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CIRCULAR DICHROISM AND ABSOLUTE CONFIGURATION OF α-CHLORO AND α-BROMO ALKYL CARBOXYLIC ACIDS

EFFECT OF α-ALKYL SUBSTITUTION ON THE n→π* COTTON EFFECT.[1a]

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Abstract—CD, ORD and UV properties are reported for seventeen α-chloro and α-bromo alkyl carboxylic acids, with alkyl groups varying from Me to t-Bu. Two CD bands are present in the n→π* absorption region, for *S* compounds a positive maximum at 195–222 nm and a negative maximum at 233–270 nm. The former CD band is the most useful for assigning absolute configuration. The CD properties of these compounds are interpreted on the basis of a conformational equilibrium and a quadrant rule is proposed to correlate the CD results with the preferred conformations. The preferred conformation of all halo acids is probably the rotamer which has the halogen eclipsed with the CO group. While 2-bromopropanoic acid shows a much stronger CD band for the other conformer this is probably due to the greater rotational strength of a halogen atom in comparison to an alkyl group. 2-Bromopropanoic acid was found to be an exception to the rule of configurational correlation using Co (III) complexes of asymmetric carboxylic acids.

INTRODUCTION

THE techniques of ORD and CD have been applied to a wide variety of optically active carboxyl compounds.[2] Many of these are α-substituted alkyl carboxylic acids, especially α-amino acids [3a–f,h,l] and α-hydroxy acids.[3a,d,g,i–k] However, the only α-halo carboxylic acids for which Cotton effect data have been reported[4] are α-chloro and α-bromo succinic acid.

During a study[5] to prepare some optically active acetals, such as may occur in wine, derivatives of α-halo acids were employed as potential resolving agents. In the course of this work[5] it became apparent that the (−)-α-bromo acid (**17**) derived from (+)-α-t-butylglycine was of uncertain absolute configuration. The *S* configuration had been assigned[6] to (−)2-bromo-3,3-dimethylbutanoic acid (**17**) but this was based upon a configurational assignment for (+)-α-t-butylglycine which later[7] was found to be in error. Therefore, we established[8] the absolute configuration of (−)-**17** and the analogous α-chloro acid, (−)2-chloro-3,3-dimethylbutanoic acid (**9**), as *R* on the basis of chemical correlation and GLC separation of diastereoisomers. However, it is noteworthy that the sodium D-line rotations for most *S*-α-bromo and α-chloro alkyl carboxylic acids were negative in contrast to *S*-(+)-**9** and *S*-(+)-**17**. Examination of ORD curves confirmed this anomalous behavior for the two t-butyl acids. Thus as shown in Fig. 1 the first Cotton effect extremum observed for *S*-(+)-**9** was positive while other *S*-α-chloro acids such as 2-chlorobutanoic acid (**2**) and 2-chloro-4-methylpentanoic acid (**5**) gave first extrema of negative Cotton effects. To obtain further insight into this behavior and in order to establish relationships between chiroptical properties and absolute configuration, a CD study of an extensive series of α-chloro and α-bromo alkyl carboxylic acids was carried out.

RESULTS

Table 1 lists the 17 compounds studied in this investigation. All compounds have been synthesized from amino acids of known configuration by halogenation, a reaction known to proceed with retention of configuration. By using a wide range of amino acids from alanine through α-t-butylglycine we have prepared α-chloro acids (**1**–**9**) and α-bromo acids (**10**–**17**) with alkyl groups ranging from methyl to t-butyl.

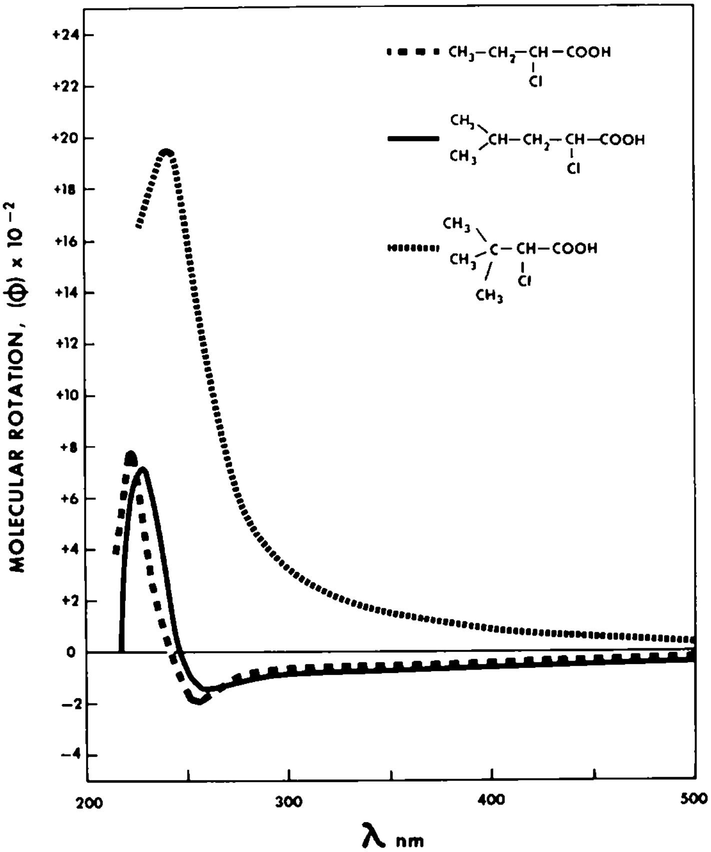
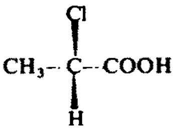
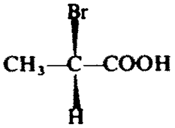
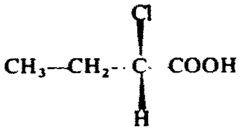
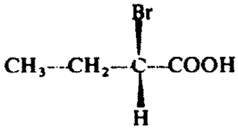
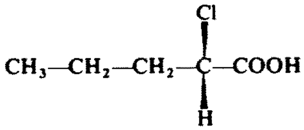
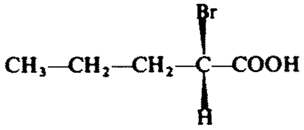
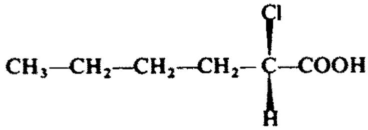
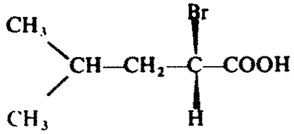
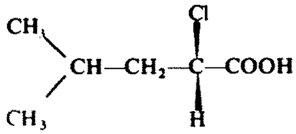
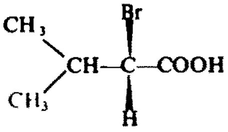
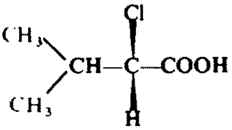
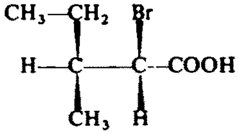
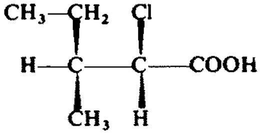
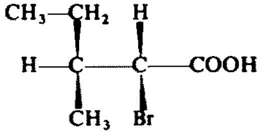
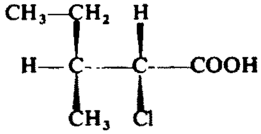
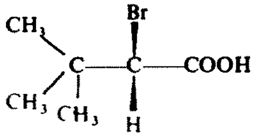
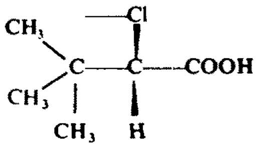


FIG 1. ORD curves of *S*-**2**,**5** and **9** in methanol.

S-α-chloro acids **1**–**5** and **7** were levorotatory at the D-line in methanol while *S*-acids **6** and **9** had a positive $[\alpha]_D$. One *R*-α-chloro acid (**8**) was studied and it gave a negative sodium line rotation in methanol. Rotations were of the same sign in cyclohexane as in methanol for all α-chloro acids except **6** which was negative in the hydrocarbon solvent. Fig. 1 shows that the sign of the first Cotton effect observed by ORD is the same as the sign of $[\alpha]_D$ for chloro acids **2**, **5** and **9** in methanol. The isopropyl α-chloro acid (**6**) behaved similarly inasmuch as the first extremum in the ORD was a peak at 233 nm. *S*-α-bromo acids (**10**–**15**) had negative $[\alpha]_D$ rotations while *S*-**17** was positive. The one *R*-α-bromo acid studied was dextrorotatory at 589 nm. ORD curves were obtained for four of the α-bromo acids and similar to the results obtained for the chloro acids, the sign of

TABLE 1. α-CHLORO AND α-BROMO ALKYL CARBOXYLIC ACIDS

No.	Chloro series	No.	Bromo series
1		10	
2		11	
3		12	
4		13	
5		14	
6		15	
7		16	
8		17	
9			

$[\alpha]_D$ was determined by the sign of the lowest energy Cotton effect. *S*-acids **10**, **14** and **15** gave negative high wavelength Cotton effects while *R*-**16** showed a peak at 275 nm. No sign changes in $[\alpha]_D$ were noted for the bromo acids in going from methanol to cyclohexane as solvent. The above rotation and ORD results provide another example[9] of aberrant rotatory behavior in configurationally identical compounds possessing similar electronic structures but having conformational mobility.

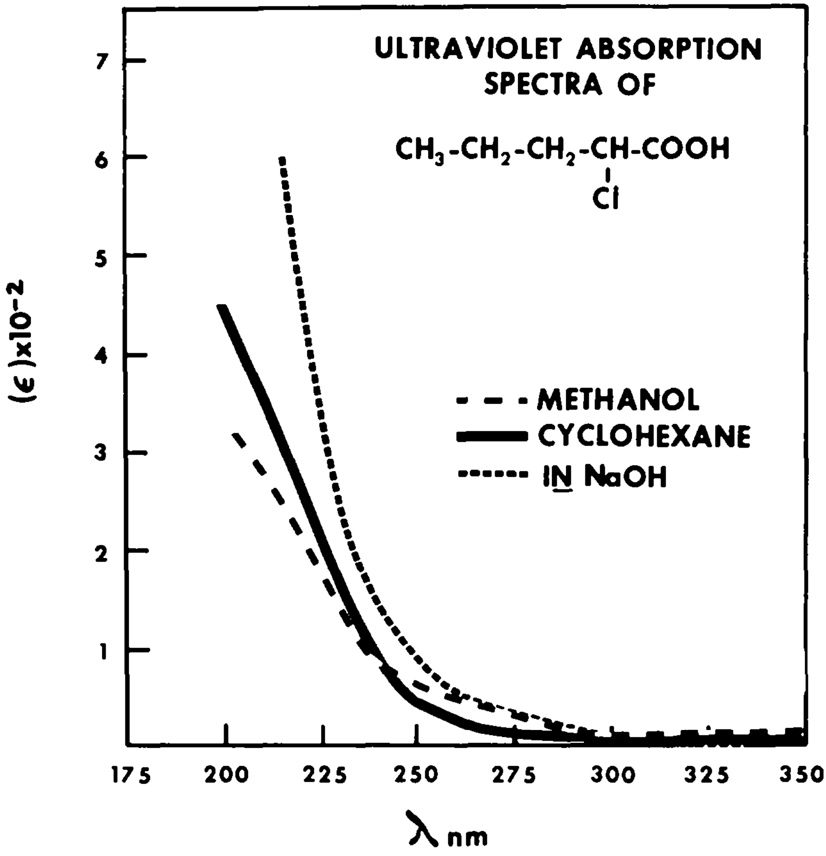


Fig 2. UV spectra of **3**.

Before proceeding to the CD results some aspects of the UV spectra of the halo acids will be presented. Fig. 2 shows the UV spectra of 2-chloropentanoic acid (**3**) in three solvents. Many of the halo acid UV spectra were similar to the curve in methanol—showing weak absorption in the 250–270 nm region with a shoulder evident at 215–220 nm. Absorption then rose sharply to the cutoff point at 200 nm. Only 4 of the 17 halo acids, **9**, **13**, **14** and **17**, showed UV maxima which occurred at 210–220 nm. For all other halo acids only shoulders were evident on the steeply rising background curves so that it was not possible to study solvent shifts in the absorption maxima. These studies were possible with CD bands (*vide infra*). The UV spectra of the less substituted α-chloro acids (**1**–**4**) did suggest[10] the presence of more than one species in solution and this was confirmed by CD data.

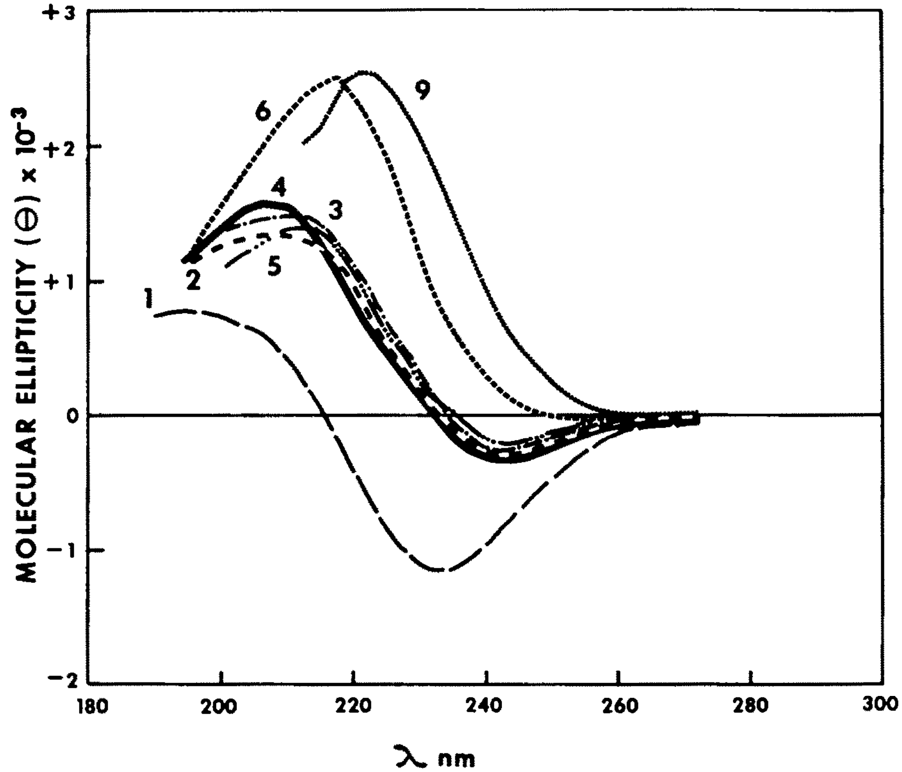


FIG 3. CD curves of S-α-chloro acids in methanol.——— ——— 2-Chloropropanoic acid (1). — — — — 2-Chlorobutanoic acid (2). —— · ——— · —— 2-Chloropentanoic acid (3). ——————— 2-Chlorohexanoic acid (4). ——————— · · · 2-Chloro-4-methylpentanoic acid (5). - - - - - - - - - 2-Chloro-3-methylbutanoic acid (6). ıııııııııııııııııııı 2-Chloro-3,3-dimethylbutanoic acid (9).

CD curves of **1–17** in methanol are presented in Figs 3–5. Each of the configurationally related *S*-α–chloro acids gave a positive CD band (band 1) at wavelengths varying from 195–222 nm. While this band varied in position and intensity (Fig 3) it was readily apparent in all cases. At higher wavelengths all seven chloro acids (Fig 3) also show a negative CD band (band 2) which diminished with increasing α-alkyl substitution until it was scarcely visible in the t-Bu analog (**9**). For easier observation Fig 4 shows only the higher wavelength band 2 (242–270 nm) for **3**, **5**, **6**, **8** and **9**. These results demonstrate that the D-line rotations reflect the magnitude of the Cotton effect at high wavelength (band 2). When this Cotton effect is very weak, as is the case for **6** or **9**, then the lower wavelength Cotton effect (band 1) determines the sign of optical rotation at high wavelength. Similar CD results (Fig 5) were obtained for α-bromo acids **10–17**. All *S*-acids gave positive Cotton effects at 205–220 nm and negative Cotton effects at 235–263 nm. The higher wavelength Cotton effect decreased in magnitude with increasing alkyl substitution similar to the chloro acid series. The weak negative Cotton effect at band 2 for the t-butyl bromo acid **17** was not strong enough to determine the sign of $[\alpha]_D$ since a positive D-line rotation was observed for **17**. Of the seventeen α-halo acids studied 2-bromopropanoic acid (**10**) is the only one in which the Cotton effect at band 2 is much larger than the lower wavelength CD band.

The results of CD measurements on several α-halo acids in cyclohexane, EPA and

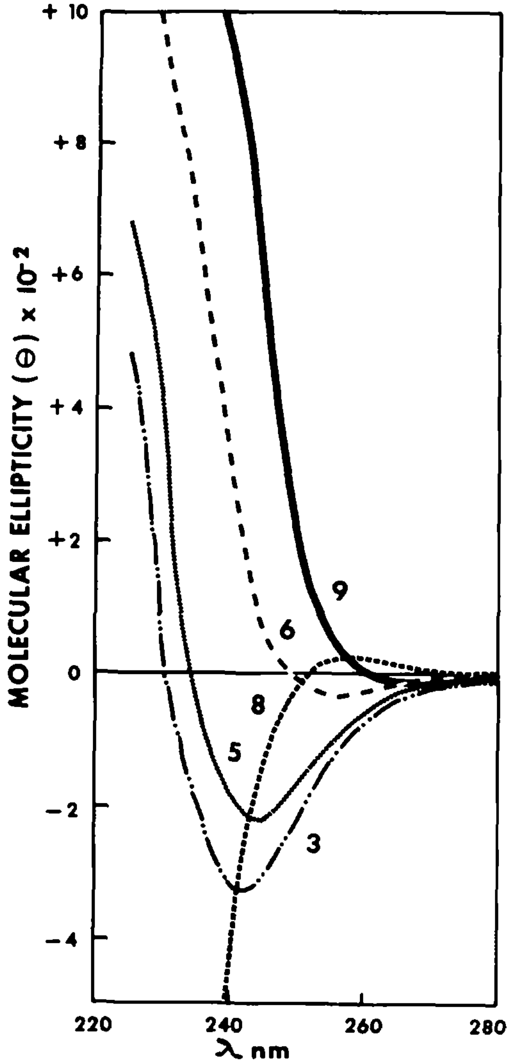


FIG 4. CD curves of α-chloro acids in methanol. ———— · · *S*-2-Chloropentanoic acid (**3**). ııııııııııııııııııııııı *S*-2-Chloro-4-methylpentanoic acid (**5**). —— —— —— *S*-2-Chloro-3-methylbutanoic acid (**6**). - - - - - - - - - - *R*-2-Chloro-*S*-3-methylpentanoic acid (**8**). ———————— *S*-2-Chloro-3,3-dimethylbutanoic acid (**9**).

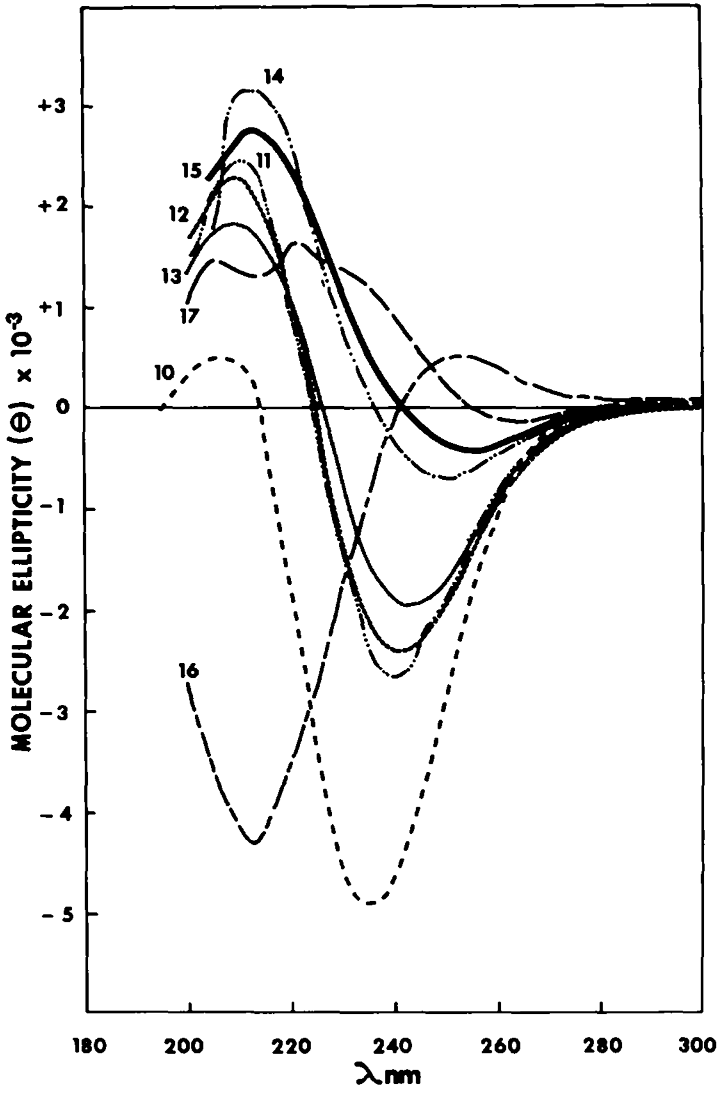


FIG 5. CD curves of α-bromo acids in methanol. — — — — — — — — *S*-2-Bromopropanoic acid (**10**). ——— · · · *S*-2-Bromobutanoic acid (**11**). - - - - - - - *S*-2-Bromopentanoic acid (**12**). ||||||||||||||||||| *S*-2-Bromo-4-methylpentanoic acid (**13**). ———— · · *S*-2-Bromo-3-methylbutanoic acid (**14**). ———— *S*-2-Bromo-*S*-3-methylpentanoic acid (**15**). ——— ——— *R*-2-Bromo-*S*-3-methylpentanoic acid (**16**). ——— ——— *S*-2-Bromo-3,3-dimethylbutanoic acid (**17**).

base provided a better understanding of the effects of solvent polarity and carboxyl ionzation. Similar relationships were observed between the intensities of band 1 and band 2 for the halo acids upon decreasing the solvent polarity but the direction of wavelength shift for the CD bands differed for cyclohexane and EPA. Thus in going from methanol to cyclohexane both band 1 and band 2 underwent a blue shift for the four α-chloro and three of the four α-bromo acids studied. The CD bands of 2-bromopropanoic acid (**10**) did not undergo a shift. The magnitudes of the blue shifts for bands 1 and 2 were fairly consistent, being 2–5 nm for the former and 3–17 nm for the latter. In going from methanol to EPA, band 1 underwent a red shift in four of five compounds studied, the fifth showing no shift at all. The wavelength shift for band 2 in going from methanol to EPA was evenly divided between red and blue shifts. The intensity relationships between band 1 and band 2 were quite consistent since eight of nine halo acids examined showed approximately a twofold decrease in the ratio band 1/band 2 in going to either of the two nonpolar solvents. This was usually manifested as a doubling of the CD intensity of band 2 with the intensity of band 1 remaining fairly constant. Compound **10** was again the exception to this generalization since it gave

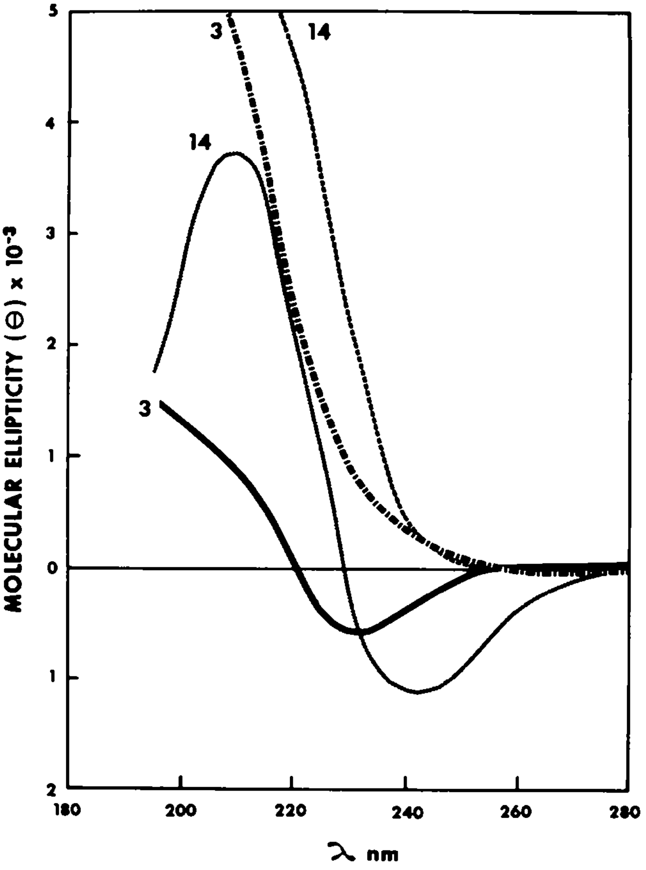


FIG 6. CD of S-2-Chloropentanoic acid (3) in cyclohexane (————————) and in 1 N NaOH (——·——·) and CD of S-2-bromo-3-methylbutanoic acid (14) in cyclohexane (||||||||||||||||||||) and in 1 N NaOH (– – – – – – – –).

about a twofold increase in band 1 with little change in the magnitude of band 2. It has been suggested[11] that the n → π* transition moves to higher energy upon ionization of the carboxyl group. All four of the chloro acids studied in base showed complete disappearance of band 2. The beginning of a strong positive Cotton effect was observed at low wavelengths but no maximum was found for band 1. Only one (**14**) of the three α-bromo acids examined showed complete disappearance of band 2 upon ionization. Two other bromo compounds (**10** and **11**) showed maxima for band 2 which were red shifted with reference to methanol by 6–10 nm. However band 2 was 5–7 times weaker in base than in methanol for **10** and **11**. A maximum for band 1 was only observed for **10** in the carboxylate form. This band was at the same position as band 1 for **10** in methanol and cyclohexane but was 5–10 times larger than the corresponding CD band in the organic solvents. Fig 6 shows CD curves for **3** and **14** both in base and in cyclohexane. These curves may be compared with the curves for **3** and **14** in methanol (Figs 3 and 5).

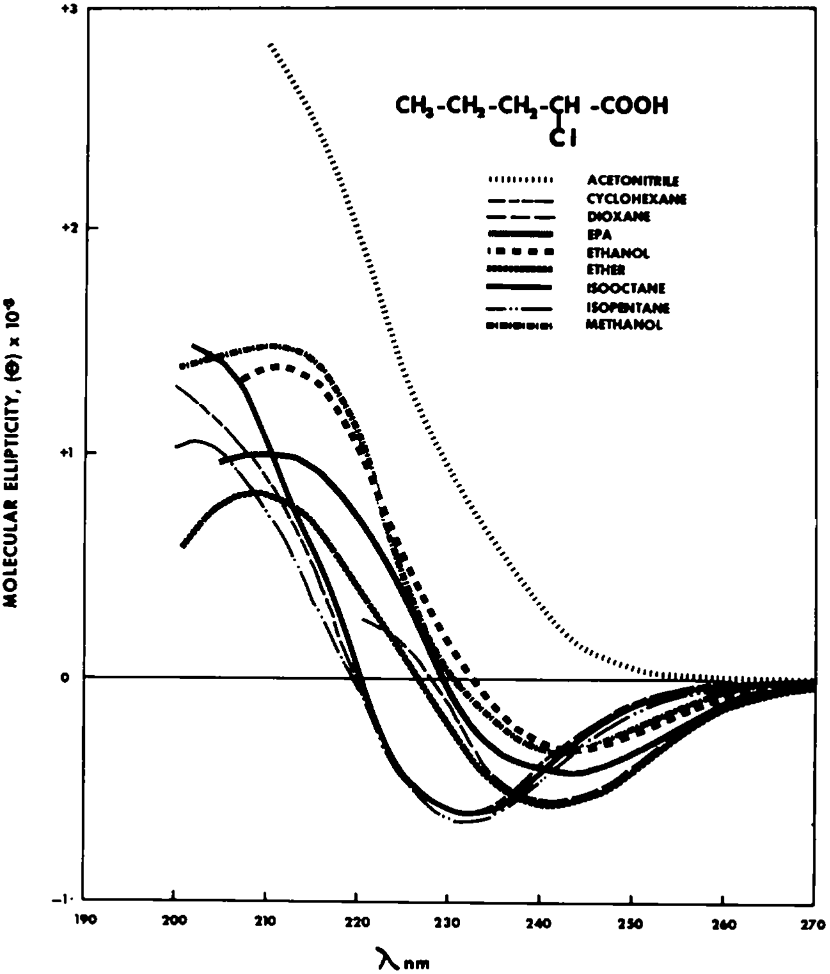


FIG 7. CD of *S*-**3** in various solvents.

Fig 7 shows CD results for 2-chloropentanoic acid (3) in nine different solvents. The intensity of band 2 increases and the band undergoes a blue shift upon decreasing solvent polarity. Band 1 is also blue shifted with decreasing solvent polarity for 2-chloropentanoic acid.

Low-temperature measurements of three α-chloro acids (3, 6 and 9) provided information on the nature of bands 1 and 2 in these compounds. The CD spectra of 2-chloropentanoic acid (3) from +25 to −185° (Fig 8) show that both bands 1 and 2 increase in intensity upon lowering the temperature. Figs 9 and 10 show variable-temperature CD spectra for the isopropyl (6) and t-Bu (9) α-chloro acids, respectively.

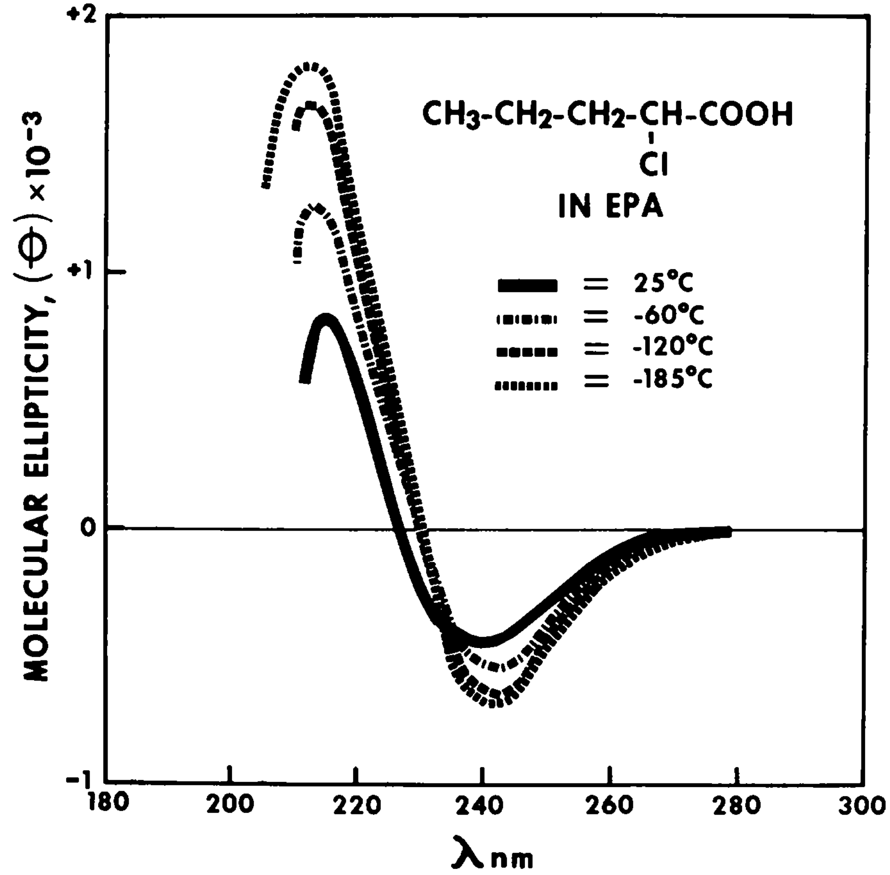


FIG 8. Variable temperature CD of *S*-3.

These two compounds behaved similarly since in both cases the weak band 2 disappeared entirely and band 1 increased in intensity upon lowering the temperature.

Cobalt (III) complexes of α-halo acids have been suggested[12] as suitable for configurational assignments. Table 2 shows CD results for the cobalt complexes of several halo acids. All of the halo acids of *S*-configuration gave a negative Cotton effect near 500 nm with the exception of 2-bromopropanoic acid (10) which gave a positive CD band.

CD, ORD and UV data, other than those presented in Figs. 1-10, are reported in the experimental section.

DISCUSSION

Recently several investigators have observed two overlapping ellipticity bands in asymmetric carboxylic acids. Anand and Hargreaves first reported the occurrence of two CD bands for lactic acid[13a] in various solvents and later published similar observations for *S*-α-amino acids.[13b] They suggested[13] that this behavior was due to two different transitions of the carboxyl group, a n→π* transition at higher wavelength and a π→π* band at lower wavelength. Djerassi *et al.*[14] also studied the CD behavior of lactic acid and its derivatives, their interpretation assumes different conformers rather than different transitions, and suggests that both bands are due to the n→π* transition.[14] Listowsky *et al.*[15] attributed double humped CD bands in uronic acids to differently solvated species. Further CD studies on aliphatic amino acids and some derivatives were reported

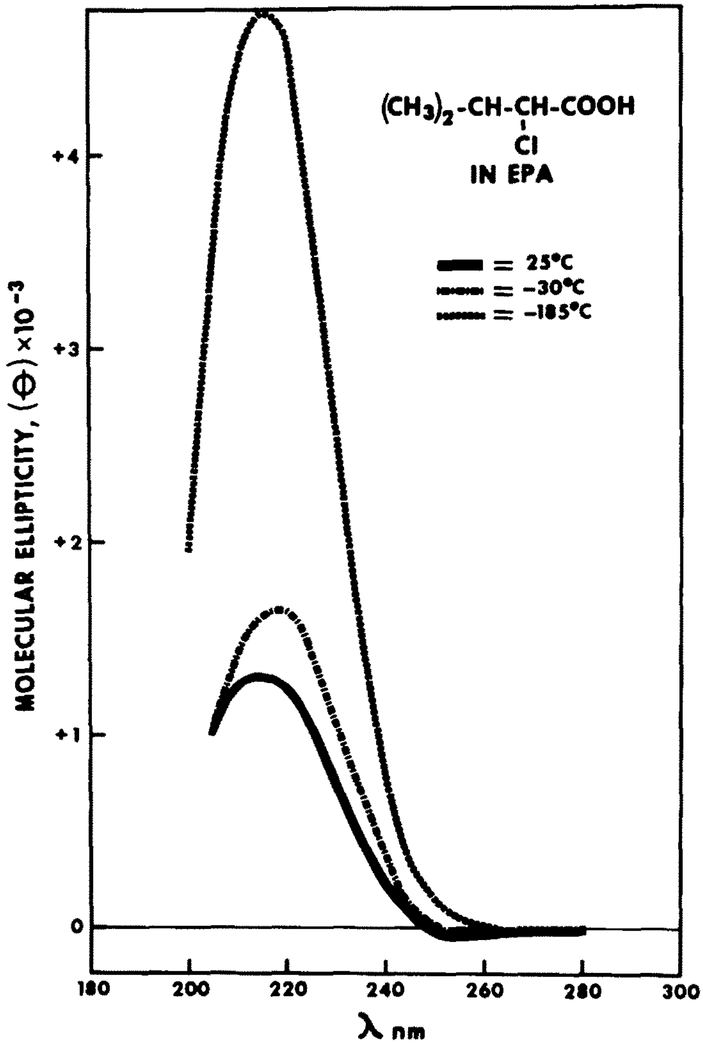


Fig 9. Variable temperature CD of *S*-6.

by Toniolo.[16] An extensive study was recently conducted on some α-substituted phenylacetic acids by Djerassi *et al.*[17] The Cotton effects appearing at 220–245 nm in these compounds have been shown[17] to be primarily associated with the n→π* transition of the carboxyl group and the Cotton effects have been interpreted as due to conformationally mobile homoconjugated systems. Configurational correlations have been made[17] on the phenylacetic acids by recourse to the extended octant rule.[18] CD studies of a wide variety of α-substituted acyclic carboxylic acids, mainly α-hydroxy and α-alkyl acids, were recently published by Listowsky *et al.*[19] These workers[19] also proposed the existence of rotational isomers to account for the presence of two overlapping Cotton effects in the n→π* absorption region of the optically active acids. Listowsky *et al.*[19] have correlated their results in terms of a simple empirical rule which also explains the Cotton effect behavior of some alkyl succinic acids studied by Klyne *et al.*[4]

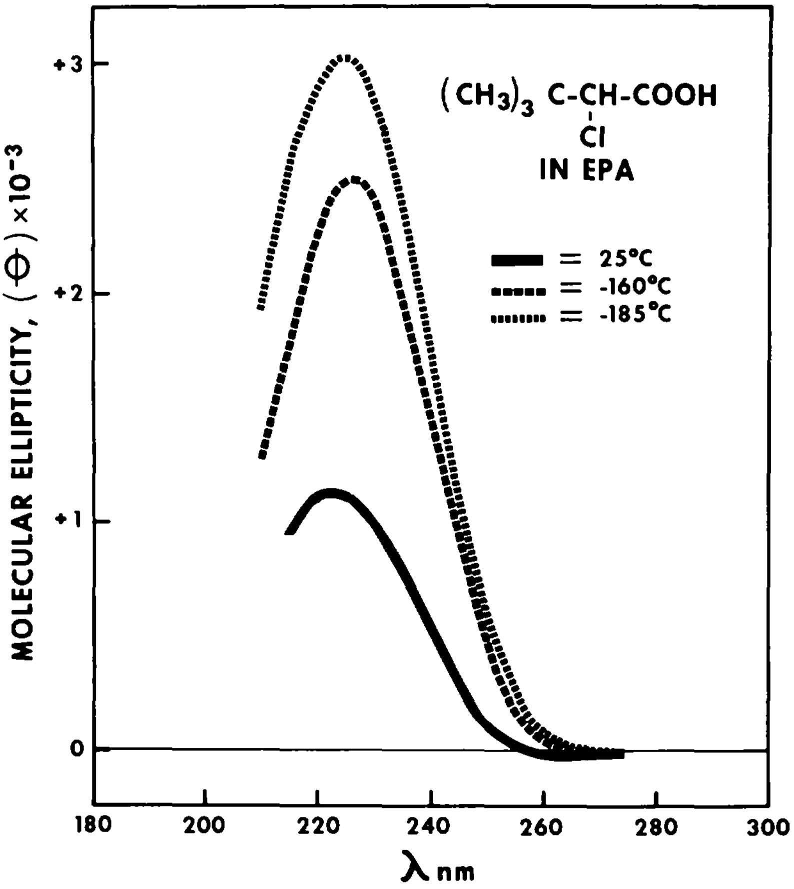
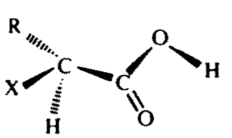


FIG 10. Variable temperature CD of *S*-9.

The foregoing establishes the occurrence of two[13-17, 19] CD bands in carboxylic compounds at 200–250 nm and that these bands can both be n→π*[14, 15, 17, 19] in origin. Our studies on α-halo acids also show dual banded behavior in all seventeen compounds studied and the two bands do not shift in opposite directions upon going to solvents of lower polarity. Thus it appears that the CD spectra of α-halo acids in the 200–275 nm region may be interpreted in terms of the effect of different species present in solution upon the $n \rightarrow \pi^*$ Cotton effects. It should be remembered that the CD band positions do not define the actual wavelength positions of the transitions responsible for the different species. The non-Gaussian CD bands observed in this study are complicated by severe overlapping. Wellman *et al.*[20] have shown that overlapping CD bands of opposite sign and with UV maxima separated by 1–20 nm give a CD curve with the extrema separated by 28–32 nm. Thus the transition responsible for band 2 is probably located at lower wavelength than is apparent from the CD spectrum. Two other possible complications in α-halo acids are overlapping of band 1 (a) with the $\pi \rightarrow \pi^*$ transition of the carboxyl group and (b) with the $n \rightarrow \sigma^*$ transition of the chloro or bromo chromophore.

In rationalizing the presence of two overlapping Cotton effects in the region of the $n \rightarrow \pi^*$ transition for α-halo acids, two likely possibilities are conformational or solvational equilibria. CD studies of **1–17** at different temperatures and in solvents of different polarity are particularly pertinent to the solvation hypothesis.[10] The increase in rotational strength of the low wavelength band 1 in **3**, **6** and **9** upon lowering the temperature (Figs 8–10) is consistent with the behavior expected for a solvated species; the loss of band 2 in compounds **6** and **9** is consistent with this band being due to a non-solvated species. However, the increase in band 2 for 2-chloropentanoic acid (**3**) upon going to −185° is inconsistent with an explanation based solely on a solvational equilibrium. The intensity of the lower wavelength CD band should decrease in going to less polar solvents if it is associated with the more highly solvated species. Upon going from methanol to the less polar EPA and cyclohexane as solvents, band 1 does decrease in nine out of thirteen cases examined. The intensity change in band 1 was generally small when compared to that for band 2. A fairly consistent pattern was observed in the positions of the two CD bands in going from methanol to cyclohexane and methanol to EPA. These results are consistent with solvational equilibria being partially responsible for the dual Cotton effects observed for the α-halo acids. Therefore, for the α-chloro and α-bromo acids studied herein solvational equilibria[21] may be more important than they are for α-alkyl acids[19] which do not show the longer wavelength band 2 or for α-hydroxy and α-alkoxy carboxylic acids in which solvational effects have been shown[17, 19] to be of only secondary importance.

In spite of the possible involvement of solvational equilibria, which we are not able to define more precisely, we prefer to qualitatively explain the double humped CD bands shown by the α-halo acids on the basis of a simple conformational equilibrium. These



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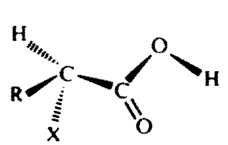

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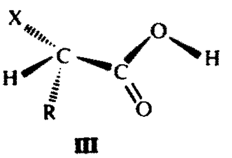

III

acyclic acids have free rotation about the C–C single bond which connects the asymmetric center to the chromophore. Two lines of evidence suggest the importance of different rotamers. First, the effect of alkyl substitution upon the CD bands is shown in Figs 3 and 5. The most striking cases are the α-halopropanoic acids **1** and **10** in which band 2 is more intense than band 1, greatly so in the case of **10**. Second, it has been shown by UV measurements that axial α-bromo ketones may undergo ~28 nm red shifts[22a] while axial α-chloroketones show a red shift of ~14–25 nm[22b] in relation to the parent ketone. This latter point is particularly applicable to the α-bromo acids where the CD bands are often separated by amounts greater than those justified[20] for UV band separations of 1–20 nm.

From conformational analysis of chloroacetaldehyde and bromoacetaldehyde, Karabatsos and Fenoglio[23] have shown that the most stable rotamer of these compounds in solution is the one in which the carbon–halogen bond eclipses the carbonyl group. This would correspond to rotamer I in the case of the α-halo acids where R = alkyl and X = Br or Cl. On the basis of x-ray diffraction Kanters *et al.*[24] concluded that the preferred crystal state conformation of α-hydroxy acids is that in which the O atoms of the OH group and CO group are eclipsed. If an α-substituent such as hydroxyl or halogen is not present, then X-ray measurements have suggested[25] a conformational preference for the rotamer in which the C_α—C_β bond eclipses the carbonyl oxygen. Thus conformations I

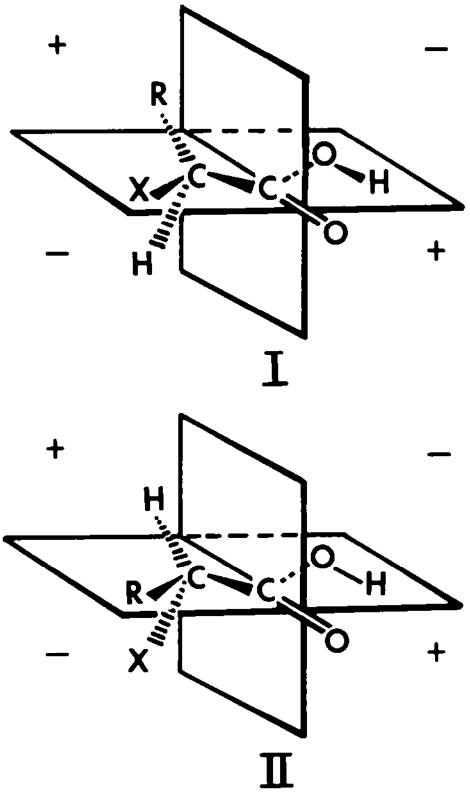

Fig 11.

and II should be most predominant[23-25] for the α-halo acids and the CD results will therefore be interpreted on this basis. Before proceeding, one other aspect of the conformational preferences of haloacetaldehydes[23] deserves mention in connection with our work. Karabatsos and Fenoglio[23] have shown that as the dielectric constant of the medium increases the rotamer having halogen eclipsed with carbonyl (similar to I) increases with respect to the other haloacetaldehyde rotamer (similar to II). This is due to the higher dipole moment of structures like I in contrast to structures like II. The increase was noted to be more pronounced among the chloroacetaldehydes than bromoacetaldehydes because of the greater polarity of the C–Cl bond. These workers also noted[23] that an increase in temperature decreases the dielectric constant of the solvent, therefore the ratio of I/II should also decrease. If we assign band 1 to rotamer I and band 2 to rotamer II, our results support these generalizations more often than not as discussed previously. Furthermore band 2 would be assigned to the rotamer having the axial halogen atom, in accordance with expectations from UV studies.[22] Thus, the reasoning used earlier to suggest the presence of solvational equilibria are similar to those for conformational equilibria when α-halo carbonyl compounds are concerned. For the reasons mentioned previously, we prefer the conformational hypothesis and will now propose a quadrant rule to accommodate our results.

In Fig 11 is represented conformations I and II for the *S*-configuration of α-halo acids. We have ignored conformation III since experimental evidence[23-25] favors I and II. Conformation III would have the alkyl group in one sector and the halogen atom in another sector of opposite sign. Thus even if III were present it would contribute little to the chiroptical properties of these compounds due to cancelling effects. As shown in Fig 11 the signs of the quadrants are such that conformer I, in which the α-halo substituent is eclipsed by the carbonyl group, gives a positive contribution since the alkyl group is in the upper left quadrant. On the other hand, conformer II, in which the alkyl group is eclipsed by the carbonyl group gives a negative contribution since the halogen group is in the lower left quadrant. As noted by Karabatsos and Fenoglio,[23] with the exception of N-methylchloroacetamide, all cases of X—CH$_2$—COY compounds where X is halogen show a ΔH° for II ⇌ I which is either negative or zero. This indicates that the rotamer of lowest energy is the one where the C—X bond eclipses the carbonyl group (i.e., I). Of the seventeen compounds studied herein twelve gave a much stronger band 1 than band 2 indicating a more stable rotamer I.

Four other halo acids, **1**, **11**, **12** and **13** gave CD bands of nearly equal magnitude and a fifth halo acid, **10**, showed a much more intense band 2 than band 1 (10:1 ratio of intensities). Since in the cyclohexanone series it is well known[26] that an axial halogen atom will far outweigh alkyl groups in contributing to the observed Cotton effect, band 2 in the α-halo acids is due to a conformer with a larger rotational strength than the conformer responsible for band 1. Thus acids, **1**, **11**, **12** and **13** should preferentially exist as rotamer I. It is very unlikely that 2-bromopropanoic acid (**10**) exists predominantly as conformer II since it has been shown that only 11%[27] of an axial halogen conformer is sufficient to completely dominate the dual banded CD spectrum[28] of (+)-*trans*-2-chloro-5-methylcyclohexanone. Also the intensity of band 1 will decrease with decreasing alkyl substitution since amplitudes for axial methyl and isopropyl groups adjacent to a carbonyl group have been found to be 67[29] and 98[30] respectively. However, the CD results of the halo acids do show that conformer II becomes progressively destabilized as the size of the alkyl group increases.

It is seen that the signs of the quadrants employed to explain the CD properties of α-halo acids are the same as those for the rear octants in the octant rule[26] for saturated ketones. They are also the same as the signs of the extended octant rule which has been proposed to correlate[17] the CD properties of α-substituted phenylacetic acids. The signs of the quadrants in Fig 11 also are the same as those of the empirical rule proposed by Listowsky *et al.*[19] for carboxylic acids and esters.

An empirical rule has been proposed by Dunlop and Gillard[12] whereby the absolute configuration of an asymmetric α-substituted carboxylate could be determined from a study of the Cotton effects shown by d→d transitions of cobalt (III) complexes. They proposed[12] that the sign of the dominant Cotton effect for the transitions under the first ligand-field absorption band indicates the absolute configuration of the coordinated carboxylate—if the dominant Cotton effect is negative, then the acid has the *L* or *S* configuration related to that of *L*-(+)-lactic acid. Under the symmetry of the central metal ion chromophore for complexes of the above type, the lowest spin-allowed excited state is no longer triply degenerate, but is split into two levels, ^1E and $^1A_2$. Hawkins and Lawson[31] have criticized Gillard's empirical rule[12] as "ill-conceived" and have pointed out that since the same transition does not always dominate the CD spectrum under the first ligand-field band, and since the lower energy ^1E and higher energy $^1A_2$ symmetry transitions have different signed Cotton effects, carboxylate ligands with the same absolute configuration can give rise to Cotton effects of opposite sign. Hawkins and Lawson[31] have examined the CD of Co (III) complexes of many amino acids and have found some anomalous results upon changing the anion from perchlorate to sulfate. Nonetheless they have stated[31] that carboxylates having the *L*-configuration do give a negative Cotton effect to the $^1A_2$ transition.

TABLE 2. CD OF COBALT (III) COMPLEXES OF HALO ACIDS

Cpd.	λ_{nm}	$[\theta]^*_\lambda$
1	510	−110
3	503	−380
6	503	−510
9	498	−140
10	502	+80
16	508	+580

* See Experimental.

The cobalt (III) complexes of several α-halo acids have been examined, using nitrate as the anion in accord with Gillard's original suggestion.[12] In all cases only one Cotton effect was observed in the d→d region. As shown in Table 2, with one exception, halo acids of *L* or *S* configuration gave negative Cotton effects, even when they have opposite $[\alpha]_D$ rotations, such as the n-propyl (**3**) and isopropyl (**6**) chloro acid derivatives. However, the cobalt (III) complex of *S*-2-bromopropanoic acid gave a positive Cotton effect near 500 nm. It will be recalled that this compound (**10**) was the only halo acid studied in which band 2 was much stronger than band 1. Thus, the cobalt complex CD method is not completely general in responding to the absolute configuration of carboxyl compounds but may instead reflect a particular rotameric species.

The results obtained in this study show that determination of the absolute configuration of α-chloro and α-bromo alkyl carboxylic acids must be made with care when utilizing chiroptical properties. Measurements of sodium D-line rotations, ORD curves and the Cotton effects of Co(III) complexes have all shown ambiguities. All *S*-α-halo acids have been found to exhibit a positive CD for band 1 and a negative CD for band 2. However in some cases band 2 gives such a weak CD signal that it could easily be missed if measurements were made on only a small amount of material. Thus the most useful method of assigning absolute configuration to α-halo acids is the presence of a positive Cotton effect at 195–222 nm for *S* compounds.

EXPERIMENTAL

General methods

Synthesis of α-halo acids. All the α-halo acids have been prepared from the corresponding α-amino acids according to the procedures of Renard[32] and Karrer[33] which involve treatment of the amino acid with HNO_3 and either HBr or HCl.

Synthesis of cobalt (III) *complexes of α-halo acids.* The procedure of Dunlop and Gillard[12] was followed for the preparation of the Co(III) complexes of various halo acids. Two equivts of the carboxylic acid and one equiv of carbonatopentammine cobalt (III) nitrate were dissolved in water and the pH of the resulting soln was adjusted to near 5 (±0·1) by adding small amounts of either conc HCl or conc NH_3. This soln was then warmed at 40° (±2°) for an hr. The resulting soln was evaporated to dryness. Attempted crystallization of several halo acid chelates was unsuccessful so the noncrystalline materials were used for CD measurements. Therefore, the ellipticity values reported in Table 2 are to be regarded as qualitative inasmuch as we have assumed stoichiometric reaction in calculating molecular ellipticity. Also, a small amount of salt could be introduced from adjustment of pH. All halo acid Co (III) chelates showed UV maxima near 500 nm. These were easily distinguished from the UV maximum of carbonatopentammine Co (III) nitrate which occurs at 515 nm. The Co(III) chelates of *S*-alanine and *L*-malic acid were prepared and gave CD results which agreed with published[12] ORD curves.

Instrumental methods

CD measurements were performed at 27° on a Cary Model 60 Spectropolarimeter* equipped with a 6001 CD accessory, except for the low temp measurements (Figs 8–10) which were made using a Dichrograph model Roussel-Jouan CD 185. ORD curves and specific rotations were measured using the spectropolarimeter described above at 27°. UV absorption spectra were recorded on a Cary 15 Spectrophotometer. Spectrograde quality solvents were used and the EPA solvent consisted of ether-isopentane-ethanol in a volume ratio of 5:5:2.

New data characteristic of individual compounds. Compound **1**,[34] b.p. 49–54°/0·5–1·0 mm; $[\alpha]_D^{27}$ −13·9° (MeOH).

Compound **2**,[35] b.p. 76–78°/1·0–2·0 mm; $[\alpha]_D^{27}$ −9·7° (MeOH).

Compound **3**,[36] b.p. 88–92°/1·0–2·0 mm; $[\alpha]_D^{27}$ −13·3° (MeOH); $[\alpha]_D^{27}$ −14·8° (C_6H_{11}); $[\alpha]_D^{27}$ −3·1° (1N NaOH).

Compound **4**,[36] b.p. 97–100°/1·0–2·0 mm; $[\alpha]_D^{27}$ −11·7° (MeOH).

Compound **5**,[37] b.p. 90–94°/4·0–5·0 mm; $[\alpha]_D^{27}$ −18·3° (MeOH); $[\alpha]_D^{27}$ −8·3° (1N NaOH).

Compound **6**, b.p. 76–80°/1·0–2·0 mm; (Found: Cl, 26·5, Calc: Cl, 26·0); $[\alpha]_D^{27}$ +1·0° (MeOH); $[\alpha]_D^{27}$ −0·4° (C_6H_{11}); $[\alpha]_D^{27}$ +1·4° (1N, NaOH).

Compound **7**, b.p. 88–90°/1·0–2·0 mm; (Found: Cl, 23·7, calc: Cl, 23·5); $[\alpha]_D^{27}$ −2·9° (CH_3OH); $[\alpha]_D^{27}$ −3·5° (C_6H_{11}).

Compound **8**, b.p. 86–89°/0·5–1·0 mm; (Found: Cl, 22·4, Calc: Cl, 23·5); $[\alpha]_D^{27}$ −7·3° (MeOH); $[\alpha]_D^{27}$ −3·6° (C_6H_{11}).

Compound **9** was studied as the optically impure enantiomer as described in Ref 8 (i.e., 82·7% optically pure *R* isomer). All optical activity data for **9** in this paper have been corrected for optical purity and are for the *S* isomer. $[\alpha]_D^{27}$ +17·3° (MeOH); $[\alpha]_D^{27}$ +13·1° (C_6H_{11}); $[\alpha]_D^{27}$ +15·1° (1N NaOH).

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* Reference to a company or product name does not imply approval or recommendation of the product by the U.S. Department of Agriculture to the exclusion of others that may be suitable.

Compound **10**,[38] b.p. 65–67°/0·5–1·0 mm; $[\alpha]_D^{27}$ −27·6° (MeOH).

Compound **11**,[38] b.p. 83–86°/1·0–1·5 mm; $[\alpha]_D^{27}$ −31·7° (MeOH); $[\alpha]_D^{27}$ −32·0° (C_6H_{11}); $[\alpha]_D^{27}$ −2·7° (1N NaOH).

Compound **12**,[39] b.p. 92–94°/0·5–1·0 mm; $[\alpha]_D^{27}$ −36·9° (MeOH).

Compound **13**,[40] b.p. 93–95°/1·0–2·0 mm; $[\alpha]_D^{27}$ −34·0° (MeOH).

Compound **14**,[41] b.p. 83–87°/1·0–1·5 mm; $[\alpha]_D^{27}$ −16·8° (MeOH); $[\alpha]_D^{27}$ −16·2° (C_6H_{11}); $[\alpha]_D^{27}$ −9·5° (*1N NaOH*).

Compound **15**,[42] b.p. 93–95°/0·5–1·0 mm; $[\alpha]_D^{27}$ −22·6° (MeOH).

Compound **16**,[42] b.p. 102–104°/1·5–2·0 mm; $[\alpha]_D^{27}$ +9·3° (MeOH); $[\alpha]_D^{27}$ +11·1° (C_6H_{11}).

Compound **17**[8] was studied as the optically impure enantiomer as described in Ref 8 (i.e., 82·7% optically pure *R* isomer). All optical activity data for **17** in this paper have been corrected for optical purity and are for the *S* isomer; $[\alpha]_D^{27}$ +12·0° (MeOH).

UV absorption spectra of α-halo acids

Absorption maxima and shoulders are presented below. The last UV absorption listed is the absorption at the lowest wavelength measured, since some of the compounds did not show either a maximum or shoulder.

Compound	Solvent	Absorption data
1	MeOH	$[\varepsilon]_{220}^{sh}$ 90, $[\varepsilon]_{200}$ 110.
2	MeOH	$[\varepsilon]_{260}^{sh}$ 30, $[\varepsilon]_{215}^{sh}$ 140, $[\varepsilon]_{200}$ 180.
3	EPA	$[\varepsilon]_{270}^{sh}$ 40, $[\varepsilon]_{215}$ 360.
3	0·1 N NaOH	$[\varepsilon]_{240}^{sh}$ 290, $[\varepsilon]_{215}$ 820.
4	MeOH	$[\varepsilon]_{260}^{sh}$ 50, $[\varepsilon]_{215}^{sh}$ 170, $[\varepsilon]_{200}$ 250.
5	MeOH	$[\varepsilon]_{210}^{sh}$ 270, $[\varepsilon]_{200}$ 340.
5	1N NaOH	$[\varepsilon]_{225}$ 560.
6	MeOH	$[\varepsilon]_{215}^{sh}$ 190, $[\varepsilon]_{200}$ 230.
6	C_6H_{11}	$[\varepsilon]_{210}^{sh}$ 230, $[\varepsilon]_{200}$ 280.
6	1N NaOH	$[\varepsilon]_{215}$ 640.
6	EPA	$[\varepsilon]_{205}$ 290.
6	0·1 N NaOH	$[\varepsilon]_{215}$ 480.
7	MeOH	$[\varepsilon]_{260}^{sh}$ 80, $[\varepsilon]_{220}^{sh}$ 260, $[\varepsilon]_{200}$ 280.
7	C_6H_{11}	$[\varepsilon]_{210}^{sh}$ 300, $[\varepsilon]_{200}$ 350.
8	MeOH	$[\varepsilon]_{210}^{sh}$ 460, $[\varepsilon]_{200}$ 500.
8	C_6H_{11}	$[\varepsilon]_{200}$ 650.
9	MeOH	$[\varepsilon]_{220}^{max}$ 80, $[\varepsilon]_{210}$ 70.
9	C_6H_{11}	$[\varepsilon]_{210}^{sh}$ 210, $[\varepsilon]_{200}$ 320.
9	1 N NaOH	$[\varepsilon]_{220}$ 170.
9	EPA	$[\varepsilon]_{220}^{max}$ 135, $[\varepsilon]_{205}$ 180.
10	MeOH	$[\varepsilon]_{230}^{sh}$ 260, $[\varepsilon]_{200}$ 470.
10	C_6H_{11}	$[\varepsilon]_{225}^{sh}$ 380, $[\varepsilon]_{200}$ 590.
10	0·1 N NaOH	$[\varepsilon]_{215}$ 730.
10	EPA	$[\varepsilon]_{220}$ 490.
11	MeOH	$[\varepsilon]_{230}^{sh}$ 280, $[\varepsilon]_{200}$ 620.
11	C_6H_{11}	$[\varepsilon]_{225}^{sh}$ 400, $[\varepsilon]_{200}$ 760.
11	1 N NaOH	$[\varepsilon]_{230}$ 590.
12	MeOH	$[\varepsilon]_{230}^{sh}$ 300, $[\varepsilon]_{200}$ 500.
13	MeOH	$[\varepsilon]_{215}^{max}$ 400, $[\varepsilon]_{200}$ 410.
14	MeOH	$[\varepsilon]_{210}^{sh}$ 600, $[\varepsilon]_{200}$ 660.
14	C_6H_{11}	$[\varepsilon]_{215}^{max}$ 680, $[\varepsilon]_{200}$ 760.
14	1 N NaOH	$[\varepsilon]_{220}$ 870.
15	MeOH	$[\varepsilon]_{220}^{sh}$ 430, $[\varepsilon]_{200}$ 730.
16	MeOH	$[\varepsilon]_{215}^{sh}$ 560, $[\varepsilon]_{200}$ 740.
16	C_6H_{11}	$[\varepsilon]_{215}^{sh}$ 690, $[\varepsilon]_{200}$ 880.
16	EPA	$[\varepsilon]_{225}$ 650.
17	MeOH	$[\varepsilon]_{210}^{max}$ 670, $[\varepsilon]_{200}$ 550.

ORD of α-halo acids

The values reported below are for the Cotton effect extrema, zero crossover and lowest wavelength measured. All measurements were performed in MeOH.

Compound	ORD data
6	$[\phi]_{233} + 1080$(pk), $[\phi]_{219}0$, $[\phi]_{218} - 90$.
7	$[\phi]_{235} + 830$(pk), $[\phi]_{220}0$, $[\phi]_{210} - 1100$.
8	$[\phi]_{232} - 1830$(tr), $[\phi]_{218}0$.
10	$[\phi]_{257} - 1950$(tr), $[\phi]_{241}0$, $[\phi]_{223} + 4420$(pk), $[\phi]_{200} + 2090$.
14	$[\phi]_{207} - 310$(tr), $[\phi]_{257}0$, $[\phi]_{230} + 1400$(pk), $[\phi]_{220} + 490$.
15	$[\phi]_{272} - 400$(tr), $[\phi]_{255}0$, $[\phi]_{232} + 860$(pk), $[\phi]_{210} - 2300$.
16	$[\phi]_{275} + 130$(pk), $[\phi]_{262}0$, $[\phi]_{232} - 1940$(tr), $[\phi]_{200} + 5640$.

CD of α-halo acids

The values reported below are for Cotton effect maxima, zero crossover and for the CD at the lowest wavelength measured.

Compound	CD data
5	(1 N NaOH), $[\theta]_{210} + 4560$.
6	(C_6H_{11}), $[\theta]_{243} - 100$(max), $[\theta]_{235}0$, $[\theta]_{210} + 1780$(max), $[\theta]_{195} + 1620$.
	(1 N NaOH), $[\theta]_{210} + 4360$.
	(0·1 N NaOH), $(\theta)_{200} + 5200$.
	(EPA), $[\theta]_{257} - 81$(max), $[\theta]_{250}0$, $[\theta]_{218} + 1680$(max), $[\theta]_{205} + 1230$.
7	(C_6H_{11}), $[\theta]_{245} - 80$(max), $[\theta]_{235}0$, $[\theta]_{197} + 1520$.
	(MeOH), $[\theta]_{215} + 1890$(max), $[\theta]_{190} + 140$.
8	(MeOH), $[\theta]_{258} + 30$(max), $[\theta]_{250}0$, $[\theta]_{215} - 3510$(max), $[\theta]_{190} - 100$.
	(C_6H_{11}), $[\theta]_{245} + 50$(max), $[\theta]_{239}0$, $[\theta]_{210} - 3130$(max), $[\theta]_{195} - 2300$.
9	(C_6H_{11}), $[\theta]_{218} + 1160$(max), $[\theta]_{210} + 1020$.
	(1 N NaOH), $[\theta]_{215} + 3080$.
	(EPA), $[\theta]_{225} + 1440$(max), $[\theta]_{205} + 820$.
10	(C_6H_{11}), $[\theta]_{235} - 4210$(max), $[\theta]_{213}0$, $[\theta]_{205} + 1130$(max), $[\theta]_{195} + 600$.
	(0·1 N NaOH), $[\theta]_{241} - 900$(max), $[\theta]_{231}0$, $[\theta]_{205} + 6470$(max), $[\theta]_{200} + 6200$.
	(EPA), $[\theta]_{242} - 4720$(max), $[\theta]_{217}0$, $[\theta]_{210} + 750$(max), $[\theta]_{200} + 250$.
11	(C_6H_{11}), $[\theta]_{237} - 3620$(max), $[\theta]_{219}0$, $[\theta]_{208} + 2200$(max), $[\theta]_{202} + 200$.
	(1 N NaOH), $[\theta]_{250} - 370$(max), $[\theta]_{238}0$, $[\theta]_{215} + 6090$.
16	(C_6H_{11}), $[\theta]_{243} + 1140$(max), $[\theta]_{232}0$, $[\theta]_{210} - 4250$(max), $[\theta]_{195} - 2360$.
	(EPA), $[\theta]_{254} + 630$(max), $[\theta]_{241}0$, $[\theta]_{215} - 3950$(max), $[\theta]_{200} - 2190$.

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REFERENCES

[1] [a] Presented in part at the *Fifth Western Regional Meeting*, American Chemical Society, Anaheim, California October (1969); cf. W. Gaffield and W. G. Galetto, *Appl. Spectrosc.* **23**, 669 (1969);

[b] National Academy of Sciences—National Research Council Resident Research Associate, 1967–1968;

[c] Western Utilization Research and Development Division, Agricultural Research Service, U.S. Department of Agriculture

[2] W. Klyne, *Proc. Roy. Soc.* (A) **297**, 66 (1967); W. Klyne and P. M. Scopes, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry* (Edited by G. Snatzke) Chapter 12, Heydon (1967)

[3] [a] I. P. Dirkx and F. L. J. Sixma, *Rec. Trav. Chim.* **83**, 522 (1964);

[b] W. Gaffield, *Chem. & Ind.* 1460 (1964);

[c] E. Iizuka and J. T. Yang, *Biochemistry* **3**, 1519 (1964);

[d] D. W. Urry and H. Eyring, *J. Am. Chem. Soc.* **86**, 4574 (1964);
[e] J. P. Jennings, W. Klyne and P. M. Scopes, *J. Chem. Soc.* 294 (1965);
[f] J. C. Craig and S. K. Roy, *Tetrahedron* **21**, 391 (1965);
[g] J. C. Craig and S. K. Roy, *Ibid.* **21**, 1847 (1965);
[h] M. Legrand and R. Viennet, *Bull. Soc. Chim. Fr.* 679 (1965);
[i] L. I. Katzin and E. Gulyas, *J. Am. Chem. Soc.* **90**, 247 (1968);
[j] L. Verbit and P. J. Heffron, *Tetrahedron* **24**, 1231 (1968);
[k] S. Uyeo, J. Okada, S. Matsunga and J. W. Rowe, *Ibid.* **24**, 2859 (1968)

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

[5] W. G. Galetto, Ph.D. Thesis, University of California, Davis, 1967; abstracted in *Dissertation Abstr.* **29**, 938-B (1968)

[6] E. Abderhalden, W. Faust and E. Haase, *Z. Physiol. Chem.* **228**, 187 (1934)

[7] N. Izumiya, S. J. Fu, S. M. Birnbaum and J. P. Greenstein, *J. Biol. Chem.* **205**, 221 (1953); R. J. Schlott, Ph.D. Thesis, Purdue University, 1963; abstracted in *Dissertation Abstr.* **25**, 849 (1964); H. Pracejus and S. Winter, *Chem. Ber.* **97**, 3173 (1964)

[8] W. G. Galetto and W. Gaffield, *J. Chem. Soc.* (C) 2437 (1969)

[9] For a related example in the carboxyl series see, D. L. Dull and H. S. Mosher, *J. Am. Chem. Soc.* **89**, 4230 (1967)

[10] A. Moscowitz, K. M. Wellman and C. Djerassi, *Proc. Natl. Acad. Sci. U.S.* **50**, 799 (1963)

[11] D. W. Urry, D. Miles, D. J. Caldwell and H. Eyring, *J. Phys. Chem.* **69**, 1603 (1965)

[12] J. H. Dunlop and R. D. Gillard, *Tetrahedron* **23**, 349 (1967)

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

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

[15] I. Listowsky, S. Englard and G. Avigad, *Biochemistry* **8**, 1781 (1969)

[16] C. Toniolo, *J. Phys. Chem.* **74**, 1390 (1970)

[17] G. Barth, W. Voelter, H. S. Mosher, E. Bunnenberg and C. Djerassi, *J. Am. Chem. Soc.* **92**, 875 (1970)

[18] A. Moscowitz, K. Mislow, M. A. W. Glass and C. Djerassi, *Ibid.* **84**, 1945 (1962)

[19] I. Listowsky, G. Avigad and S. Englard, *J. Org. Chem.* **35**, 1080 (1970)

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

[21] For a recent critique of solvational effects see, D. J. Severn and E. M. Kosower, *Ibid.* **91**, 1710 (1969)

[22] [a] R. C. Cookson, *J. Chem. Soc.* 282 (1954);
[b] R. C. Cookson and S. H. Dandegaonker, *Ibid.* 352 (1955)

[23] G. J. Karabatsos and D. J. Fenoglio, *J. Am. Chem. Soc.* **91**, 1124 (1969)

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

[25] L. Leiserowitz and G. M. Schmidt, *Acta Cryst.* **18**, 1058 (1965)

[26] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.* **83**, 4013 (1961)

[27] A. Moscowitz, K. Wellman and C. Djerassi, *Ibid.* **85**, 3515 (1963)

[28] K. M. Wellman, E. Bunnenberg and C. Djerassi, *Ibid.* **85**, 1870 (1963)

[29] C. Beard, C. Djerassi, J. Sicher, F. Sipos and M. Tichy, *Tetrahedron* **19**, 919 (1963)

[30] C. Djerassi, P. A. Hart and C. Beard, *J. Am. Chem. Soc.* **86**, 85 (1964)

[31] C. J. Hawkins and P. J. Lawson, *Chem. Commun.* 177 (1968)

[32] M. Renard, *Bull. Soc. Chim. Biol.* **28**, 497 (1946)

[33] P. Karrer, H. Reschofsky and W. Kaase, *Helv. Chim. Acta* **30**, 271 (1947)

[34] H. J. Lucas and H. K. Garner, *J. Am. Chem. Soc.* **70**, 990 (1948)

[35] K. Freudenberg and W. Lwowski, *Liebigs Ann.* **597**, 141 (1955)

[36] P. A. Levene and H. L. Haller, *J. Biol. Chem.* **83**, 591 (1929)

[37] S. Kodama, *J. Tokyo Chem. Soc.* **40**, 825 (1919)

[38] P. A. Levene and M. Kuna, *J. Biol. Chem.* **141**, 391 (1941)

[39] P. A. Levene, T. Mori and L. A. Mikeska, *J. Biol. Chem.* **75**, 337 (1927)

[40] E. Fischer and H. Carl, *Ber. Dtsch. Chem. Ges.* **39**, 3996 (1906)

[41] E. Fischer and H. Scheibler, *Ibid.* **41**, 889 (1908)

[41] E. Abderhalden and W. Zeisset, *Z. Physiol. Chem.* **200**, 179 (1931)