dispersion curves in the 275–700 nm range. Because of the desirability of performing measurements through regions of absorption, recourse was frequently made to such "chromophoric" derivatives as acylthioureas[6] and, more importantly, thionamides[7] derived from carboxylic acids. The recent improvements in instrumentation largely obviate the necessity of the utilization of such "chromophoric" derivatives and permit the direct observation of either the onset[8] or the complete[9] ORD Cotton effects associated with the $n \rightarrow \pi^*$ band of the carboxyl chromophore as well as the Cotton effects associated with the phenyl transitions.[10,11]

Other workers have confirmed these results by means of CD,[12–14] which, because of the inherently better resolution of CD *vs.* ORD, frequently permits the direct observation of the Cotton effects associated with closely spaced electronic transitions. In the case of such simple aromatic systems as methylphenylcarbinol[12b] and α-phenylethylamine[14] CD measurements enable one to identify the weaker Cotton effects associated with the ^1L_b phenyl transition (around 260 nm) and the stronger ones associated with the ^1L_a phenyl transitions (around 210 nm) with greater certainty than is possible with ORD. Several authors have emphasized some of the advantages derived from the measurement and analysis of CD and ORD spectra.[15]

The present communication is an outgrowth of a recent study in this laboratory concerning the CD of some α-hydroxy acid–molybdate complexes.[16] In the course of measuring the CD spectra of the uncomplexed α-hydroxy acids we had occasion to reexamine[1] "the lactic acid anomaly."[17a] In the present communication we report the results of our investigation of the solvent and temperature dependency of the CD spectra of a closely related series of α-substituted phenylacetic acids. In addition, we have attempted to address ourselves to another, although as yet only briefly considered, controversy; namely, the origin of the Cotton effects in the

---

[1] Paper CXVI. G. Barth, W. Voelter, E. Bunnenberg, and C. Djerassi, *Chem. Commun.*, 355 (1969).

[2] We are indebted to the National Science Foundation (Grant No. GP-9432), to the National Institutes of Health (Grant No. GM-12173), and to NATO (Grant No. 377) for financial aid.

[3] (a) Recipient of a Eugen Wigner Stipendium, Technical University of Berlin (1968–1969). (b) Recipient of a Carl Duisberg Stipendium (1968) while on leave from the University of Tübingen.

[4] (a) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960; (b) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965; (c) L. Velluz, M. Legrand, and M. Grosjean, "Optical Circular Dichroism. Principles, Measurements and Applications," Verlag Chemie, Weinheim, 1965.

[5] B. Sjöberg, *Acta Chem. Scand.*, **14**, 273 (1960).

[6] (a) C. Djerassi and K. Undheim, *J. Amer. Chem. Soc.*, **82**, 5755 (1960); (b) C. Djerassi, K. Undheim, and A.-M. Weidler, *Acta Chem. Scand.*, **16**, 1147 (1962).

[7] (a) J. V. Burakevich and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 51 (1965); (b) C. Aaron, D. Dull, J. L. Schmiegl, D. Jaeger, Y. Ohashi, and H. S. Mosher, *J. Org. Chem.*, **32**, 2797 (1967).

[8] (a) I. P. Dirkx and F. L. J. Sixma, *Rec. Trav. Chim. Pays-Bas*, **83**, 522 (1963); (b) J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 294 (1965).

[9] (a) W. Gaffield, *Chem. Ind.*, 1460 (1964); (b) D. W. Urry and H. Eyring, *J. Amer. Chem. Soc.*, **86**, 4578 (1964); (c) G. Gottarelli, W. Klyne, and P. M. Scopes, *J. Chem. Soc., C*, 1366 (1967); (d) G. Gottarelli and P. M. Scopes, *ibid.*, 1370 (1967).

[10] For recent reviews see: (a) P. Crabbé in "Topics in Stereochemistry," N. L. Allinger and E. L. Eliel, Ed., Vol. I, Interscience Publishers, New York, N. Y., 1967, p 93; (b) P. Crabbé and W. Klyne, *Tetrahedron*, **23**, 3449 (1967).

[11] A. Moscowitz, A. Rosenberg, and A. E. Hansen, *J. Amer. Chem. Soc.*, **87**, 1813 (1965).

[12] (a) L. Verbit, *ibid.*, **88**, 5340 (1966); (b) *ibid.*, **87**, 1617 (1965).

[13] M. Legrand and R. Viennet, *Bull. Soc. Chim. Fr.*, 2798 (1966).

[14] J. C. Craig, R. P. K. Chan, and S. K. Roy, *Tetrahedron*, **23**, 3573 (1967).

[15] (a) C. Djerassi, H. Wolf, and E. Bunnenberg, *J. Amer. Chem. Soc.*, **84**, 4552 (1962); (b) in the hydroxy and amino acid series see: L. I. Katzin and E. Gulyas, *ibid.*, **90**, 247 (1968); (c) for a more detailed analysis based on the numerical evaluation of the Kramers–Kronig relations see: C. A. Emeis, L. J. Oosterhoff, and G. de Vries, *Proc. Roy. Soc.* (London), *A*, **297**, 54 (1967).

[16] W. Voelter, E. Bayer, G. Barth, E. Bunnenberg, and C. Djerassi, *Chem. Ber.*, **102**, 2003 (1969).

[17] (a) R. D. Anand and M. K. Hargreaves, *Chem. Commun.*, 421 (1967); (b) *Chem. Ind.* (London), 880 (1968).

Table I. CD Maximum Values of Some α-Substituted Phenylacetic Acid Derivatives in Different Solvents

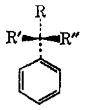
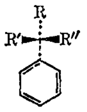
					λ$_{max}$ (nm), [θ]$_{max}$ (deg mol^{-1} cm^2)		
No.	R′	R	R″	Solvent	Band 1	Band 2	Band 3^a
Ia^{b,c}	OH	COOH	CF_3	0.5 *N* HCl	218 (+5,200)	235 (−1,800)	258 (+295)
				Water	220 (+9,900)	235 (−600)	258 (+140)
				0.15 *N* NaOH	220 (+9,800)	230 (−340)	257 (+105)
				Ethanol	220 (+22,500)	245 (−350)	260 (+135)
				Cyclohexane	222 (+11,200)		261 (−130)
Ib^{b,c,k}	OH	COOMe	CF_3	Ethanol	220 (+6,500)	235 (−4,200)	260 (+660)
				Cyclohexane	220 (+77,000)		260 (−450)
				Acetonitrile	220 (+14,600)	237 (−2,300)	260 (+475)
Ic^{b,c}	OCH_3	COOH	CF_3	0.5 *N* HCl		232 (−3,200)	259 (+245)
				Water		222 (−2,900)	259 (+220)
				0.15 *N* NaOH		225 (−3,300)	260 (+230)
				Ethanol		235 (−4,400)	260 (+435)
				Cyclohexane	206 (+5,700)	235 (−8,200)	260 (+580)
Id^{b,c}	OCH_3	COOMe	CF_3	Ethanol		229 (−8,200)	261 (+555)
				Cyclohexane		230 (−7,400)	261 (+665)
IIa^d	OH	COOH	CH_3	0.5 *N* HCl	220 (+17,900)	242 (−360)	260 (−100)
				Water	220 (+16,200)	240 (−270)	261 (−55)
				0.15 *N* NaOH	Positive		260 (+105)
				Ethanol^e	224 (+25,900)	243 (−285)	260 (+95)
IIb^f	OH	COOMe	CH_3	Ethanol	221 (+14,700)	240 (−1,150)	260 (−80)
				Cyclohexane	222 (+44,500)	245 (−130)	256 (+83)^l
IIc	OCH_3	COOH	CH_3	0.5 *N* HCl	220 (+2,150)	242 (−170)	
				Water	220 (+1,650)	240 (−220)	
				0.15 *N* NaOH		232 (−390)	
				Ethanol^e	222 (+1,200)	239 (−500)	
IId	OCH_3	COOMe	CH_3	Ethanol	215 (+8,050)	238 (−5,400)	263 (−120)
				Cyclohexane		232 (−13,200)	263 (−130)
IIIa^b	OH	COOH	H	0.5 *N* HCl	222 (+34,400)		260 (−420)
				Water	218 (+23,300)		260 (−370)
				0.15 *N* NaOH	217 (+20,000)		260 (−370)
				Ethanol^e	223 (+40,300)		262 (−200)
IIIb^b	OH	COOMe	H	Ethanol	222 (+41,000)		262 (−270)
				Cyclohexane	222 (+72,500)		262 (−230)
IIIc^b	OCH_3	COOH	H	0.5 *N* HCl	222 (+33,900)		261 (−565)
				Water	222 (+28,700)		261 (−505)
				0.15 *N* NaOH	218 (+19,400)		261 (−575)
				Ethanol	223 (+34,700)		261 (−285)
				Cyclohexane	227 (+29,700)		263 (−240)
IIId^b	OCH_3	COOMe	H	Ethanol	224 (+34,800)		262 (−250)
				Cyclohexane	222 (+29,900)		262 (−200)
IVa	OH	COOH	C_6H_{11}	0.15 *N* NaOH	224 (+35,700)		260 (+930)
				Ethanol^e	225 (+48,500)		261 (+304)
IVb	OH	COOMe	C_6H_{11}	Ethanol	225 (+53,400)	245 (−120)	260 (+170)
				Cyclohexane	223 (+68,600)		259 (+205)
IVc	OCH_3	COOMe	C_6H_{11}	Ethanol	222 (+15,000)		262 (+370)
				Cyclohexane	224 (+19,700)		263 (+475)
Va^g	CH_3	COOH	H	0.5 *N* HCl	220 (+16,100)		255 (+150)
				Water	220 (+16,300)		259 (+110)
				0.15 *N* NaOH	Positive		261 (−295)
				Ethanol	222 (+17,400)		261 (+190)
				Cyclohexane	221 (+20,000)		260 (+225)
Vb^g	CH_3	COOMe	H	Ethanol	222 (+20,700)		261 (+300)
				Cyclohexane	222 (+23,800)		261 (+360)
VIa^h	CF_3	COOH	H	0.5 *N* HCl	217 (+21,500)		259 (−350)
				Water	214 (+13,400)		260 (−330)
				0.15 *N* NaOH	225 (+1,500)		261 (−250)
				Ethanol	221 (+10,700)		261 (−240)
				Cyclohexane	225 (+12,500)		261 (−270)
VIb^h	CF_3	COOMe	H	Ethanol	217 (+18,400)		260 (−235)
				Cyclohexane	218 (+12,700)		261 (−100)
VIIa^{b,h}	C_2H_5	COOH	H	0.5 *N* HCl	219 (+12,800)		260 (+45)
				Water	219 (+6,200)		
				0.15 *N* NaOH	224 (−6,900)		261 (−550)
				Ethanol	219 (+16,600)		261 Positive
				Cyclohexane	222 (+7,800)		261 (+100)
VIIb^{b,h}	C_2H_5	COOMe	H	Ethanol	220 (+15,400)		260 (+220)
				Cyclohexane	220 (+18,200)		261 (+250)
VIIIa^h	*t*-Bu	COOH	H	0.15 *N* NaOH	223 (−12,900)	238 (+400)	262 (−215)
				Ethanol ^{e}	215 (+11,300)		260 (+266)
VIIIb^h	*t*-Bu	COOMe	H	Ethanol	220 (+13,300)		261 (+440)
				Cyclohexane	218 (+13,100)		261 (+480)

Table I (*Continued*)

No.	R′	R	R″	Solvent	λ_{max} (nm), $[\theta]_{max}$(deg mol^{-1}cm^2) Band 1	Band 2	Band 3[a]
IX[i]	OH	H	CF_3	Ethanol			260 (+85)
				Cyclohexane			260 (+143)
Xa[b,f]	CF_3	CH_2OH	H	Ethanol	Weak negative		259 (−50)
				Cyclohexane	Weak negative		261 (+40)
Xb[f,i]	CF_3	CH_2Cl[j]	H	Ethanol			261 (+250)
				Cyclohexane			261 (+95)

[a] Usually this Cotton effect is split into three sharp peaks; only the position and intensity of the middle and most intense one is given. [b] Measured as the *R* enantiomer. [c] See J. A. Dale and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969). [d] A. McKenzie and G. W. Clough, *J. Chem. Soc.*, 1016 (1910). [e] Not soluble in cyclohexane. [f] See Experimental Section. [g] See H. S. Raper, *J. Chem. Soc.*, 2558 (1923), [h] See ref 7b. [i] See D. M. Feigl and H. S. Mosher, *J. Org. Chem.*, **33**, 4242 (1968). [j] Although having the same absolute configurational designation as Xa according to the Cahn, Ingold, Prelog scheme, the CH_2Cl group has higher priority than the CF_3 group and the depicted formula shows therefore the (*R*) configuration. The (*S*) enantiomer was measured. [k] Sample had an enantiomeric purity of 40%; values are corrected to 100% optical purity, see Experimental Section. [l] Band 3 is strongly overlapped by band 2.

Table II. Temperature Dependence of CD Maximum Values for Some α-Substituted Phenylacetic Acids[a]



	R′	R	R″	Temp, °C	λ_{max} (nm), $[\theta]_{max}$ (deg mol^{-1} cm^2) Band 1	Band 2	Band 3[d]
Ib[e,f]	HO	COOMe	CF_3	+20	220 (+12,700)	239 (−1,800)	261 (+380)
				−5	221 (+4,900)	235 (−1,800)	*b*
				−41	223 (+1,800)	232 (−3,300)	*b*
				−74		228 (−6,800)	261 (+1,100)
				−192		223 (−31,300)	261 (+2,600)
Id[e]	MeO	COOMe	CF_3	+20		233 (−6,200)	261 (+1,400)
				−74		225 (−14,800)	261 (+1,400)
				−192		223 (−27,000)	261 (+2,100)
IIb	HO	COOMe	Me	+20	223 (+8,900)	240 (−310)	*b*
				−74	224 (+5,200)	239 (−1,100)	*b*
IId	MeO	COOMe	Me	+20		234 (−7,400)	*b*
				−74		233 (−12,900)	*b*
IIIb	HO	COOMe	H	+20	222 (+62,000)		260 (−225)
				−74	226 (+96,000)		262 (−230)[c]
				−192	226 (+97,600)		264 (−290)
IIId	MeO	COOMe	H	+20	223 (+64,000)		262 (−230)
				−74	225 (+97,500)		262 (−330)[c]
				−192	226 (+98,200)		263 (−240)
Vb[g]	CH_3	COOMe	H	+20	221 (+22,200)		262 (+320)
				−74	223 (+43,000)		262 (+700)
				−192	223 (+53,100)		261 (+1,100)

[a] Measurements were carried out in EPA (ether–isopentane–ethanol 5:5:2). [b] Not measured. [c] Band 3 is strongly overlapped by band 1. [d] Usually this Cotton effect is split into three sharp peaks; only the position and intensity of the middle peak is shown. [e] See Table I, footnote *c*. [f] Taken on sample 40% enantiomerically pure; value adjusted to 100% purity. [g] See ref 7b.

200–240 nm region of aromatic carboxylic acids. The assignment of the transitions responsible for these Cotton effects is of fundamental importance in the consideration and formulation of rules for the correlation of absolute configurations and rotatory strength particularly since some exceptions can be found for rules based on the sign of the ^1L_b Cotton effects in conformationally mobile systems.

Experimental Section

Circular dichroism measurements were made using a Japan Spectroscopic Co. spectropolarimeter–circular dichrometer (Durrum-JASCO Model ORD/UV/CD-5). Concentrations and path lengths were chosen such that the optical densities were less than 2. Although measurements were usually made using a sensitivity setting of 1×10^{-4} ΔA/cm, very weak Cotton effects were investigated using the 2×10^{-5} ΔA/cm sensitivity setting afforded by a recent modification to our instrument made by Sproul Instruments.[18a] The organic solvents used were of Spectrograde quality. The EPA solvent consisted of ether–isopentane–ethanol in a ratio of 5:5:2 by volume. Low-temperature CD measurements were made using a cell constructed in our laboratory.[18b] The determinations in some cases were made on compounds which were not enantiomerically pure but the molar ellipticities collected in Tables I and II have been calculated for the pure enantiomer.

Structures and configurations of compounds discussed in the text are given in Table I with suitable references. α-Cyclohexylmandelic acid was a gift from Dr. T. D. Inch.[19] The other compounds investigated were synthesized in the laboratories of one of us (HSM).[20] The methyl esters were prepared with diazomethane from the corresponding acids. (*R*)-(−)-Mandelic acid was obtained from Aldrich Chemical Co., $[\alpha]^{24}$D −154.2° (H_2O). Id, IId, IIId, and IVd

---

(18) (a) Sproul Scientific Instruments, Boulder Creek, Calif., through Durrum Instruments Corp., Palo Alto, Calif. (b) Construction details are available from the authors.

(19) T. D. Inch, R. V. Ley, and P. Rich, *J. Chem. Soc., C*, 1693 (1968).

(20) (a) D. L. Dull and H. S. Mosher, *J. Amer. Chem. Soc.*, **89**, 4230 (1967); (b) see Table I, footnote *c*. Ia in Table I and Figure 1 corresponds to (*S*)-(+)-α-trifluoromethyimandelic acid, $[\alpha]^{20}$D +23° ($CHCl_3$); note that this has $[\alpha]^{20}$D − in CH_3OH and H_2O. Ib corresponds to (*S*)-(+)-methyl α-trifluoromethylmandelate, α^{19}D +17.2° (neat). Ic corresponds to (*S*)-(−)-methyl O-methylmandelate, α^{20}D −124° (neat). Id corresponds to (*S*)-(−)-O-methylmandelic acid, $[\alpha]^{24}$D −71° (CH_3OH).

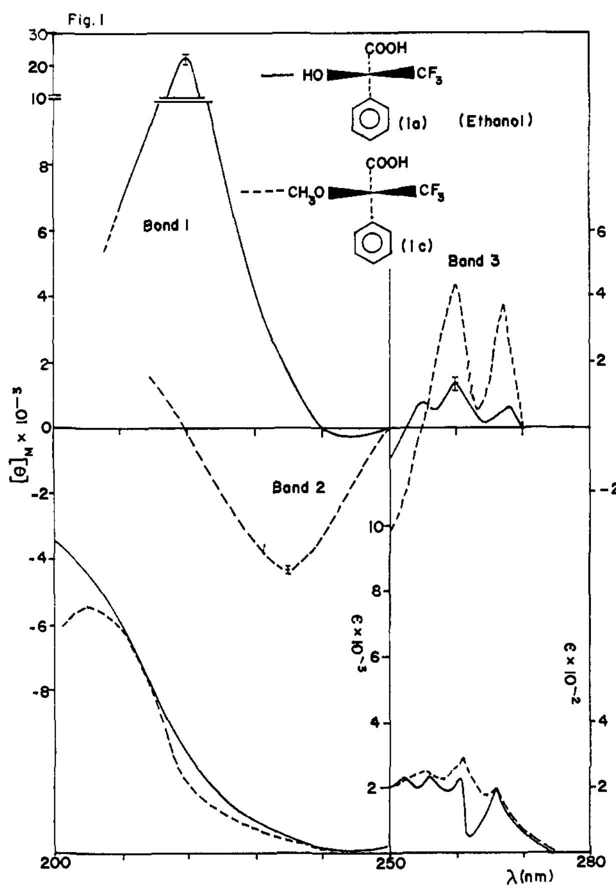


Figure 1. Absorption (lower curve) and CD spectra of (*S*)-(+)-α-trifluoromethylmandelic acid (Ia) (———) and (*S*)-(−)-O-methyl-α-trifluoromethylmandelic acid (Ic) (------) in ethanol.

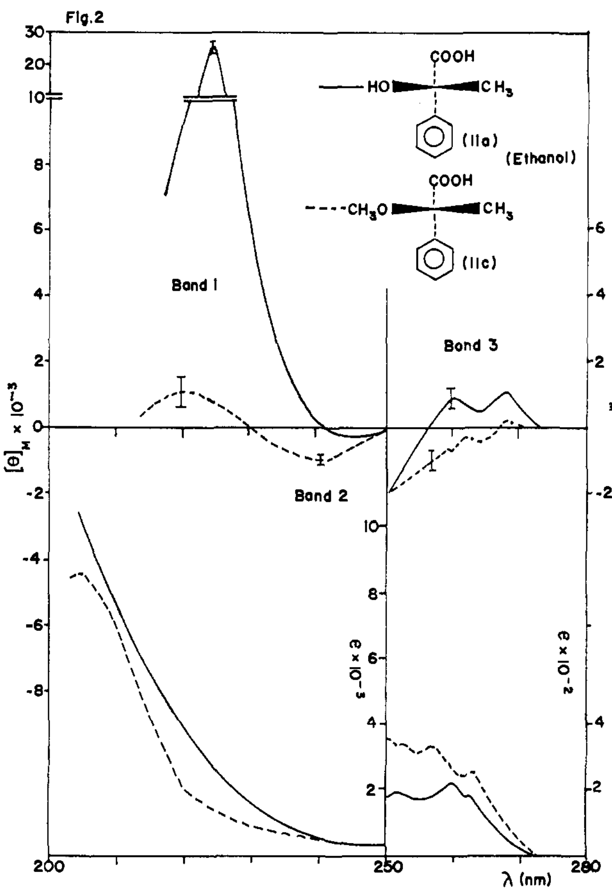


Figure 2. Absorption (lower curve) and CD spectra of (*S*)-(+)-atrolactic acid (IIa) (——) and (*S*)-O-methylatrolactic acid (IIC) (-----) in ethanol.

were prepared from the corresponding hydroxy esters using methyl iodide and silver oxide.[21] It was necessary to use reaction times of 3 to 4 days in the preparation of IId and IVd. Compounds Ic, IIc, and IIIc were prepared from the corresponding esters by hydrolysis in the presence of dilute sulfuric acid.

(*R*)-(+)-2-Phenyl-3,3,3-trifluoro-1-propanol (Xa). (*R*)-(−)-α-Trifluoromethylphenylacetic acid, 9.92 g, $[\alpha]^{25}\text{D}$ −70.30° ($CHCl_3$), in ether was reduced with lithium aluminum hydride (0.09 mol). Hydrolysis, extraction, and drying gave an ether solution of the product from which the carbinol could not be satisfactorily recovered in pure form by distillation alone because of its high volatility. It was concentrated by distillation and then crystallized at −20° from ether-pentane, 3.79 g, mp 51–52°, $[\alpha]^{24.4}\text{D}$ +37.79 ± 0.4° (*c* 5.08, $CHCl_3$).

Anal. Calcd for $C_9H_9F_3O$: C, 56.84; H, 4.77. Found: C, 56.60; H, 4.71.

(*S*)-(+)-2-Phenyl-3,3,3-trifluoro-1-chloropropane (Xb). To the above carbinol (4.95 g) dissolved in pyridine (6.4 ml) at 0° was added thionyl chloride (5.00 g) with stirring over a 40-min period. After 2.5 hr the mixture was allowed to warm to room temperature, poured onto ice, and the product recovered by extracting with ether, washing the ether extracts with dilute acid, water, sodium bicarbonate and water, drying ($MgSO_4$), and distilling to give 4.54 g, bp 78–82° (22 mm); $[\alpha]^{26}\text{D}$ +72.84° (neat, 1 = 1). This product by gas chromatographic analysis was shown to have present 7% impurity of the olefin α-trifluoromethylstyrene. Assuming no racemization and that this olefin impurity only affects the rotation by dilution, then the rotation for enantiomerically pure (*S*)-(+)-2-phenyl-3,3,3-trifluoro-1-chloropropane would be $\alpha^{26}\text{D}$ +77.84° (neat, 1 = 1).

The CD and absorption spectral data observed in different solvents and at different pH's for the α-substituted phenylacetic acids and derivatives as well as the data observed for several reference compounds are collected in Table I and typical curves are displayed in Figures 1–3. The results of our low-temperature CD measurements are contained in Table II and the low-temperature CD spectra of two compounds are graphically presented in Figures 4 and 5.

Results

In a previous communication[20a] it was noted by one of us (H. S. M.), that great caution should be exercised in assigning absolute configurations based on the sign of ORD Cotton effects in conformationally mobile molecules. In particular it was shown that, although the ORD Cotton effects exhibited by configurationally related mandelic and malic acids and their methyl ethers have the same sign,[22] (*S*)-(+)-α-hydroxy-α-trifluoromethylphenylacetic acid (Ia) and its configurationally related methyl ether (Ic) exhibit ORD Cotton effects of opposite sign. The reason for this ORD anomaly has now become apparent from a comparison of the CD (Figure 1) and ORD spectra (Figure 1 of ref 20a) of the two compounds. Whereas the ORD curve of Ia showed only the first extremum (at about 225 nm) of a positive Cotton effect, the CD spectrum is considerably more complex showing Cotton effects in three regions. The position of the Cotton effect of greatest intensity, band 1, is in approximate correspondence with the positive ORD Cotton effect; however, the negative CD band (band 2) at 245 nm and the several positive CD bands (band 3) in the 260-nm region do not have obvious counterparts in the ORD spectrum. On the

---

[21] K. Mislow, *J. Amer. Chem. Soc.*, 73, 4043 (1951).

[22] T. R. Emerson, D. F. Ewing, W. Klyne, D. G. Neilson, D. A. V. Peters, L. H. Roach, and R. J. Swan, *J. Chem. Soc.*, 4007 (1965).

Fig.3

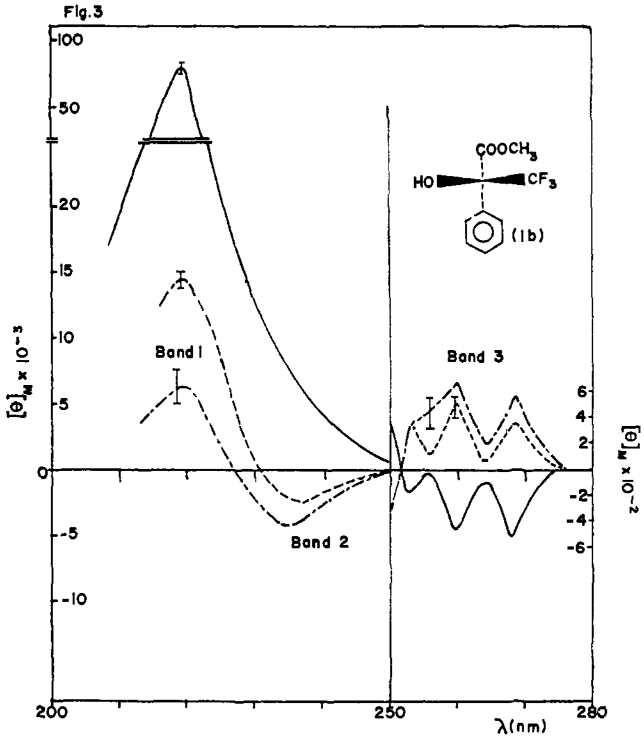


Figure 3. CD spectra of (*S*)-(+)-methyl α-trifluoromethylmandelate (Ib) in cyclohexane (———), acetonitrile (-----), and ethanol (-·-·-·).

Fig.4

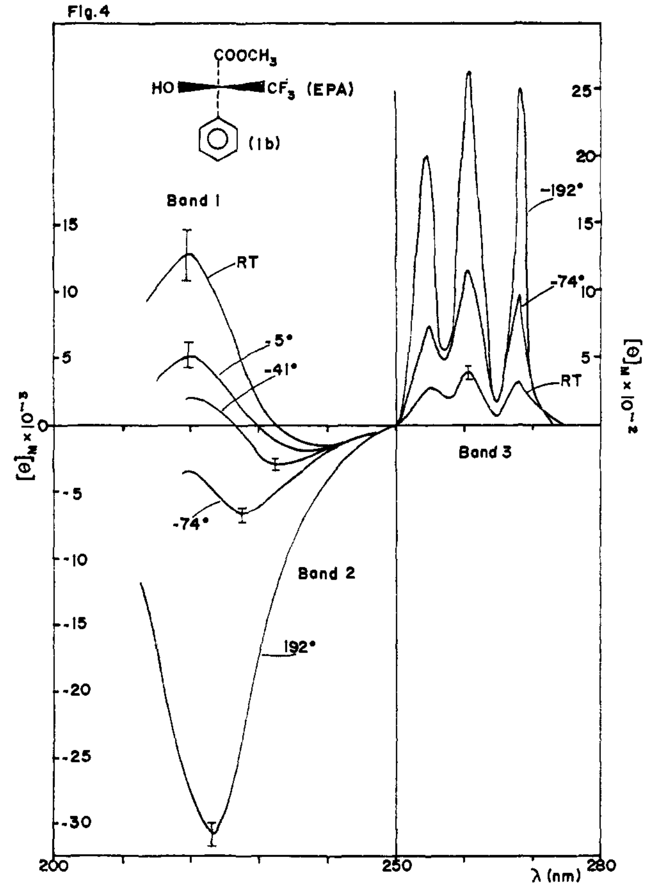


Figure 4. Low-temperature CD spectra of (*S*)-(+)-methyl α-trifluoromethylmandelate (Ib) in EPA (ether–isopentane–ethanol, 5:5:2).

Fig.5

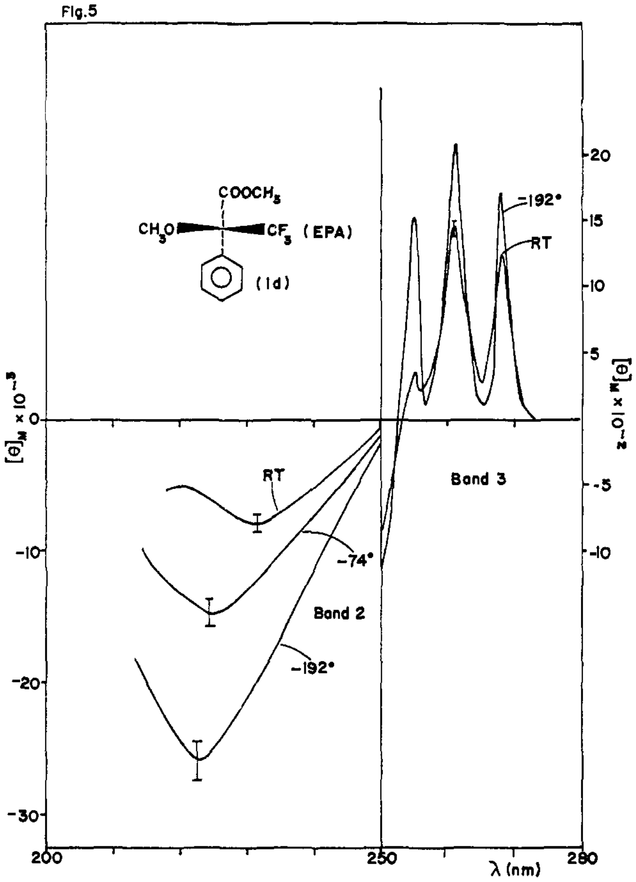


Figure 5. Low-temperature CD spectra of (*S*)-methyl O-methyl-α-trifluoromethylmandelate (Id) in EPA (ether–isopentane–ethanol, 5:5:2).

other hand, instead of the anticipated positive ORD Cotton effect, the configurationally related methyl ether, Ic, shows a negative ORD extremum at about 240 nm. The counterpart of the fine structure observed in the ORD curve of Ic in the 260-nm region is found in CD band 3 whereas the negative ORD extremum can be associated with the strongly negative CD band 2 at 235 nm. Although the CD curve of Ic becomes positive below 220 nm, a maximum corresponding to band 1 of Ia could not be reached. Band 1 can be clearly observed, however, in cyclohexane at 206 nm whereas in the case of Ia band 2 cannot be observed in cyclohexane (Table I). Thus, although the CD spectra of Ia and Ic presented in Figure 1 do not, in themselves, clarify the anomalous ORD behavior of these compounds, they do reveal that several Cotton effects must be considered. Furthermore, it will be noted in Figure 1 that while the positions of band 3 in the two compounds are in close correspondence, the positions of band 2 (and presumably band 1) are quite different. Although this observation lends some support to the suggestions[20] that the aberrant rotatory dispersion behavior of these two electronically similar compounds has its origin in the conformational mobility inherent in these molecules, other factors must be considered as well.

Examination of the CD spectra of (*S*)-(+)-atrolactic acid (IIa) and its methyl ether (IIc) shown in Figure 2 reveals that although a similar situation exists in this pair of configurationally related compounds, the intensity of CD band 2 is too low to engender the ORD anomaly observed for the trifluoromethyl analogs. Since neither IIa nor IIc are soluble in hydrocarbon solvents, the disappearance of band 2 observed for Ia in cyclohexane could not be investigated for IIa. The methyl esters of these compounds are soluble in cyclohexane and exhibit solvent dependencies which roughly parallel those of the acids. Thus, in the case of IIb band 2 is about 9 times weaker in cyclohexane than in ethanol and in Ib band 2 vanishes in cyclohexane. Since the similarities in the CD spectra of (*S*)-(+)-atrolactic acid (IIa) and (+)-α-hydroxy-α-trifluoromethylphenylacetic acid (Ia in $CHCl_3$) and their molybdate complexes[16] indicate that these acids have the same absolute configuration, we assign the *S* configuration to the latter in accordance with the assignment[23] based on nmr measurements in a chiral solvent.

A comparison of the CD data of the various α-substituted phenylacetic acid derivatives collected in Table I shows that, *in general*, the number of CD bands observed depends on the nature of the substituents at the asymmetric carbon atom. Thus, bands 1 and 3 can be observed in at least one derivative of each of the compounds investigated, but with one exception (VIIIa) band 2 is not found in the acids which bear only a single substituent (other than hydrogen) in the α position. In the case of VIIIa band 2 is very weak and was observed only in alkaline solution. Although the *t*-butyl group is the bulkiest of the substituents in the phenylacetic acid series (V–VIII), the situation is reversed in the mandelic acid series (I–IV) since the intensity of band 2 is much weaker in the α-cyclohexyl derivative (IVb) than in the α-methyl derivative (IIb). It will also be noted in Table I that the intensities of bands 1 and 2 are highly solvent dependent, but that the sign of these bands remains unchanged. This is in contrast to the sign inversions observed in band 3 for several members of the mandelic acid series (I–IV). The phenylacetic acids (V–VIII) present a similar picture in so far as the solvent dependency of band 1 is concerned except that inversion of the sign of band 3, in organic solvents was not observed. In both series sign inversions occurred in going from acidic to basic media but a consistent pattern was not evident.

In order to gain a better insight into the origin of bands 1 and 2 we measured the CD spectra of Ib in several organic solvents. Figure 3 shows that the intensity of band 1 increases as the polarity of the solvent decreases and that band 2 experiences a progressive diminution in intensity as well as an apparent red shift. The intensity changes in band 3 are opposite to those observed in band 1 and it will be noted that in cyclohexane the sign of band 3 is opposite to that in ethanol. Furthermore, comparison of the data presented in Table I shows that this relationship between the intensities of the various bands and the polarity of the solvent is not always maintained. Thus, for example, in IId band 2 is about 2.5 times stronger in cyclohexane than in ethanol; in the case of Ia although band 2 cannot be observed in cyclohexane, the intensity of band 1 in cyclohexane is only one-half that in ethanol; and in the case of Ic the intensity of band 3 decreases in going from cyclohexane to ethanol. A similar, but less dramatic, lack of consistency in solvent effects in bands 1 and 3 will also be noted in the phenylacetic acid series (V–VIII).

Further insight into the origin of bands 1 and 2 could be obtained from low-temperature measurements. Attention has already been directed to the observation that, with the exception of VIIIa those acids which have a hydrogen atom attached to the asymmetric carbon atom (III, V, VI, VII) show only two CD bands, namely bands 1 and 3, at room temperature. That this situation is not altered over the temperature range +20° to −192° is evident on comparison of data presented in Table II for IIIb, IIId, and Vb, where it will be noted that bands 1 and 3 become more intense at progressively lower temperatures. On the other hand, the CD spectra of the α-substituted mandelic acids are very temperature dependent, as illustrated in Figures 4 and 5 for (*S*)-(+)-methyl α-trifluoromethylmandelate (Ib) and its methyl ether (Id). It is of particular interest to note that, whereas in the case of IIIb and Vb band 1 increased in going to lower temperatures, in Ib and Id it is band 2 that becomes more intense at lower temperatures. Thus, in the case of Ib, which shows both bands 1 and 2 at room temperature, only the latter can be observed at −192°. The same behavior, namely a decrease in intensity of band 1 and an increase in intensity of band 2, is shown by IIb and IId (Table II) although measurements could only be made down to −74°. It is also evident from a comparison of the CD curves in Figures 4 and 5 why band 1 is not seen in some of the α-substituted mandelic acid derivatives. In Ib (Figure 4) band 2 experiences the greater relative increase in intensity as well as the larger blue shift (16 nm) in going from room temperature to −192°, whereas the blue shift of band 2 of Id is only 10 nm. Thus, in the case of Id, even at room temperature the relative intensities of bands 1 and 2 are such as to obscure the observation of the higher energy band. Figure 4 clearly illustrates our earlier observation[24] that the real difference in the wavelength position of two Cotton effects of opposite sign need only be of the order of 1–2 nm whereas, depending on the relative rotational strengths of the two bands, the observed maxima may be separated by 20 or more nm.

Discussion

Before discussing our CD results it will be useful to first make some brief comments on some features of the absorption and CD spectra exhibited by compounds containing either one or the other of the two chromophores involved, and then to examine the possibility of interaction between them.

The Cotton effects appearing around 220 nm in aliphatic carboxylic acids,[9c,9d] esters and lactones,[25,26] α-hydroxy and α-amino acids[8,9a] are commonly attributed to an $n \rightarrow \pi^*$ transition.[27] Nevertheless Anand and Hargreaves[17a] suggested recently that the very weak CD Cotton effect which they observed for lactic acid at 240–250 nm, depending on the solvent, should be associated with an $n \rightarrow \pi^*$ transition and that

---

[23] W. H. Pirkle and S. D. Beare, *Tetrahedron. Lett.*, 2579 (1968).

[24] K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *J. Amer. Chem. Soc.*, 87, 66 (1965).

[25] (a) J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 7211 (1965); (b) W. Klyne, *Proc. Roy. Soc.* (London), *A*, **297**, 66 (1967).

[26] A. F. Beecham, *Tetrahedron Lett.*, 3591 (1968).

[27] (a) W. D. Closson and P. Haug, *J. Amer. Chem. Soc.*, **86**, 2384 (1964); (b) W. D. Closson, P. J. Orenski, and B. M. Goldschmidt, *J. Org. Chem.*, **32**, 3160 (1967).

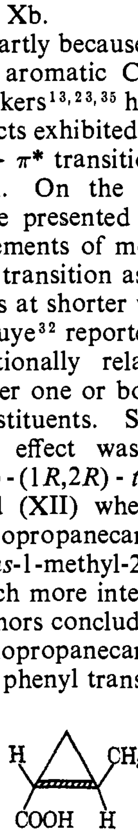
the more intense CD Cotton effect found at 210 nm could be attributed to a $\pi \rightarrow \pi^*$ transition. It appeared to us that this situation was more reflective of the conformational and solvational equilibria effects which have been extensively studied in this laboratory[28] and elsewhere[29] than of separate electronic transitions. In a recent communication[1] we reexamined the "lactic acid anomaly" and presented evidence that the two CD bands observed in lactic acid derivatives, and presumably in α-amino acids,[17b] are not of separate electronic origin but rather are associated with the same electronic transition ($n \rightarrow \pi^*$) and most plausibly can be considered as arising either from differently solvated species or from different rotamers.

Compounds containing the phenyl group exhibit three electronic absorption bands in the wavelength range covered by modern spectropolarimeters and circular dichrometers. The weak characteristically structured transition appearing in the 250–275 nm region of substituted benzene derivatives is designated, in Platt's terminology,[30] as the ^1L_b band; and the stronger absorption bands found near 193 and 215 nm are designated as the $^1B_{a,b}$ and ^1L_a bands, respectively. Moscowitz[11] presented ORD evidence that the 260-nm absorption band of phenylalanine was indeed optically active and pointed out that the intensity differences in the structured Cotton effects[31] associated with this band in phenylalanine and in its *p*-hydroxy derivative, tyrosine, could be attributed to differences in the local symmetry of the dissymmetrically perturbed phenyl chromophore; the facile observation of these Cotton effects in the latter compound was thus a matter of degree rather than kind. In the CD spectra of the substituted phenylacetic acid derivatives presented in Figures 1–5 the Cotton effects associated with the ^1L_b transition will be recognized as band 3 and are characterized by their very low intensity and by their vibrational fine structure. Following the work of Moscowitz,[11] other investigators using CD confirmed the optical activity of the ^1L_b transition in phenylalanine[13] and in other compounds in which the only chromophore absorbing above 200 nm was the phenyl group.[12,14] Shortly thereafter the results of additional investigations were reported[14,32] which confirmed an earlier report[12b] of a CD Cotton effect associated with the ^1L_a band. Verbit[12b] found two relatively strong negative Cotton effects in the CD spectrum of (*S*)-(−)-methylphenylcarbinol at 205 nm ($[\theta]_{max} \sim 3000$) and 212 nm ($[\theta]_{max} \sim 2000$) as well as the weak structured positive Cotton effects associated with the ^1L_b transition in the 260–270 nm region. Craig and coworkers[14] observed a single CD Cotton effect in the ^1L_a region (216 nm, $[\theta]_{max}$ −2130) as well as CD Cotton effects in the ^1L_b region (λ_{max} 269 nm, $[\theta]_{max}$ +401) for the hydrochloride salt of the tertiary amine (*S*)-(−)-N,N-dimethyl-α-phenylethylamine, but were unable to observe either an ORD or a CD Cotton effect in the ^1L_a region in the case of the hydrochloride of the parent base, (*S*)-(−)-α-phenylethylamine. The anistropy ratio, $\Delta\epsilon/\epsilon$, for aromatic systems containing only alkyl substituents, is generally such as to preclude (at least at present) the observation of CD Cotton effects in the ^1L_a region. Thus, for example, only the first extremum (223 nm) of the positive ^1L_a ORD Cotton effect was found for (*S*)-(+)-2-(*p*-tolyl)-butane.[33]

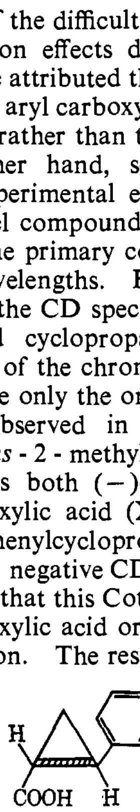
This situation is reflected in the CD spectra of some reference compounds which were measured in our laboratory. Examination of the CD data (ethanol and cyclohexane) presented in Table I for phenyltrifluoromethylcarbinol (IX), (*R*)-(+)-2-phenyl-3,3,3-trifluoro-1-propanol (Xa), and (*S*)-(+)-2-phenyl-3,3,3-trifluoro-1-chloropropane (Xb) reveals that although the structured ^1L_b Cotton effects were observed in the three reference compounds, the ^1L_a Cotton effects were of such very low intensity as to be barely distinguishable above noise level for only one of the three samples.

That an assignment of the electronic origin of the band 1 Cotton effects observed in the α-substituted phenylacetic acids cannot be made solely on the basis of the magnitudes of the Cotton effects observed for model or reference compounds is apparent from a consideration of the data presented in Table I for IIIa where it will be noted that the intensity of band 1 (λ_{max} 222 nm, $[\theta]_{max}$ +34,400 in 0.5 *N* HCl) is 7–14 times the combined intensities reported for such aliphatic carboxylic acids as (*S*)-(+)-lactic acid[1] (λ_{max} 212 nm, + 2200 in 0.5 HCl) or (*S*)-(−)-2-hydroxy-4-methylpentanoic acid[34] (λ_{max} 209 nm, + 5200 in 0.1 *N* HCl) and the intensities observed (∼0) for the reference compounds IX, Xa, and Xb.

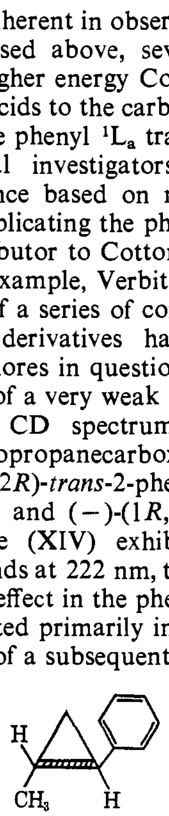
Partly because of the difficulties inherent in observing the aromatic Cotton effects discussed above, several workers[13,23,35] have attributed the higher energy Cotton effects exhibited by aryl carboxylic acids to the carboxyl $n \rightarrow \pi^*$ transition rather than to the phenyl ^1L_a transition. On the other hand, several investigators[32,36] have presented experimental evidence based on measurements of model compounds implicating the phenyl ^1L_a transition as the primary contributor to Cotton effects at shorter wavelengths. For example, Verbit and Inouye[32] reported the CD spectra of a series of configurationally related cyclopropane derivatives having either one or both of the chromophores in question as substituents. Since only the onset of a very weak Cotton effect was observed in the CD spectrum of (−)-(1*R*,2*R*)-*trans*-2-methylcyclopropanecarboxylic acid (XII) whereas both (−)-(1*R*,2*R*)-*trans*-2-phenylcyclopropanecarboxylic acid (XIII) and (−)-(1*R*,2*R*)-*trans*-1-methyl-2-phenylcyclopropane (XIV) exhibited much more intense negative CD bands at 222 nm, these authors concluded that this Cotton effect in the phenylcyclopropanecarboxylic acid orginated primarily in the ^1L_a phenyl transition. The results of a subsequent CD



XII



XIII



XIV

---

[28] W. S. Briggs and C. Djerassi, *Tetrahedron*, **21**, 3455 (1965).

[29] G. Snatzke, *Proc. Roy. Soc.* (London), *A*, **297**, 43 (1967).

[30] J. R. Platt, *J. Chem. Phys.*, 17, 484 (1949).

[31] An analysis of the vibrational fine structure in the ^1L_b band of some phenylalanine derivatives has recently been reported: J. Horowitz, E. H. Strickland, and C. Billups, *J. Amer. Chem. Soc.*, **91**, 184 (1969).

[32] L. Verbit and Y. Inouye, *ibid.*, **89**, 5717 (1967).

[33] L. Verbit, A. S. Rao, and J. W. Clark-Lewis, *Tetrahedron*, **24**, 5839 (1968).

[34] L. Verbit and P. J. Hefron, *Tetrahedron*, **24**, 1231 (1968).

[35] A. Fredga, J. P. Jennings, W. Klyne, P. M. Scopes, B. Sjöberg, and S. Sjöberg, *J. Chem. Soc.*, 3928 (1965).

[36] A. Rosenberg, *J. Biol. Chem.*, **241**, 5119 (1966).

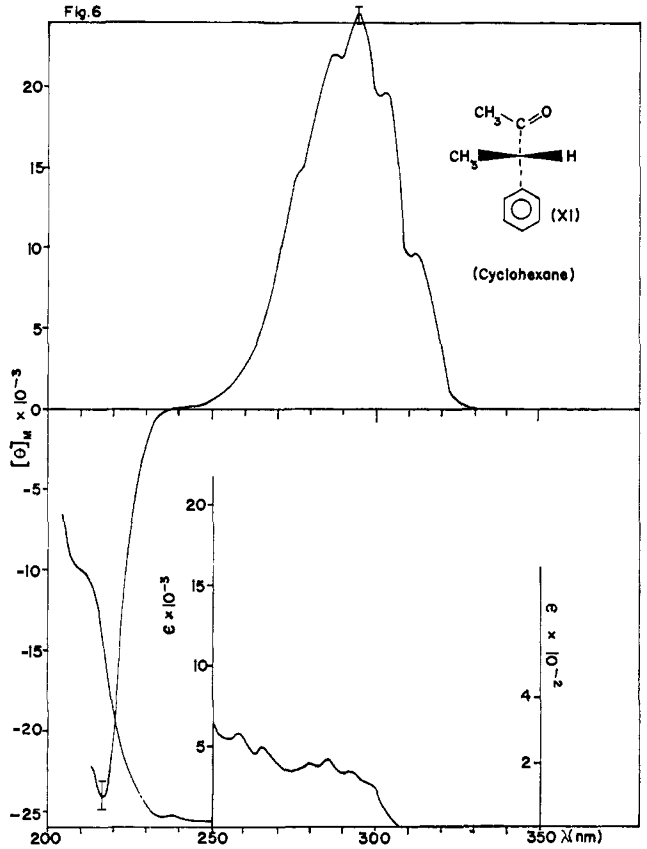


Figure 6. Absorption (lower curve) and CD spectra of (*S*)-(+)-3-phenyl-2-butanone (IX) in cyclohexane.

investigation[34] of α-substituted phenylacetic acids and α-substituted β-phenylpropionic acids were also interpreted as indicating that the Cotton effects found in the 220-nm region in the CD spectra of *both* series are due mainly to a transition associated with the aromatic ring.

The optical properties of molecules containing coupled although not formally conjugated chromophores, often referred to as homoconjugated systems, have been the subject of many investigations in recent years. The areas in which the interaction of such coupled chromophores is pertinent encompasses such apparently diverse systems as polypeptides and polynucleotides as well as the simpler rigid and flexible molecules which contain as few as two suitably oriented π systems. Moscowitz[37] has pointed out that some of the rigid optically active systems in the latter category serve as useful prototypes for the more complex polymeric systems.

Examination of the ORD curves of β,γ-unsaturated ketones resulted in an extension of the octant rule[38] initially in the charge-transfer framework of Labhart and Wagniere[39] and subsequently[37] in terms of a more general approach. The extended octant rule,[38] taken in the context of optically active β,γ-unsaturated ketones, stated that "there exist substituents whose geometric disposition in a particular far octant is sufficient for the determination of the sign of the long-wavelength Cotton effect." The extended octant rule, secure for rigid molecules, could be further extended to more conformationally mobile systems such as 3-phenylcholestan-2-one and open chain α-phenyl ketones. In the case of the acyclic α-phenyl ketones, which are particularly germane to the present discussion, the sign of the enhanced $n \rightarrow \pi^*$ carbonyl Cotton effect exhibited by either enantiomer could be interpreted on the basis of the particular conformer having, on the basis of reasonable steric arguments, the phenyl group in a positive or negative octant. The salient features predicted, irrespective of the particular theoretical approach employed,[40–42] and observed, in the CD spectra of optically active β,γ-unsaturated ketones having a favorable geometric disposition of the two interacting chromophores, are the enhanced equal and opposite rotation strengths found in the regions of absorption of the component chromophores. In addition, one frequently observes a bathochromic shift in the positions of the aromatic and carbonyl absorption and CD bands. Homoconjugation is also evident in isotropic absorption spectra from the enhanced intensity of the $n \rightarrow \pi^*$ carbonyl transition and by the diminished intensity (due to intensity borrowing) of the $\pi \rightarrow \pi^*$ transition of the coupled π system. It should be noted that these features will be less dramatically evident in the spectra of conformationally mobile systems. In the CD spectrum of (*S*)-(+)-3-phenylbutan-2-one (XI) presented in Figure 6 attention is drawn to the greatly enhanced and positive carbonyl Cotton effect centered at 294 and to the oppositely signed and equally intense aromatic Cotton effect at 217 nm (either the locally excited ^1L_a phenyl or a charge-transfer transition—for brevity we henceforth assume the former). Examination of the data presented in Table I for (*S*)-(+)-hydratropic acid (Va) which served as the starting material for the ketone XI reveals that this compound exhibits a very strong and positive Cotton effect (band 1) at about 220 nm in addition to the very weak Cotton effects associated with the ^1L_b phenyl transition (band 3). A necessary consequence of the theories of the optical activity of coupled chromophores and one which is observed experimentally[40b] is that the intensities of the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ Cotton effects will increase as the energy difference between the transitions becomes smaller. Thus, assuming only that the transition of lower energy is the carboxyl $n \rightarrow \pi^*$ transition, one would expect to observe in the CD spectra of the (*S*)-α-substituted phenylacetic acids very strong positive Cotton effects (band 1) for this transition around 220 nm *and* equally intense negative Cotton effects associated with the aromatic transition in the 200–215 nm region. The negative Cotton effects (band 2) found at 230–245 nm are also considered to be of $n \rightarrow \pi^*$ origin and will be discussed in some detail later. It should be emphasized, however, that the observed intensities and positions of two closely spaced and oppositely signed CD Cotton effects will be considerably different from their real values.[24] The data collected in Table I show that a strongly positive Cotton effect is present in the region of the carboxyl $n \rightarrow \pi^*$

---

(37) A. Moscowitz, A. E. Hansen, L. S. Forster, and K. Rosenheck, *Biopolym., Symp.*, 1, 75 (1964).

(38) A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Amer. Chem. Soc.*, 84, 1945 (1962).

(39) H. Labhart and G. Wagniere, *Helv. Chim. Acta*, 42, 2219 (1959).

(40) (a) R. C. Cookson, *Proc. Roy. Soc.* (London), *A*, 297, 27 (1967); (b) D. E. Bays, R. C. Cookson, and S. Mackenzie, *J. Chem. Soc.*, 215, (1967).

(41) A Moscowitz, *Proc. Roy. Soc.* (London), *A*, 297, 40 (1967).

(42) For recent comments on optical activity in coupled systems as well as the complexities of the benzene chromophore, see H. Eyring, H.-C. Lin, and D. Caldwell, *Chem. Rev.*, 68, 525 (1968).

transition. On the other hand, we have not been able to detect a negative Cotton effect at lower wavelengths. Two factors can be cited for our failure to observe this Cotton effect. First, the very unfavorable anistropy ratios prevailing in this region, coupled with the sharply falling light-source energies around 200 nm, may be such as to preclude sensitive enough measurements in this region. Second, one of the higher energy phenyl transitions may be implicated. In this case the intensity of the ^1L_a Cotton effect may be weak and its sign, like that of the ^1L_b Cotton effect (*vide infra*), indeterminant.

In summary, it is on the basis of the arguments discussed above that *we suggest that the higher energy Cotton effects (bands 1 and 2) exhibited by α-substituted phenylacetic acids should be primarily associated with the enhanced* n → π* *transition of the carboxyl group and only secondarily, if at all, to a transition of the phenyl group.* Additional support for this assignment comes from the similar solvent and temperature effects observed for derivatives of (*S*)-(+)-α-trifluoromethylmandelic acid (I) and (*S*)-(+)-atrolactic acid (II) and those reported[1] for lactic acid derivatives.

If one accepts the arguments proposed in the preceding section that it is the carboxyl n → π* transition rather than the phenyl ^1L_a transition that is primarily responsible for the Cotton effects observed in bands 1 and 2 of the α-phenylacetic acid derivatives investigated in the present study, then the CD spectra can be rationalized using the basic tenets of the extended octant rule.[38] Since we regard the α-substituted phenylacetic acids as an inherently dissymmetric—albeit conformationally mobile—system, we will consider only those conformations in which the carboxyl and phenyl groups have the proper orientation for high optical activity. Since in these particular spatial distributions a relatively minor populated conformation will make an inordinately large contribution to the observed optical activity, we are effectively analyzing our CD data relative to particular and perhaps relatively less populated conformations in contradistinction to the usual practice in flexible systems[9,24] which contain noninteracting chromophoric groups. In addition to this restriction in the number of conformations examined, we also consider that in the coupled systems under consideration it is not necessary to invoke projections leading to sector rules[25] but rather that the α-substituted phenylacetic acid derivatives may be viewed in the usual octant projection as indicated in Figure 7. In conformity with the results of dipole moment measurement[43] we have oriented the alkoxyl group in that configuration in which the alkyl group is *cis* to the carbonyl group.

In Figure 7 we have represented two conformations resulting from rotation about the carbonyl–C_α bond; in each case the conformer shown is that one having the *S* configuration when the groups R′ and R″ are as indicated in Table I. If the C_α substituent labeled R″ is eclipsed by the carbonyl oxygen atom, then the phenyl group is necessarily placed in the far lower left negative octant as shown in **1**. When, however, the group labeled R′ is oriented so as to eclipse the carbonyl oxygen atom, one finds the phenyl group in the far upper left positive octant as indicated by **2** in Figure 7.

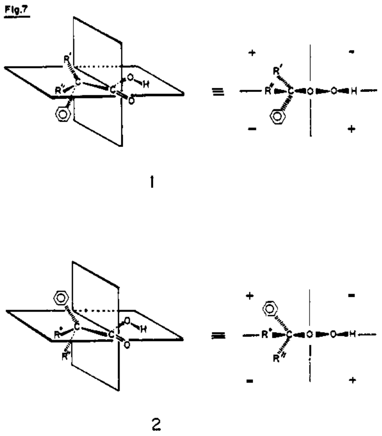


Figure 7.

The conformer in which the phenyl group is eclipsed by the carbonyl oxygen is excluded from consideration since in this case the perturbing π system would lie in a symmetry plane of the carbonyl group and would thus no longer fit the geometrical requirements for effective coupling between the two chromophores. Conformations **1** and **2** clearly place the phenyl group in the appropriate negative or positive octants, respectively, thereby satisfying one of the requirements of the extended octant rule.[38] It is, however, equally important that the π system be capable of assuming a geometrical disposition in a particular far octant that is favorable for effective homoconjugation between the two groups. This requirement is most clearly in evidence in the derivatives of (*S*)-(+)-α-cyclohexylmandelic acid (IV) (*vide infra*). In considering conformations **1** and **2** it is important to bear in mind that in the compounds studied, R′ and R″ may represent hydrogen, alkyl, trifluoromethyl, hydroxyl, and methoxyl groups, and that it is the forces tending to stabilize either conformation **1** or conformation **2** in the compounds of known absolute configuration (namely *S*[44] investigated in this study) which will be of determining importance in their CD spectra.

Considering first the α-substituted phenylacetic acid series, V–VIII, in which R″ represents hydrogen and R′ represents in turn CH_3, CF_3, C_2H_5, and $C(CH_3)_3$, we note in Table I that in either ethanol or cyclohexane solution these compounds show only a single Cotton effect at shorter wavelengths and that without exception they are strongly positive and centered closely about 220 nm. Leiserowitz[45] has suggested, from X-ray measurements, that in alicyclic carboxylic acids, that conformation in which the carbonyl oxygen eclipses a C_α–C_β bond is preferred, and Klyne[9d] has found that the ORD spectra of an extensive number of cholanic and steroid acids can be better correlated assuming this conformation than is possible on the basis of that conformation having the α hydrogen eclipsed with the carbonyl oxygen atom. Additional evidence for this conformational preference comes from nmr spectroscopy.[46] It is apparent that this conformational pref-

---

(43) J. W. Smith, "Electric Dipole Moments," Butterworths, London, 1955, p 239.

(44) R. S. Cahn, C. K. Ingold and V. Prelog, *Angew. Chem. Intern. Ed. Engl.*, 5, 385 (1966).

(45) L. Leiserowitz and G. M. Schmidt, *Acta Crystallogr.*, 18, 1058 (1965).

(46) G. J. Karabatsos and N. Hsi, *J. Amer. Chem. Soc.*, 87, 2864 (1965).

erence rationalizes the data in Table I for the (*S*)-α-substituted phenylacetic acid series, V–VIII, since it is conformation **2** which leads to the positive Cotton effect found in band 1.

In comparison, the CD results (Table I) obtained in the α-hydroxy acid series I–IV, in which R′ represents either OH or OCH_3 and R″ represents in turn CF_3, CH_3,H, and C_6H_{11} present a more varied picture. In a recent study of aliphatic carboxylic acids and α-hydroxy acids by means of X-ray diffraction, Kanters[47] concluded that the preferred conformation of α-hydroxy acids in the crystal state is that in which the oxygen atoms of the α-hydroxyl and carbonyl groups are eclipsed, and that this conformational preference is inherent in the free molecule itself. In addition, these authors asserted that this conformational preference was due to forces (unspecified) other than those which could be attributed to intramolecular hydrogen bonding. On the other hand, there is a considerable body of infrared evidence[48] implicating intramolecular hydrogen bonding, particularly to the carbonyl oxygen atom, with the formation of a hydrogen bond to the ester oxygen being of considerably less importance. The latter conformation is not depicted in Figure 7 since in this conformation the phenyl group is less favorably oriented for homoconjugation than it is in either **1** or **2**. Therefore, restricting ourselves still to a consideration of conformations **1** and **2**, one would anticipate that in the case of (*S*)-(+)-mandelic acid IIIa, and its methyl ester IIIb, it is conformation **2** that is the more energetically preferred. This conclusion is indeed supported by the CD data observed for IIIa and IIIb and collected in Table I where it will be noted that the amplitudes found in band 1 are, on the whole, larger than those observed for any of the compounds so far discussed. Further support derives from the low-temperature CD data observed for IIIb in EPA. In Table II it will be noted that in the case of IIIb the intensity of band 1 increases by about 34,000 deg cm^2/mol when the temperature is lowered from +20° to −74° whereas at −192° the intensity of band 1 increases by only 1600 deg cm^2/mol. This behavior may be compared to the low-temperature CD data summarized in Table II for (*S*)-(+)-methyl α-methylphenylacetate (Vb). In the case of the latter compound, where the α-methyl group is eclipsed with the carbonyl oxygen atom,[43] decreasing the temperature from −74° to −192° results in a considerably greater intensity increase (10,000 deg cm^2/mol), since in both IIIb and Vb, R″ = H, these results serve to gauge the extent to which conformation **2** is preferred when R′ = OH or CH_3, respectively. Returning now to the methoxyl derivatives, comparison of the intensities found in band 1 of IIIc and IIIa and, on the other hand, of IIId and IIIb, reveals that in each pair it is the methyl ether derivative that has the smaller $[\theta]_{max}$ value in band 1. This result would, of course, be expected since not only is the stabilization afforded by intramolecular hydrogen bonding precluded but, in addition, the methyl ether group can assume rotameric conformations which destabilize those rotameric conformations of the phenyl group which lead to enhancement of the n–π^* Cotton effect.

In the (*S*)-(+)-α-trifluoromethylmandelic acid (I) and in the (*S*)-(+)-atrolactic acid (II) derivatives (R′ = OH or OCH_3 and R″ = CF_3 or CH_3) a particular conformation preference for either **1** or **2** may be more equivocal. Comparison of the data collected in Table I for the several derivatives of I and II with the data presented for the compounds discussed above, namely III and V–VIII, reveals that, in the case of I and II, conformation **1** is sufficiently populated as to be observable in each derivative of I and II, although in several instances, in only one solvent. Again it should be noted that both I and II are of the *S* configuration and that according to our hypothesis it is conformation **1** which leads to the negative Cotton effect found in band 2, whereas conformation **2** results in the positive, and in the series III and V–VIII ubiquitous, Cotton effect found in band 1. The relatively small energy barrier between conformations **1** and **2** is also evident from the relatively more pronounced solvent and temperature dependencies exhibited by the several derivatives of I and II. Although it is necessary to keep in mind the qualifications previously stated as to the possibly indeterminant contribution of the phenyl (presumably the ^1L_a) transition to the Cotton effect of band 1, it is interesting to note that the CD data for Ia and IIa support the observations made above (for IIIb and Vb) as to the relative preference for the conformation in which the carbonyl group eclipses the hydroxyl group over that in which the carbonyl group is eclipsed by the C_α–C_β bond. Thus, in the CD spectra of Ia and IIa presented in Figures 1 and 2, the large difference in the intensities of the Cotton effects in bands 1 and 2 indicates that it is conformation 2 (R′ = OH) that is the more highly populated. In the methyl ethers, Ic and IIc, the loss of the stabilization afforded by intramolecular hydrogen bonding is reflected in their dramatically altered CD spectra (Figures 1 and 2). Although both bands 1 and 2 are clearly evident in the CD spectrum (Figure 2) of IIc, only band 2 could be observed in the CD spectrum (Figure 1) of Ic. It should be noted, however, in Table I that Ic in cyclohexane solution exhibits a positive CD band at lower wavelengths. This band, which is listed under band 1 in Table I, reaches a maximum at 206 nm, some 14 nm toward lower wavelength compared to the normal position for band 1. Although it is tempting to identify this band with the ^1L_a phenyl transition, this disparity could equally well reflect the larger difference in apparent CD band position resulting when a relatively weak CD band overlaps a much stronger CD band of opposite sign.[24] Comparison of the data presented in Table I for derivatives of I and II (specifically compare the data collected for Id and IId) suggests that in the two series, the one having an α-trifluoromethyl group (I) and the other having an α-methyl group (II), there is a slight but significant preference in conformation **1** for the case where R″ = CF_3 than when R″ = CH_3.

The relatively delicate balance between conformations **1** and **2** in the α-trifluoromethyl series is illustrated by the low-temperature CD spectra (Figures 4 and 5) observed for Ib and Id. In Figure 4 it will be noted that, although conformer **2** (R′ = OH) is apparently more highly populated at room temperature, conformer **1** (R″ = CF_3) is the more highly populated one at −192°; in the case of Id (Figure 5) the only evidence available

---

[47] J. A. Kanters, J. Kroon, A. F. Peerman, and J. C. Schoone, *Tetrahedron*, 23, 4027 (1967).

[48] For example, see N. Mori, S. Omura, N. Kobayashi, and Y. Tsuzuki, *Bull. Chem. Soc. Jap.*, **38**, 2149 (1965).

for conformer **2** ($R' = OCH_3$) is the apparent blue shift of band 2 at progressively lower temperatures. Further evidence for this rather delicate balance is obtained from a comparison of the solvent-dependent CD spectra of Ib. In Figure 3 it will be noted that the ratio of the intensities of bands 1 and 2 progressively increases as the polarity of the solvent decreases. This is the order expected on the basis of the relative abilities of these solvents for destroying conformational stabilization due to intramolecular hydrogen bonding. Thus in ethanol the competition between intramolecular and intermolecular hydrogen bonding is such that conformer **2** ($R' = OH$) is sufficiently destabilized to permit a significant contribution from conformer **1** ($R'' = CF_3$) whereas in cyclohexane only the strongly positive Cotton effect associated with conformer **2** ($R' = OH$) can be observed. When the possibility of intramolecular hydrogen bond formation is removed, as in Id, it is apparent from the data collected in Table I that conformer **1** is the preferred one in either ethanol or cyclohexane.

As previously noted, the CD data collected in Table I for (*S*)-(+)-α-cyclohexylmandelic acid (IVa) and its derivatives are of particular interest with regard to one of the tenets of the extended octant rule:[38] namely, that it is the geometrical disposition of the π system in a particular far octant that is of overriding importance, especially in conformationally mobile molecules, for determining the signs of the Cotton effects exhibited by homoconjugated systems. In particular, an examination of molecular models of (*S*)-(+)-α-cyclohexylmandelic acid (IVa) oriented as in conformations **1** and **2** ($R' = OH$ or OCH_3; $R'' = C_6H_{11}$) reveals that in conformation **2**, which we have associated with a positive Cotton effect in band 1, the phenyl group can assume an orientation relative to the plane of the carboxyl group which will result in high optical activity and that in this orientation steric compression between the phenyl *ortho* hydrogen atoms and the bulky cyclohexyl group are minimized even in the most sterically unfavorable rotameric conformation assumed by the cyclohexyl group. In conformation **1**, which leads to the negative Cotton effect found in band 2, there is severe steric compression between the phenyl group, when properly oriented, and the cyclohexyl group in nearly all of the rotameric conformations which the latter group can assume. It is perhaps worthwhile to again emphasize that in referring to conformer populations we are directing our attention only to those in which spatial dispositions of the phenyl group are such as to result in the most effective interaction between the orbitals of the two chromophores. The plausibility of this argument is, in general, reflected by the CD data collected for compounds IVa–IVc in Table I. In conformity with the results obtained in the (*S*)-(+)-α-trifluoromethylmandelic (I) and in the (*S*)-(+)-atrolactic acid (II) series, the formation of the ether derivative, IVc, destabilizes conformation **2** leading to a reduction in the intensity of CD band 1. The observation of a very small negative Cotton effect in band 2 for (*S*)-(+)-methyl α-cyclohexylmandelate (IVb) is somewhat surprising and suggests either a breakdown of our oversimplified octant representation or that conformations other than **1** and **2** should not have been excluded from consideration.

In rationalizing band 1 and 2 it should be noted that in principle one could also implicate an equilibrium between two or more differently solvated species[24] and one can readily envision the presence of several species engendered by the interplay of both effects. We believe, however, that our CD results can be most economically attributed to conformational equilibria, in particular $\mathbf{1} \rightleftharpoons \mathbf{2}$, on the following grounds. First, in the CD spectra (Figure 3) of Ib the negative CD band at 235 nm and the positive CD band at 220 nm in ethanol are of roughly the same intensity. If we view this curve as reflecting an equilibrium between differently solvated species having opposite rotational strengths and absorbing at slightly different wavelengths, then we would anticipate that the intensity of the CD band at 220 nm associated with the more highly solvated species would decrease in going to less polar solvents. In fact, the CD spectra presented in Figure 3 show just the opposite behavior. Second it would also be anticipated that a redistribution of intensities in the CD bands associated with the more highly solvated species would occur at progressively lower temperatures; the higher energy Cotton effect of the solvated species increasing at the expense of the lower energy less solvated species. Again, the low-temperature CD spectra (Figure 4) of Ib are inconsistent with a rationalization based solely on a solvational equilibrium. That this behavior is not peculiar to Ib is revealed on comparison with the low-temperature data collected for IIb in Table II. Finally, one would expect to observe, on the whole, a consistent pattern in the positions and intensities of the carboxyl Cotton effects in cyclohexane and in ethanol solution. In fact, examination of the data collected in Table I reveals no such pattern. Thus, our data, while not excluding solvational equilibria, suggest that such effects are of secondary importance.

Although attention has been directed to the Cotton effects in the 220–245-nm regions in this communication, the data collected in Table I for the ^1L_b Cotton effects also merit some consideration. In particular, it has been proposed[33,34] that the sign of the ^1L_b Cotton effects exhibited by α-substituted phenylacetic acids can be correlated with their absolute configurations—compounds having the *S* configuration giving negative ^1L_b Cotton effects. Examination of the CD data for the considerably more extensive series of (*S*)-α-substituted phenylacetic acids collected in Table I reveals that such configurational correlations are otiose. The inapplicability of any such simplistic configurational correlations prevails irrespective of the solvent and whether these compounds are considered on the basis of common functionality (*i.e.*, acids, ester, etc.) or on the basis of the substituents at the asymmetric center (as in Table I). Consequently, contrary to earlier assumptions in the literature,[34] there appears to be no obvious correlation between the signs of the ^1L_b Cotton effects and the Cotton effects at lower wavelengths.

In conclusion, we should emphasize that we have limited ourselves to a consideration of only those aromatic carboxylic acids, the α-substituted phenylacetic acids, which in our opinion are most amenable to treatment in terms of the coupled chromophore theory. We do not suggest that this approach provides a general answer to the electronic origin of the shorter wavelength Cotton effects exhibited on the one hand by aromatic carboxylic acids having more than one carbon atom interposed between the phenyl and the carboxyl groups or on the other hand by those systems for which it can be reasonably supposed that the interacting carboxyl n–π and the phenyl transitions are juxtaposed. The latter case seems to us to be an intriguing and fruitful area for further investigation.

Formation and Spectrum of Tetracyanoethylene Dimer Anion $(TCNE)_2^-$[1]

Michiya Itoh[2]

Contribution from the Laboratory of Molecular Structure and Spectra, Department of Physics, University of Chicago, Chicago, Illinois 60637.

Received June 11, 1969

Abstract: The reversible complex formation of TCNE (tetracyanoethylene) anion radical with its parent molecule in MTHF (methyltetrahydrofuran) or in THF was confirmed spectroscopically at low temperature. The complex, $(TCNE)_2^-$, shows a strong visible absorption band at 5330–5350 Å (ϵ_{max} 15,500). Analysis of the spectra yields an equilibrium constant in MTHF for $TCNE^-, Na^+ + TCNE \rightleftharpoons (TCNE)_2^-, Na^+$ at 161 °K of 1.32×10^3 l./mol, $-\Delta H°$ of 1.46 kcal, and $\Delta S°$ of 3.95 eu. Thermodynamic data depend very strongly on the metal cation and also on the solvent composition. Using the equilibrium constant, the spectrum of pure $(TCNE)_2^-, M^+$ was obtained. The equilibrium of the complex formation and the absorption spectrum are discussed.

Recently, electronic spectra and structures of the dimers of anion,[3–5] neutral,[6–9] and cation[5,10,11] radicals have been reported in both liquid and solid states. However, only a few spectroscopic studies of complexes (such as the naphthalene dimer cation) between anion or cation radicals and their parent molecules have been reported[12–15] although this kind of complex formation was rather often suggested, and also electron-transfer rates have been determined between anion radical and parent molecule in the liquid state. Among such studies, Ishitani and Nagakura[16] reported the electronic spectrum and structure of paracyclophane monoanion radical as a model for CT (charge-transfer) interaction between benzene anion and neutral molecule. Complex formation of tetracyanoethylene with its anion was first suggested by Phillips and Powell[17] on the basis of the reversible color change of THF (tetrahydrofuran) solution with temperature.

In this paper, the equilibrium of the formation of $(TCNE)_2^-$ from TCNE and $TCNE^-$ was studied for Li, Na, and K salts in MTHF (2-methyltetrahydrofuran), and in mixtures with THF at low temperature. Thermodynamic quantities of the equilibrium are reported. The absorption spectrum of the pure dimer anion, $(TCNE)_2^-, M^+$, was obtained from the analysis of this equilibrium.

Experimental Section

A good commercial sample of TCNE was used after sublimation in high vacuum. 2-Methyltetrahydrofuran was distilled over sodium metal after refluxing with sodium metal for 10 hr. The refluxing and distillation were repeated two times. THF was also purified using the same procedures as for MTHF. These solvents were kept with a Na mirror in bottles connected to the vacuum system.

The TCNE anion radical was prepared by reduction with a sodium or potassium mirror for about 5 or 10 sec, respectively. The TCNE anion and TCNE mixed solution was obtained. After that, the tube containing the Na or K mirror was sealed off from the solution tube with the 1-cm optical cell. For $TCNE^-, Li^+$, freshly cut lithium metal was used.

Alternatively, $TCNE^-,Na^+$ solid was prepared in acetonitrile from NaCN and TCNE *in vacuo* following the method reported by Webster, *et al.*[18] The molar absorption coefficient of the TCNE anion was determined from the solution of the solid salt dissolved in MTHF or THF, and also from the solution made by contacting TCNE with sodium or potassium. The coefficient was also determined by the following electron-transfer reaction from 1-methyl-4-carbomethoxypyridinyl radical[8,19] to TCNE. The absorption spectrum of an MTHF solution of the 1-methyl-4-carbomethoxypyridinyl radical was carefully determined at room temperature. The molar coefficient of the absorption band at 3920 Å of this radical has been reported (ϵ_{max} 4500).[7,19] TCNE was added to the MTHF solution of the pyridinyl radical through a breakable seal. Complete electron transfer from the pyridinyl radical to

---

[1] This research was assisted by the Office of Naval Research, Physics Branch, under Contract No. N00014-67-A-0285-0001.

[2] Address correspondence to: Faculty of Pharmaceutical Sciences, University of Tokyo, Bunkyo-ku, Tokyo, Japan.

[3] N. Hirota and S. I. Weissman, *J. Amer. Chem. Soc.*, **86**, 2538 (1964).

[4] R. H. Boyd and W. D. Phillips, *J. Chem. Phys.*, **43**, 2927 (1965).

[5] K. Kimura, H. Yamada, and H. Tsubomura, *ibid.*, **48**, 440 (1968).

[6] K. H. Hausser and J. N. Murrell, *ibid.*, **27**, 500 (1957).

[7] M. Itoh and S. Nagakura, *J. Amer. Chem. Soc.*, **89**, 3959 (1967).

[8] M. Itoh and E. M. Kosower, *ibid.*, **89**, 3955 (1967); *ibid.*, **90**, 1843 (1968).

[9] D. A. Wiersma and J. Kommandeur, *Mol. Phys.*, **13**, 241 (1967).

[10] See references in ref 5.

[11] E. M. Kosower and J. L. Cotter, *J. Amer. Chem. Soc.*, **86**, 5521 (1964).

[12] I. C. Lewis and L. S. Singer, *J. Chem. Phys.*, **43**, 2712 (1965).

[13] O. W. Howarth and G. K. Fraenkel, *J. Amer. Chem. Soc.*, **88**, 4514 (1966).

[14] B. Badger, B. Brocklehurst, and R. D. Russell, *Chem. Phys. Lett.*, **1**, 122 (1967).

[15] L. R. Melby, R. J. Harder, W. R. Hertler, W. Mahler, R. E. Benson, and W. E. Mochel, *J. Amer. Chem. Soc.*, **84**, 3374 (1962).

[16] A. Ishitani and S. Nagakura, *Mol. Phys.*, **12**, 1 (1967).

[17] W. D. Phillips and J. C. Powell, *J. Chem. Phys.*, **33**, 626 (1960).

[18] O. W. Webster, W. Mahler, and R. E. Benson, *J. Amer. Chem. Soc.*, **84**, 3678 (1962).

[19] E. M. Kosower and E. J. Poziomek, *ibid.*, **86**, 5515 (1964).