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CONFORMATION AND CHIROPTICAL PROPERTIES OF MANDELIC ACIDS

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Abstract—Using CD data (solution, solid state, various temperatures), X-ray data and MO calculations for a number of substituted mandelic acids (phenylglycolic acids) an attempt was made to explain the different results for the relation between sign of the ^1L_b CD band and substitution pattern as described in the literature for various types of aromatic compounds. Moreover the reported sector rule has been reconsidered taking into account the sign and magnitude of the spectroscopic moments. It has been found that in any explanation of the signs of the ^1L_b CD bands of substituted aromatic compounds both the conformational behaviour and the spectroscopic moments should be taken into account.

INTRODUCTION

The relevant data on substituent effects on the chiroptical properties of aromatic compounds have been interpreted on the basis of sector rules for the chiral second and third sphere by Snatzke and *et al.*[1,2] Different rules were developed for the ^1L_b and the ^1L_a band as well as for the chiral second and third sphere. Snatzke's treatment starts from the assumption that a sector rule should reflect the symmetry of the transition. The ^1L_b band sector rule therefore has nodal planes through the benzene carbon atoms. The plane of the benzene ring is also a nodal plane. The signs of the various sectors follow empirically. The influence of substitution is taken into account by vector addition of the appropriate spectroscopic moments. For the third sphere contribution to the ^1L_b band (the relevant rule for mandelic acids, phenylglycolic acids) this leads to the prediction that in a homochiral family of compounds the third sphere contribution to the ^1L_b band has the same sign for the parent and *p*-substituted compounds, but the opposite sign for the *m*- and *o*-isomers. Figure 1 summarizes the sector rules for the third sphere contributions to the ^1L_b band.[3]

It has been stated by Snatzke[4] that these rules "are more a guide to understanding why the circular dichroism (CD) can change with substitution, than a means for unequivocal prediction of signs". Inspection of the data relevant to these rules indeed shows discrepancies. Agreement with the predictions is found for phenylalanine and its hydroxy substituted derivatives.[5] Deviating results are found for mandelic acids[6,7] (where unsubstituted and *m*-derivatives have signs opposite to those of the *o*- and *p*-derivatives), phenylhydracrylic acids[8] (showing the same behaviour) and 2-phenoxypropionic acids[9] (where unsubstituted, *o*-, *m*- and *p*-derivatives show the same sign). Snatzke[3] explains the difference between the phenylalanines (obeying the rule) and the mandelic acids (not obeying the rule) in the following way. In compounds of the type PhCHRR′ (mandelic acids, phenylhydracrylic acids) two groups are available for hyperconjugation ($\sigma-\pi$ conjugation) and it is reasonable to assume that different substitution of the aromatic ring will change the ability of the π-system to participate in such an interaction with the σ-bonds C–R and C–R′. This leads to different rotamer populations for the differently substituted compounds, explaining aberrant chiroptical properties. In a compound of the type $PhCH_2R$ the conformational equilibrium will not depend much on substitution because only one possibility of hyperconjugation exists. The suggestion that different conformational equilibria explain the substituent influence in mandelic acids has been made earlier.[6] It was thought surprising, however, that the sign pattern was identical for all the substituents studied (e.g. the electron donating OCH_3 and the electron withdrawing F) and that the temperature influence is very similar for nearly all compounds.

This paper describes the results of work undertaken in an attempt to clarify the situation with respect to the aromatic sector rule for third sphere contributions to the ^1L_b band. Five types of data are presented and discussed:

(1) CD measurements of *o*-Br-, *o*-Cl- and *m*-Br-mandelic acids were effected at ambient and low temperature to obtain a more representative series of solution data. CD data of *m*-F-mandelic acid are included as well, because earlier results were erroneous.[6]

(2) Solid state CD (KBr-pellet) was measured. The sign of the ^1L_b band was compared with the sign predicted from the sector rule on the basis of the solid state conformation as found by X-ray analyses.

(3) X-ray analyses were carried out to determine the conformations of mandelic acid and the *o*-Br, *m*-F and *p*-F substituted derivatives.

(4) Molecular orbital (MO) calculations were carried out for differently substituted mandelic acids for various conformations in order to find the stable conformations. Also a direct calculation of the rotational strength of the ^1L_b transition was attempted.

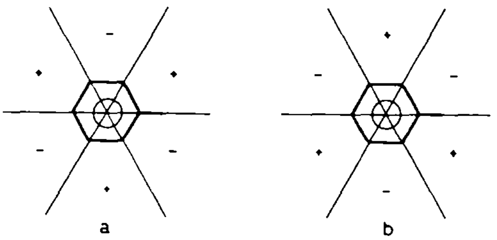

Fig. 1. Sector rules for third sphere contribution to the ^1L_b band; (a) unsubstituted and *p*-substituted compounds; (b) *o*- and *m*-substituted compounds. Signs are for the sectors above the plane of the benzene ring, the sectors under this plane having opposite signs.

(5) To solve the problem of the 2-phenoxypropionic acids (compounds essentially similar to the phenylalanines in that they do not have two possibilities of hyperconjugation) the sector rules were recalculated according to Snatzke's method but using spectroscopic moments of varying length and sign. The results of this calculation were then applied to the compounds under consideration.

RESULTS

CD measurements in solution. CD data on those mandelic acids on which no ambient and low temperature data have yet been published, and on *m*-F-mandelic acid where published data are erroneous are collected in Table 1. Inspection of all the data (including those of Ref. 6) shows that. (a) The sign pattern is the same for all substituents except F. (b) The temperature effect on the ^1L_b band is small except for *o*-Br† and *o*-Cl-mandelic acid where sign inversion upon cooling takes place. (c) The effect of lowering the temperature from 25° to −185° on the 220 nm band is an intensity increase of about a factor 2.

CD measurements in the solid state. The signs of the ^1L_b band transition of (R)-mandelic acids in solid state and in solution are given in Table 2. It is realized that measurement of CD in the solid state presents dangers (stray light, polarization). Examples in the literature, however, indicate that at least the sign of a CD band can be trusted, e.g. cystine.[12] Table 2 shows that the signs in the solid state and in solution are identical except for the parent compound, *o*-Cl- and *o*-Br-mandelic acids (if the room temperature spectrum is taken) and *m*-F-mandelic acid.

X-ray analyses. The results of X-ray analyses of (R)-mandelic acid, (R)-*o*-Br-, (R)-*p*-F- mandelic acids are presented in Fig. 2 as projections on a plane perpendicular to the plane of the benzene ring and the C_{Ar}–C_{OH} bond. The molecule is viewed from the benzene ring to the asymmetric carbon atom. For mandelic acid and the *o*-Br-derivative two conformations are found in the crystal. Every molecule in one conformation is accompanied by a molecule in the other conformation. In *o*-Br-mandelic acids the hydrogen bonding scheme is different for the two independent molecules, explaining the occurrence of two carbonyl bands (1680 and 1740 cm^{-1}) in the solid state IR spectrum. In mandelic acid itself the position of the phenyl ring is different for the two independent molecules, the hydrogen bonding scheme is identical, however.

An X-ray analysis of *o*-Cl- and *o*-F-mandelic acid has not been carried out. The IR spectrum of *o*-Cl-mandelic acid also shows two carbonyl bonds (1690 and 1720 cm^{-1}), making it reasonable to assume conformations in the crystalline state similar to those of *o*-Br-mandelic acid. Moreover, both *o*-Br- and *o*-Cl-mandelic acid show sign inversion of the ^1L_b band in CD on lowering the temperature, again suggesting similar conformational behaviour. All the other mandelic acids, including *o*-F,[14] and *o*-OCH$_3$ have only one carbonyl band in the IR region.

The crystal structure of *m*-F-mandelic acid is isomorphous with that of *p*-F-mandelic acid, which implies that the orientation of the phenyl plane with respect to the rest of the molecule is identical for these two compounds. However, there is disorder in the *m*-F-mandelic acid crystal. About half of the molecules have their phenyl planes rotated 180° about the C_1–C_7 bond.

Table 1. CD data of some (R)-mandelic acids

Substituent	EPA + 25° λ (nm)	Δε	EPA − 185° λ (nm)	Δε	Methanol λ (nm)	Δε
o-Br	228	−15.11	230	−28.8	228	−12.24
	265	−0.079	254	+0.080	266	−0.055
			260	+0.082		
			267	+0.061		
			274	+0.041		
o-Cl	225	−17.0	228	−26.7	226†	−20.5
	263.5	−0.048	259	+0.006	257.5	−0.034
	268	−0.050	266	+0.038	263	−0.046
	275	−0.039	272	+0.035	270	−0.040
					277	−0.040
m-Br	227	−10.6	230	−18.7	226†	−11.3
	267	+0.012	260	+0.026	262	+0.103
	274	+0.012	266	+0.051	268	+0.173
			272.5	+0.063	275	+0.167
m-F§	222	−14.8	229	−16.8	221	−10.90
	261	−0.012	263.5	−0.050	261	−0.050
	268	−0.012			270	−0.012

†Low temperature data have been corrected for shrinkage of the solvent.[11]

‡From Ref. 8.

§The data in Ref. 6 are erroneous.

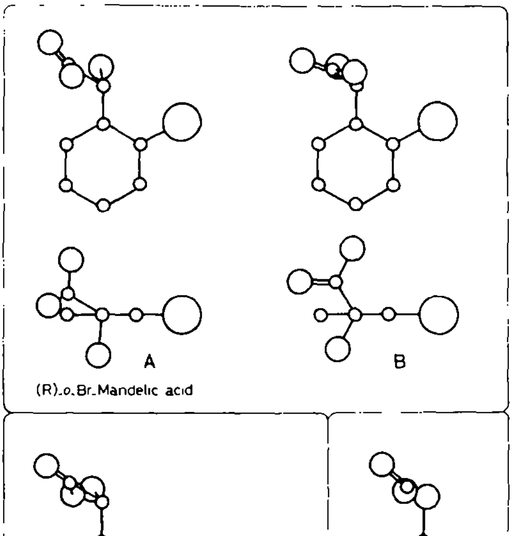

Fig. 2. Results of X-ray analyses of mandelic acids.

MO calculations. The conformational energy curves for unsubstituted *m*-F- and *p*-F-(R)-mandelic acids can

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†The published Δε value[10] for the ^1L_b (+0.27, λ = 283) is erroneous (D. G. Neilson, personal communication).

Table 2. Sign of ^1L_b band CD of (R)-mandelic acids

Substituent	Solid state (KBr)	Solution (EPA 25°)	Calculated
H	−	+	−
2-Br	+	− (+ at −185°)	
2-Cl	−	− (+ at −185°)	
2-F	−	−	−
3-Br	+	+	
3-Cl	+	+	
3-F	+	−	−
4-Br	−	−	
4-Cl	−	−	
4-F	−	−	−
2-OCH_3	−	−	
4-OCH_3	−	−	

hardly be distinguished from the parent compound (Fig. 3). The *o*-F derivative deviates in the region where the carboxyl group approaches the fluorine substituent too closely, but otherwise it is very similar to the other compounds. The results of the rotational strength calculations of the ^1L_b transitions in the same compounds as a function of the conformation are depicted in Fig. 4. Conformationally averaged rotational strengths have been computed for a number of temperatures using Boltzmann-statistics. For all compounds a negative ^1L_b-Cotton effect was obtained over a wide temperature range (Table 2).

The sector rule based on more realistic spectroscopic moments. The results of recalculation of the sector rule with the spectroscopic moments given in Table 2 indicate that depending on the magnitudes and the signs of these moments three sign patterns are possible for disubstituted aromatics, viz:

All signs are the same.

The sign of the unsubstituted compound is opposite to that of the other three.

Unsubstituted and *p*-substituted compounds have signs opposite to those of the *o*- and *m*-substituted ones.

The latter applies to those regions where the spectroscopic moments have equal sign and length. Figure 5 indicates the various regions. It is noteworthy that the pattern +−+− for unsubstituted, *o*-, *m*-, *p*-substituted, as found in mandelic acids, does not occur.

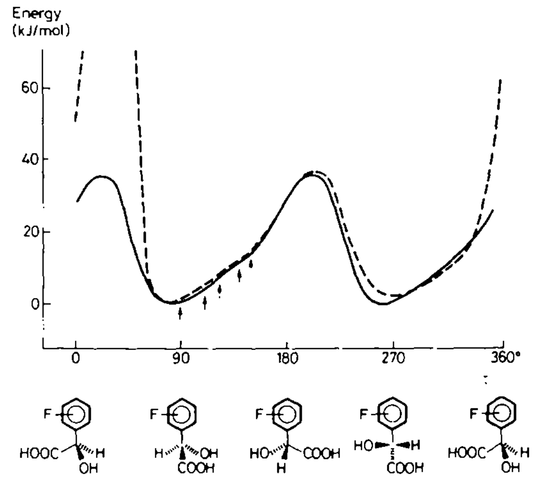


Fig. 3. Conformational energy curves of unsubstituted, *p*- and *m*-substituted (——) and *o*-substituted (-----) mandelic acids. Experimentally found torsion angles for a number of mandelic acids are indicated by arrows.

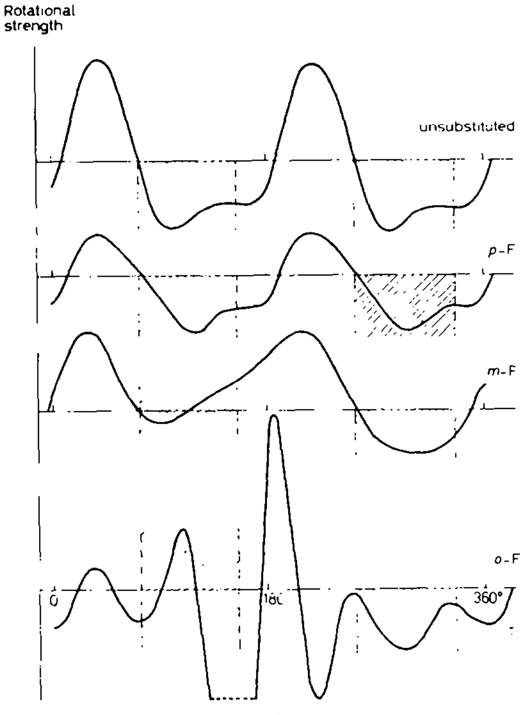


Fig. 4. Rotational strengths of the ^1L_b bands in mandelic acid and its F-derivatives as a function of conformation. Hatched area indicate regions of conformational preference.

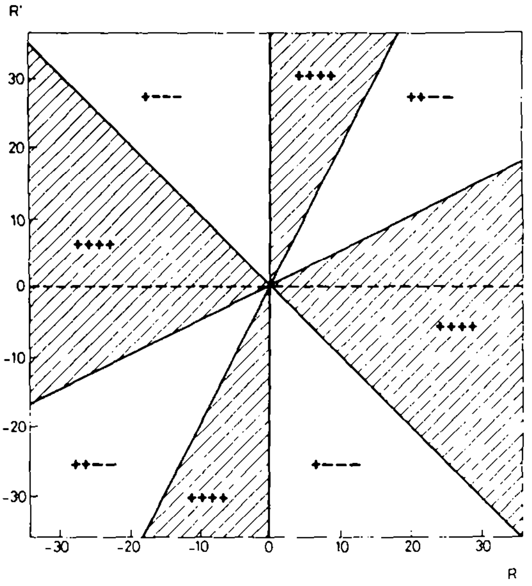


Fig. 5. Sign patterns for the ^1L_b band of unsubstituted, *p*-, *m*- and *o*-substituted aromatic compounds of the type.

DISCUSSION

CD in solution. Comparison of CD spectra at different temperatures may give an indication of the importance of conformational equilibria. The behaviour of mandelic acids clearly shows a difference between the *o*-substituted compounds and the other ones. Two of the *o*-substituted compounds show sign inversion of the ^1L_b band on lowering the temperature to −185°. Moreover the ratio of the intensities of the low-wavelength band at 25° and −185° is somewhat larger for the *o*-Br-, *o*-F- and *o*-OCH_3-mandelic acids than for the other compounds, as observed before,[6] again indicating the deviating conformational behaviour of the *o*-compounds. On the basis of these results it would not be surprising if *o*-substituted mandelic acids would not conform to the sign pattern of the CD predicted by the sector rule.

The unsubstituted, *m*- and *p*-compounds except *m*-F behave similarly towards temperature lowering. Thus there is no indication from temperature-dependent CD measurements that different rotameter populations exist in the variously substituted mandelic acids. The aberrant behaviour of the *o*-compounds is possibly better explained by steric arguments than by invoking different degrees of hyperconjugation. *m*-F-Mandelic acid has a sign opposite to that of the other *m*-substituted compounds, in contrast to earlier reports.[6] Perhaps the influence of the electronegativity of the F-atom is felt in this case.

Solid state CD and X-ray analyses. Table 2 shows that *o*-Br- and *o*-Cl-mandelic acids also deviate with respect to their solid state CD, the sign of the ^1L_b band in the solid state is different from that in solution at 25°, but identical to that observed by the low-temperature measurement. This is again an indication that the behaviour of the *o*-compounds is different from that of the other mandelic acids.

The results of the X-ray analyses make it possible to apply the sector rule directly to a situation where the conformation is known. Application of the sector rule of Fig. 1b to the solid state conformation of *o*-Br-mandelic acid, as depicted in Fig. 2b, gives the following results.

(a) In conformation **A** (Fig. 2b) the carboxyl group lies completely in a negative sector, the OH group being distributed over a positive and negative sector. The overall result will be a negative contribution of the ^1L_b band.

(b) In conformation **B** (Fig. 2b) the situation is only slightly different. It is safe to assume, however, that here also the overall contribution is negative.

The solid state CD for (R)-*o*-Br-mandelic acid shows a positive sign, giving rise to a discrepancy between experiment and sector rule treatment which is not explicable in terms of conformation. *p*-F-Mandelic acid has essentially the same solid state conformation as *o*-Br-mandelic acid depicted in Fig. 2b (**B**). Therefore a positive sign (Fig. 1a) for the ^1L_b band of (R)-*p*-F-mandelic acid is predicted on the basis of the sector rule, again pointing to a discrepancy. *m*-F-Mandelic acid is isomorphous with *p*-F-mandelic acid. On the basis of the sector rule (Fig. 1b) a negative sign would be predicted. This is in agreement with experiment.

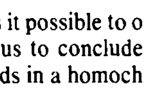
The situation for (R)-mandelic acid is more difficult to assess, conformation **C** (Fig. 2a) contributes positively and conformation **D** (Fig. 2a) negatively to the ^1L_b band (sector rule Fig. 1a). The overall result is hardly predictable. The experimental solid state result is negative, implying that the rotational strength of **D** is larger than that of **C**. From this part of the investigation it may be concluded that in cases where the conformation is fixed the sector rule proposed by Snatzke does not predict the sign of the ^1L_b-band CD accurately in every case.

MO calculations of conformational energies. The main feature of the conformational energy curves of mandelic acids (Fig. 3) is the absence of any significant influence of substitution on the conformational behaviour. This is in direct conflict with Snatzke's assumptions. Our calculated results are validated by the rough coincidence of the torsion angles found by the X-ray analyses of some mandelic acids with the valleys in the conformational energy curves. Keeping in mind that the X-ray results apply to the solid state conditions where strong intermolecular forces are operative, whereas the calculations refer to isolated molecules, one may not expect better agreement.

It is not apparent that the difference between *o*-F-mandelic acid and the other compounds is so great as to lead to a markedly different conformational behaviour. One can, however, imagine that the bulkier Cl and Br substituents give rise to a broader potential energy barrier at $\tau \approx 20°$, thus affecting the relative heights and shapes of the two energy minima to such an extent as to severely alter the rotamer populations. On these grounds the different conformational and hence chiroptical behaviour of *o*-Cl- and *o*-Br-mandelic acids is not surprising.

MO calculations of rotational strengths. Although the rotational strengths clearly depend on the conformation, it is seen that the regions of conformational preference (Fig. 3, indicated by the hatched area in Fig. 4) roughly coincide with the regions of negative Cotton effects. As a result, the average ^1L_b-Cotton effect is calculated to be negative and independent of the temperature. The latter result is in general accordance with the absence of an important temperature effect as appears from the CD-measurements. Comparing the calculated signs with the experimentally determined signs (Table 2), we observe agreement for *o*-F- and *p*-F-mandelic acids which have negative signs both in solution and in solid state. For unsubstituted and *m*-F-mandelic acids the calculated signs agree with the solid state and solution results respectively. However, we have not analysed these results in detail. Actually the extended Hückel method is not particularly suited for the calculation of excited state wave functions for aromatic chromophores. It may be possible to improve this part of our calculation by using the INDO–CI method.

The sector rule based on more realistic spectroscopic moments. Inspection of Fig. 5 shows that three sign patterns occur when varying the spectroscopic moments over a large range, e.g. ++++, ++−−, +−−−. It is immediately obvious that in a system

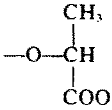


variation of R′ makes it possible to obtain any of the three patterns. This leads us to conclude that in a number of substituted compounds in a homochiral family it depends on the nature of the substituents which sign pattern prevails.

It is interesting to discuss the experimental findings on the various series of substituted aromatic compounds mentioned in the introduction, using the data of Fig. 5.

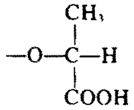
Tyrosines.[5] The substituent is OH (spectroscopic moment = +34[15]). The experimentally found ++−− pattern can only be found for values of the spectroscopic moment of the $-CH_2CHNH{\cdot}COOH$ group larger than about 15 (Fig. 5). Compared with values for other alkyl groups, this is not unreasonable. It may be concluded now that the tyrosines conform to Snatzke's rule (developed on the basis of spectroscopic moments of equal sign and magnitude) because the substituents present are of equal sign and do not differ too much in magnitude.

2-Phenoxypropionic acids.[9] Compounds relevant to this discussion are the unsubstituted, CH_3O-substituted and 2,4,5-tri-Cl-substituted-2-phenoxypropionic acids. The latter is essentially a *p*-Cl-derivative because of the compensating spectroscopic moments of the 2- and 5-Cl-substituents. All the compounds have the same sign for the ^1L_b band. The spectroscopic moment of OCH_3 is +31.[15] Inspection of Fig. 5 indicates that a ++++ pattern then necessitates a value for the



$$\begin{array}{c} CH_3 \\ | \\ -O-CH \\ | \\ COOH \end{array}$$

spectroscopic moment between 0 and +14 or smaller than −31. In view of known values for spectroscopic moments the latter value is not realistic. The *p*-Cl-derivative also has the same ^1L_b band sign. On the basis of the present results, however, it is not possible to decide whether the ++++ or ++−− pattern is valid for the Cl-derivatives. Measurement of the CD of the *m*-Cl-compound would indicate which pattern applies and (using the known spectroscopic moment of Cl (+6)) make it possible to narrow the region of the spectroscopic moment for



$$\begin{array}{c} CH_3 \\ | \\ -O-C-H \\ | \\ COOH \end{array}$$

Mandelic acids. A possible explanation for the behaviour of mandelic acids may be as follows:

The experimentally found pattern +−+− does not occur in Fig. 4. On the basis of the experimental results presented in this paper, however, it is clear that the conformational behaviour of the *o*-derivatives differs from that of the *m*- and *p*-compounds. Also the parent compound shows signs of a different conformational behaviour (two conformations in the solid state, different signs for solid and solution CD). If we leave out these compounds, the pattern should be one where *m*- and *p*-derivatives have a different sign, i.e. ++−− except for the F-compounds where *m*- and *p*-derivatives have the same sign. Inspection of Fig. 5 shows that the experimental data fall in the correct region for Br, Cl and F. Methoxy compounds come into a wrong region, however, in this case the strongly electron-donating substituent may well give rise to different conformational behaviour. It is realized that this explanation is to a large extent speculative. It is clear, however, that in any explanation of the signs of the ^1L_b bands of aromatic compounds both the conformational behaviour and the spectroscopic moments should be taken into account.

EXPERIMENTAL

CD measurements at 25° and −185° were carried out as described before.[6] *o*-Br-Mandelic acid was obtained from Dr. D. G. Neilson, Dundee, and *o*-Cl-, *m*-Br- and *m*-F-mandelic acids from Drs. Collet and Jacques, Paris. CD measurements in KBr-pellets were made on conventionally prepared pellets of 2 mg mandelic acid and 100 mg KBr. The pellets were fully transparent.

X-rays analyses. Intensity measurements of the reflections of crystals of mandelic acid and its *o*-Br, *m*-F and *p*-F derivatives were done on different (semi-)automatic diffractometers, i.e. Philips PW 1100 (mandelic acid and *m*-F), Philips PAILRED (*o*-Br) and Nonius CAD 4 (*p*-F). The intensity data were processed with a special version (containing MULTAN) of the X-ray system of crystallographic computer programs on a CDC 6600. The crystal and molecular structures of these compounds were determined by means of the heavy atom method (*o*-Br), MULTAN (*p*-F) and isomorphism (mandelic acid and *m*-F). A full account of this work will be published elsewhere.

MO calculations were performed according to the extended Hückel method.[16] The exponents and the valence orbital ionization potentials (eV) of the atomic orbitals were given the following values:[17] H1s (1.2/13.6), C2s (1.625/21.4), C2p (1.625/11.4), O2s (2.275/32.3), O2p (2.275/14.8), F2s (2.56/40.0), F2p (2.56/18.1). Off-diagonal Hamilton matrix elements were calculated with the empirical K parameter set at 1.75.[16] Bond lengths and bond angles were given standard values.[18] Both OH bonds were oriented in such a way as to form intramolecular hydrogen bonds with the carbonyl group. The only conformational freedom was the rotation of the –CH(OH)COOH group with respect to the benzene ring. The corresponding torsion angle, τ, was varied from 0 to 360° in steps of 30°. Rotational strengths, were calculated from the extended Hückel wave functions using a program written by R. Gould and kindly put at our disposal by Prof. Hoffman.[19]

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