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OPTICAL ROTATORY DISPERSION AND CIRCULAR DICHROISM OF SUBSTITUTED MANDELIC ACIDS

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Abstract—ORD at 25° and CD data (at 25° and − 185°) are given for *R*-mandelic acid and the following substituted *R*-mandelic acids and *R*-methyl mandelates:

4-Br, 4Cl, 3Cl, 4F, 3F, 2F, $4OCH_3$, $3OCH_3$, $2OCH_3$

For comparison, ORD and CD data are given of *S*-tropic acid, *R*-α-methoxy phenylacetic acid and *R*-β-phenyllactic acid and their methyl esters.

The absolute configuration and optical purity were determined by measurement of the NMR spectra of their methyl esters in (+)α-(1-naphtyl)ethylamine.

It is concluded that the low-wavelength Cotton effect of the aromatic chromophore is negative for the *R*-mandelic acids and their esters. The ^1L_b Cotton effect of the aromatic chromophore is positive for the unsubstituted and 3-substituted *R*-mandelic acids and their esters but negative for the 2- and 4-substituted derivatives.

MANDELIC acid shows two absorption bands in the UV spectrum: a weak band with fine structure in the 250–275 nm region (termed ^1L_b in the Platt notation and corresponding to a symmetry-forbidden $\pi \rightarrow \pi^*$ transition) and a stronger band between 215 and 225 nm. There is some controversy about the origin of this second band. On the one hand, certain arguments have been put forward to assign the band to the benzene ^1L_a transition.[1–3] On the other hand, it has been stated that the major contribution to this band is due to the $n \rightarrow \pi^*$ transition of the carboxyl group.[4, 5] The arguments for the second possibility seem the more convincing.

ORD and CD measurements on mandelic acid have been reported. The first ORD measurements indicated only one extremum of a Cotton effect at about 230 nm.[6–8] Later, weak Cotton effects in the region of the ^1L_b transition were found by ORD[9] and CD.[4, 5, 10] The ORD curves of *ortho*-methoxymandelic acid and the ORD and CD spectra on α-methoxy phenylacetic acid have also been reported,[5, 8, 11] as well as the CD spectrum of β-phenyllactic acid.[10] However, a systematic study of the substitution effect on the chiroptical properties of mandelic acids or other aromatic compounds has not been reported. Such a study is important because a better understanding of the relation between the sign of the aromatic Cotton effects and the configuration at the asymmetric centre(s) is useful in view of the occurrence of the aromatic chromophore in natural substances e.g. alkaloids, proteins. At the moment, the knowledge of the chiroptical properties of the aromatic chromophore is inadequate.[12]

In this paper, the results of an ORD and CD investigation of a series of substituted mandelic acids and methyl esters and some related compounds are given. The compounds studied have the general structure I. The substituents are tabulated in Table 1. Apart from ORD and CD spectra at room temperature, CD spectra were recorded at − 185°.

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Formula I

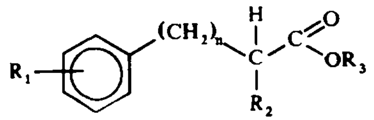


TABLE 1. INVESTIGATED COMPOUNDS WITH STRUCTURE I

Compound	R_1	R_2	R_3	n	Compound	R_1	R_2	R_3	n
1	H	OH	H	0	**14**	2F	OH	CH_3	0
2	H	↑	CH_3	↑	**15**	4-OCH_3	↑	H	↑
3	4-Br		H		**16**	4-OCH_3		CH_3	
4	4-Br		CH_3		**17**	3-OCH_3		H	
5	4-Cl		H		**18**	3-OCH_3		CH_3	
6	4-Cl		CH_3		**19**	2-OCH_3	↓	H	
7	3-Cl		H		**20**	2-OCH_3	OH	CH_3	
8	3-Cl		CH_3		**21**	H	CH_2OH	H	
9	4-F		H		**22**	H	CH_2OH	CH_3	
10	4-F		CH_3		**23**	H	OCH_3	H	↓
11	3-F		H		**24**	H	OCH_3	CH_3	0
12	3-F	↓	CH_3	↓	**25**	H	OH	H	1
13	2-F	OH	H	0	**26**	H	OH	CH_3	1

NMR measurements were made on the methyl esters in (+)α-(1-naphtyl-ethyl amine following the method of Pirkle and Beare[13] in order to be sure of the absolute configuration and to determine the optical purity of the compounds studied.

RESULTS

Optical rotatory dispersion. ORD results are shown in Table 2 (acids in methanol) and Table 3 (methyl esters in hexane). The ^1L_b Cotton effects discernible in most ORD curves, are not included in the Tables because they overlap and lie on the slope of the low-wavelength Cotton effect; therefore, amplitude and wavelength cannot be stated accurately. Some representative curves are shown in Figs 1 and 2.

Circular dichroism. CD results are shown in Table 4 (acids in methanol), Table 5 (methyl esters in hexane) and Table 6 (low temperature CD results regarding acids and esters). The ^1L_b Cotton effects are much better separated than in the ORD curves. However, they also lie on the slope of the low-wavelength Cotton effects. A characteristic example of ^1L_b CD bands of methyl esters (**10**) in hexane (where the vibrational fine structure is most pronounced) is given in Fig 3.

The extrema in the CD curves coincided, in most cases, with the UV maxima. In some cases, where overlap of bands displaced the maxima, low temperature UV measurements (−185°), where the vibrational fine structure is much better resolved, were used for comparison.

Nuclear magnetic resonance. The methoxycarbonyl signal in the NMR spectra of the optically active methyl mandelates coincided with the high-field signal of the methoxycarbonyl resonances in the racemic mixture, except for **8** and **20** where the reverse was true. Following Pirkle and Beare,[13] this means that all the mandelic acids and esters used in this study have the same absolute configuration except **7**, **8**, **19** and **20**. Compound **1** was the commercially available *R*(−) antipode. The other mandelic acids

TABLE 2. ORD RESULTS REGARDING *R*-MANDELIC ACIDS AND RELATED COMPOUNDS IN METHANOL

Compound	λtrough (nm)	$[\phi]$trough	λcrossover (nm)	λpeak (nm)	$[\phi]$peak	Amplitude
1	233	−21900	224	212	+35900	578
3	238	−23500	231	220	+41750	652
5	237	−23900	228	219	+31200	551
7[a]	233	−22040	226	219	+10170	322
9	233	−16600	222	214	+19430	359
11	233	−16300	223	212	+15450	317
13	228	−14220	218	211	+10340	246
15	242	−19600	233	223	+29340	490
17	237	−9660	228	209	+10300	200
19[a]	236	−16940	230	223	+16300	332
21	232	−6020	221	211	+10970	170
23	235	−18700	224	214	+18300	380
25[a]	228	−5100	222	216	+10600	157

[a] Measured as the antipode

TABLE 3. ORD RESULTS REGARDING *R*-METHYL MANDELATES AND RELATED COMPOUNDS IN HEXANE

Compound	λtrough (nm)	$[\phi]$trough	λcrossover (nm)	λpeak (nm)	$[\phi]$peak	Amplitude
2	231	−33200	222	215	+31900	651
4	238	−41200	229	219	+47000	882
6	233	−51040	226	216	+54350	1054
8[a]	231	−25230	222	216	+9600	348
10	230	−33800	222	211	+54350	882
12	228	−23400	222	211	+26200	496
14	227	−18500	220	207	+33250	517
16	241	−29800	232	223	+41200	710
18	238	−32000	228	213	+33880	659
20[a]	234	−56800	227	220	+37900	947
22	233	−16250	221	211	+27280	435
24	238	−11500	226	215	+15700	272
26[a]	225	−8850	217	211	+6000	149

[a] Measured as the antipode

were prepared by resolution of the racemates via the ephedrine salts. In all cases, the diastereomer crystallizing first from ethanol was used. This apparently gives **7** and **19** with the *S*-configuration, and all other compounds with the *R*-configuration.

The NMR method failed for **22**, **24** and **26** but the absolute configuration of these acids are known from the literature.[5, 8, 10, 14] The antipode with the negative low-wavelength Cotton effect is the *R*-antipode for **24** and **26** and the *S*-antipode for **22**. The *S*-antipode of **22** has the same absolute configuration as *R*-mandelic acid where OH has been replaced by CH$_2$OH.

From the NMR spectra it followed that all mandelic acids were optically pure after three crystallizations of the ephedrine salts from ethanol except **17**, which was 80% optically pure. The ORD and CD data for **17** and **18** have been corrected to 100% optical purity.

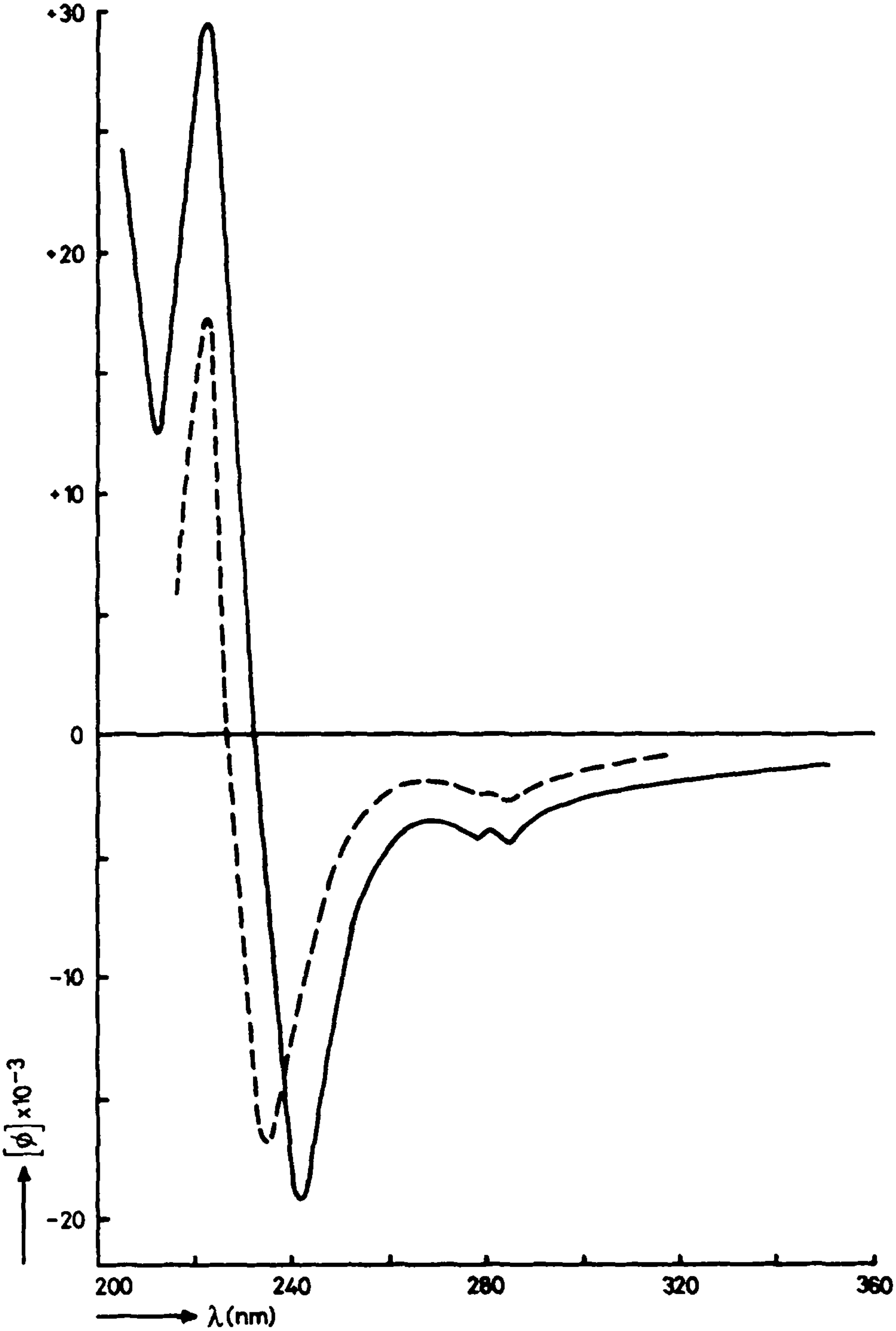
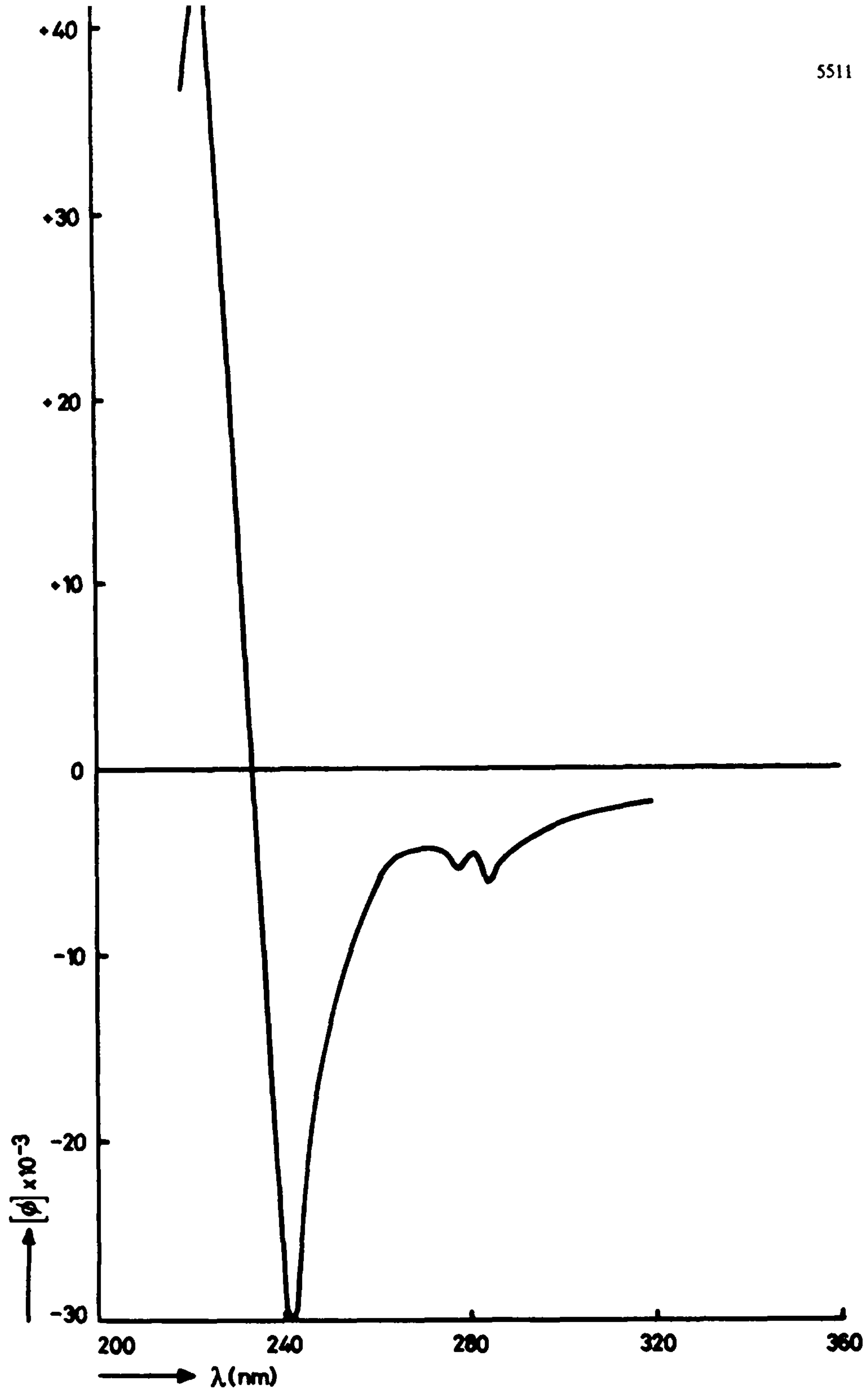


FIG 1. ORD curves of p-CH_3O (**15**, drawn line) and o-CH_3O (**19**, dotted line) mandelic acid in methanol. The latter compound was measured as the antipode.



Fɪɢ 2. ORD curve of p-CH_3O methyl mandelate (**16**) in hexane.

TABLE 4. CD AND UV RESULTS REGARDING *R*-MANDELIC ACIDS AND RELATED COMPOUNDS IN METHANOL. ELLIPTICITY VALUES WERE CORRECTED FOR BACKGROUND.

Compound	Low-wavelength Cotton effect		^1L_b Cotton effects		Isotropic absorption maxima of the ^1L_b band
	λ (nm)	[θ]	λ (nm)	[θ]	λ
1	221	−40280	267	+170	264
			261	+190	258
			256	+110	252
3	230	−38580	275·5	−280	275
			268	−270	266
			261·5	−160	258
5	228	−43160	275	−340	275
			268	−440	266
			262	−350	259
7[a]	226	−40150	264	+450	266
			257	+400	258
			250	+110	251
9	221	−34460	267	−400	271
			257·5	−520	265
			255	−490	252
11	221	−27070	270	+100	269
			262	+160	262
					257
13	218	−23530	264	−280	269
					263
					257
15	236	−22450	280	−760	281
			274	−650	274
17	228	−18120	278	+360	282
					275
19[a]	228	−34000	273	−1640	274
	215	+7600			
21	220	−11180	262	−80	265
			255	−140	258
					252
23	222	−33760	267	+200	267
			261	+240	264
			254	+170	258
					253
25[a]	221	−27280	269	+100	268
			264	+40	264
			261	+90	261
			254	+50	258
			249	+100	253
					247
					242

[a] Measured as the antipode

TABLE 5. CD AND UV RESULTS REGARDING *R*-METHYL MANDELATES AND RELATED COMPOUNDS IN HEXANE. ELLIPTICITY VALUES WERE CORRECTED FOR BACKGROUND.

Compound	Low-wavelength Cotton effect		^1L_b Cotton effects		Isotropic absorption maxima of the ^1L_b band in EPA at −185°
	λ (nm)	[θ]	λ (nm)	[θ]	λ
2	220	−66870	267	+130	263
			262	+170	258
			257	+70	252
			250	+30	
4	235	−63500	276	−260	281
			268	−280	275
			260	−200	271
			250	−70	268
					264
6	227	−71900	275	−450	281
			267·5	−500	275
			261	−350	271
			254	−140	264
					258
8[a]	224	−43790	283	+70	275
			275	+320	267
			268	+370	261
			261·5	+220	254
10	220	−52680	270	−200	270
			263	−245	265
			257·5	−190	259
					257
12	221	−44000	270	+630	269
			263·5	+570	262
			255	+200	256
14	218	−38120	262	−200	269
					262
					257
16	236	−72600	280	−820	282
			274	−730	275
					268
18	228	−24130	275	+200	282
					275
20[a]	230	−48890	282	−900	281
			275	−630	274
					268
22	218	−37400	267	−380	267
			260	−470	263
			255	−430	257
					252
					248

continued

Compound	Low-wavelength Cotton effect		$^{1}L_{b}$ Cotton effects		Isotropic absorption maxima of the $^{1}L_{b}$ band in EPA at −185°
	λ (nm)	[θ]	λ (nm)	[θ]	λ
24	222	−28900	267	+150	269
			260	+180	264
			253	+240	261
					258
					252
26[a]	218	−37720	268·5	+70	268
			264·5	+90	264
			261	+120	261
			253·5	+60	256
			249	+50	254
			244	+60	252
					247
					242

[a] Measured as the antipode

TABLE 6. CD RESULTS AT 25° AND −185° REGARDING *R*-MANDELIC ACIDS AND METHYL ESTERS IN EPA (ONLY LOW-WAVELENGTH COTTON EFFECT IS GIVEN, THE $^{1}L_{b}$ COTTON EFFECTS HAVE THE SAME SIGN BUT LARGER INTENSITIES THAN THOSE STATED IN TABLES 4 AND 5)

Compound	25°		−185°[b]	
	λ (nm)	[θ]	λ (nm)	[θ]
1	223	−51480	224	−91900
2	222	−39770	222	−71150
3	229	−46200	230	−86130
4	230	−40430	230	−74580
5	228	−56430	229	−90980
6	228	−42740	228	−78080
9	222	−45540	222	−74350
10	221	−42770	222	−81580
13	220	−25080	221	−56760
14	218	−35150	221	−71310
19[a]	229	−47850	231	−106850
20	229	−41350	232	−94250
21	220	−13070	219	−29200
22	218	−15310	219	−37060
23	224	−30060	224	−70160
24	224	−27360	226	−61640
25[a]	220	−12240	221	−42500
26	218	−13450	221	−42010

[a] Measured as the antipode.

[b] In the calculation of these values a 30% correction was made for the concentration because of shrinkage of the solvent.

DISCUSSION

The low-wavelength Cotton effect (215–235 nm). The sign of the Cotton effect in the low-wavelength region is negative for the compounds with *R*-configuration. Apparently, changes at the asymmetric centre, as in **21** and **23**, do not influence this relation. From the data presented here and those reported earlier[5–11] it may be concluded that the absolute configuration of the mandelic acids and esters may be safely

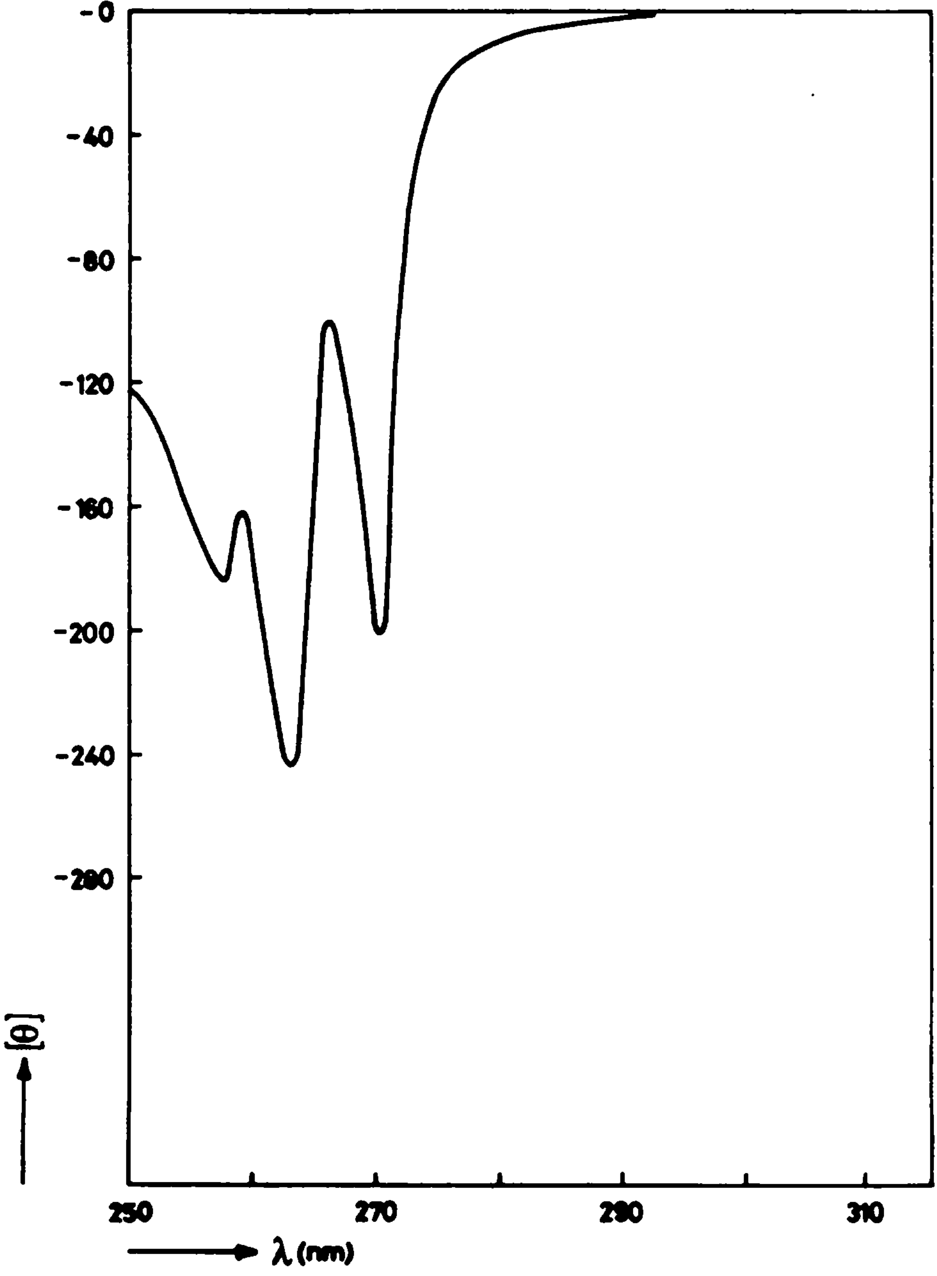


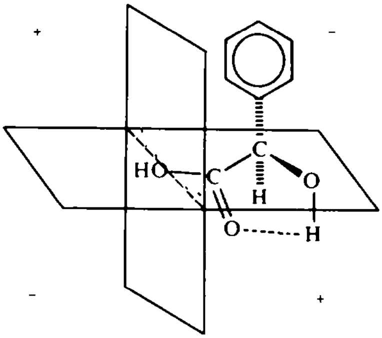
FIG 3. CD spectrum of ^1L_b transition of *p*-F methyl mandelate (**16**) in hexane.

deduced from the sign of this Cotton effect. It is already known that in compounds like **25** where the aromatic ring is one C atom removed from the asymmetric centre, a similar relation holds.[10]

Barth *et al.*[5] associated the low-wavelength Cotton effect of α-substituted phenylacetic acids with the n → π* transition of the carboxyl group. The optical activity is enhanced by homoconjugation of the carbonyl with the phenyl group. If this is true, mandelic acids may be treated as inherently dissymmetric systems.

From IR measurements[15] it is known that in mandelic acids, H-bonds[5] are formed between the carboxyl group and the α-OH group. It follows that conformations like II (where also the phenyl group is in a suitable position for π- orbital-overlap with the carbonyl group) are favoured.

Formula II



Use of the extended octant rule[16] shows that *R*-mandelic acids should have negative Cotton effects. Irrespective of the type of substitution, these negative Cotton effects are indeed found.

Theory predicts that in cases where chromophores are coupled, two Cotton effects should be produced of equal magnitude and opposite sign. It is noteworthy, therefore, that in one case (**19** in MeOH) two bands of opposite sign are actually observed. It should be realized, however, that **19** is a special case: apart from H-bonding between carboxyl and α-OH group, H-bonding between the *ortho*-substituent and the α-OH group is possible. That H-bonding occurs in the latter direction may be deduced from the high intensity of the ^1L_b Cotton effect in **19**.

Both ellipticities and ORD amplitudes are larger for the methyl esters in hexane than for the acids in methanol. This may be explained in terms of conformational mobility. In hexane, only intramolecular H-bonds are possible. This decreases the conformational mobility. When intermolecular H-bonds with the solvent are possible (as in methanol) more conformations with comparable energy will be present. This decreases the intensity as a result of an averaging effect.

The low temperature CD spectra show there is an increase in intensity at −185°, which is somewhat smaller than a factor 2 for the unsubstituted and *p*-substituted compounds but larger for the *o*-substituted compounds (~2·25) and for **23**, **24**, **25** and **26** (~2·25). For **21** and **22**, the increase is more than 3-fold. The increase in intensity is comparable for acids and esters.

These results may be rationalized in the following way. In cases where only one possibility for H-bonding exists, conformation II is already preferred. In compounds where more possibilities for H-bonding exist (as in **13**, **14**, **19**, **20** with the *ortho* substituent) or where the α-OH group is either not present (**23**, **24**) or one C atom further removed (**25**, **26**), or where more conformational mobility exists because of an extra free rotating C—C— bond) conformations with a somewhat higher energy may be populated. Upon cooling, the conformational equilibrium shifts to II again. When comparing **1** with **23** it is seen that it is indeed the room temperature ellipicities that differ.

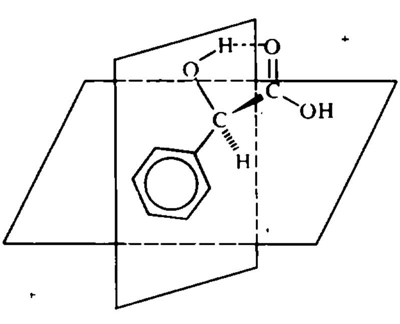
The ^1L_b *Cotton effects.* No systematic study has been reported regarding substituent effects on the aromatic ^1L_b Cotton effects.

Inspection of Tables 4 and 5 shows that the sign of the ^1L_b Cotton effect is directly related to the substitution pattern of the aromatic ring: for the *R*-mandelic acids and their esters the sign of the ^1L_b Cotton effect is positive for the unsubstituted and *meta*-substituted compounds (i.e. opposite to the sign of the low-wavelength Cotton effect) and negative for the *ortho*- and *para*-substituted compounds (i.e. of the same sign as the low-wavelength Cotton effect).

For an explanation, two lines of reasoning are possible. The first is that the electronic effect of the substituent may influence the rotamer populations and therefore the sign of the ^1L_b Cotton effect. However, there are arguments against this proposition. Because of the fact that the sign of the low-wavelength band is negative for all compounds studied it is hardly likely that the rotamer populations are so different that they can reverse the sign of the ^1L_b Cotton effect. Moreover, one would expect a large difference between mandelic acids with an electron-donating substituent (*p*-OMe) and an electron-attracting one (*p*-F).

Recently, a sector rule has been proposed for the unsubstituted aromatic chromophore,[17] predicting opposite signs for the ^1L_b and low-wavelength Cotton effects. Taking conformation II as the most favourable for mandelic acids and viewing the molecule from the aromatic ring, one obtains the picture given in III. On the basis of the sector rule[17] proposed, a positive Cotton effect is predicted for **1** and also actually found.

Formula III



The preferred conformation postulated in the previous section on the basis of the sign of the low-wavelength Cotton effects is therefore also in agreement with the sign of the ^1L_b Cotton effect. If substitution does not alter the rotamer population drastically (which one would not expect on the basis of the data for the low-wavelength Cotton effect) there must be another explanation for the differences in sign upon substitution.

An attractive suggestion might be that for substituted phenyl rings, different sector rules should be used.

When OH is replaced by CH_2OH (compare **1** with **21**, or **2** with **22**), the sign of the ^1L_b Cotton effect changes. This might be explained by the fact that there is a larger group in the negative sector of III for **21** than for **1**—assuming that conformation II is still the most favourable.

Compounds **25** and **26** are more complicated cases for here the Cotton effects are very small. For *S*-**26**, these effects have been reported as being positive in water (acid and ester) and methanol (ester).[10] In this study of *R*-acids, we have found positive Cotton effects for **25** in methanol and for **26** in hexane, but negative Cotton effects in EPA at 25° for **25** and **26**. On cooling to − 185°, the sign changes to positive. Because the small CD peaks lie on the slope of the large low-wavelength band (Table 6), it is very difficult to assign definitive signs, except for the low temperature measurement. It seems, however, that the sign is both solvent and temperature dependent. A further study of these effects is in progress.

EXPERIMENTAL

The ORD and CD curves were obtained partly with a FICA Spectropol I with CD attachment and partly with a Jouan Dichrograph 185[11]. All low-temp CD measurements were made with the Jouan. Concentrations were adjusted such that the absorbance was not larger than 2.

NMR measurements were carried out on a Varian A 60 spectrometer. The racemic substituted mandelic acids (with the exception of **7**, **11** and **13**) as well as **21**, **23** and **25** were commercially available. **1** and **25** were also available in optically active form. Racemic **7**, **11** and **13** were prepared according to Compère.[18] Resolution of the racemic mixtures was effected via crystallization of the ephedrine salts.

(+)α-(1-naphtyl)ethylamine was obtained from Aldrich. The esters were prepared via the diazomethane method. Use of the calculated amount of diazomethane does not result in methylation of the OH-group at the asymmetric centre (as proved by NMR).

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