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THE OPTICAL ROTARY DISPERSION AND CIRCULAR DICHROISM OF α-AMINO AND α-HYDROXY ACIDS[1]

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Abstract—The weak negative long-wavelength (230–245 nm) CD maxima in α-amino- and α-hydroxy acids of the S-configuration (in addition to the known strong positive CD maximum in the 210–215 nm region) is shown not to be caused by hydrogen bonding effects. It is related to the nucleophilic character of the heteroatom attached to the asymmetric center, and is suggested to be due to the existence of two conformers, in one of which coupling of the non-bonding orbital of the heteroatom with the chromophoric transition of the carbonyl may occur.

IT WAS SHOWN[2] earlier that the optical rotatory dispersion spectra of α-amino- and α-hydroxy acids of the S-series gave a single positive Cotton effect in the 215 nm region, due[3,4] to the n—π^* transition of the carboxyl group. While our studies on the circular dichroism (CD) spectra of these acids were in progress,[1] Anand and Hargreaves[5] reported for S(+)lactic acid a weak negative CD band in the 245 nm region as well as the expected strong positive CD maximum at lower wavelength. Since the CD spectrum in alkaline solution showed no negative Cotton effect, they[5] ascribed the band at 245 nm to the n—π^* transition, and the strong positive maximum at 210 nm to other, including π—π^*, transitions of the molecule.

Subsequently, Anand and Hargreaves[6] described for S(+)alanine and S(−)proline a very weak negative CD band in the 236 nm region, in addition to the strong positive CD band previously reported[7] at shorter wavelengths. In these amino acids, however, the CD spectrum in alkaline solution showed the negative band to have substantially *increased* in intensity. They[6] attributed the strong positive Cotton effect below 215 nm to n—σ^* and π—π^* transitions, and the dichroic bands in alkaline solution to the same transitions displaced to longer wavelengths.

However, a different interpretation is suggested by our CD spectra of α-amino and α-hydroxy acids (Tables 1 and 2).[8]

Firstly, our results (Table 1), together with those of a recent communication,[9] demonstrate that the long wavelength CD band is not due to intramolecular or intermolecular hydrogen bonding, since it is not confined to lactic acid (**1**) itself, but is also shown by ester and ether derivatives (**5–7**). This is of special importance because of the known[11] propensity to dimerization and polymerization of lactic acid, with resultant marked changes in rotation depending on internal conformation.[12] (In order to exclude variations due to solvent effects, all compounds were examined in 95% ethanol. However, lactic acid showed similar behavior in water.)

Secondly, the presence of the 240 nm band in other α-hydroxy acids (**2, 3**), and its absence in a β-hydroxy acid derivative (**9**) and a non-hydroxylic aliphatic acid (**8**)

(with ten-fold reduction in the molecular ellipticity values of the latter two compounds) demonstrates that the 240 nm band is not due to the n—π^* transition of the carbonyl group alone.

Thirdly, in alkaline solution the 240 nm CD band is absent and the normal (210 nm) CD band decreased to a lower intensity. This is explicable on the basis of the symmetry of the carboxylate ion, which would make the two conformations (which are approximately of mirror-image type) tend to cancel in their effects at 240 nm. Under these conditions, it was possible to observe part of the CD maximum associated with the high intensity π—π^* transition below 200 nm (Table 1).

We interpret this data to mean that the 240 nm CD band is due not to the interaction of the non-bonding electrons of the oxygen attached to the ester or acid carbonyl group with the π-orbitals of that carbonyl group, but may be caused by coupling with the carbonyl chromophore of one of the non-bonding orbitals of the oxygen atom attached to the asymmetric center. Since participation of the non-bonding electrons of the oxygen atom in the chromophoric transition of the carbonyl group can only occur in one of the rotamers I and II, this suggests a conformational equilibrium effect, as indicated by the temperature-dependence reported,[9] rather than one of solvation differences. The more stable form would presumably be that in which the maximum angle between dipoles exists, i.e., form I.

It is not possible to observe the n—σ^* transition of the heteroatom attached to the asymmetric center in α-hydroxy acids. Since the CD spectrum of S(+)-octanol-2 showed no measurable molecular ellipticity above 190 nm, the n—σ^* transition of the hydroxyl oxygen must occur below 190 nm. However, examination of α-amino acids permits a test of this hypothesis (Table 2).

The CD spectrum of S(+)alanine methyl ester (**11**) showed positive maxima at 199 nm (n—σ^* transition of a non-bonding electron on nitrogen) and 209 nm (n—π^* of the ester), and a negative band at 236 nm, which could be attributed to a coupling of the lone pair orbital of nitrogen with the ester carbonyl, possibly by the transition of a non-bonding electron on nitrogen to an anti-bonding π^*-orbital of the ester function in III. These assignments receive some support from the CD spectrum of the hydrochloride, in which *both* the n—σ^* transition and the 236 nm band are abolished, coupling being no longer possible when the nitrogen is protonated.

The same effects are observed in the case of S(−)proline methyl ester (**12**) and S(−)N-methylproline methyl ester (**13**), showing that primary, secondary, or tertiary amino groups may all lead to the presence of the 230 nm CD band. Hydrogen bonding effects are therefore ruled out.

The nucleophilic character of the heteroatom attached to the asymmetric center may be expected to determine the amplitude of the 240 nm CD band. Thus the weak interaction of the hydroxy substituent (**1,2,3,5**) is intensified on going to the more basic methoxy group (**6,7**) while the strongly nucleophilic amino group gives even higher intensity CD bands (**11,12,13**). This can be seen in the ratio of the molecular ellipticity of the 240 nm band to that of the parent (212 nm) band for the closely related methyl esters **5, 6, 11, 12** and **13**, where it is, respectively, 2·5, 10, 12, 18 and 30% with increasing nucleophilicity of the α-substituent.

Under alkaline conditions, the interactions between the heteroatom and the carbonyl chromophore will be greatly reduced due to the conversion of carboxyl to carboxylate. In the case of oxygen, this reduction is such as to render the (already

weak) negative CD band unobservable while in the case of the amino compounds, the stronger overlap, although markedly reduced in intensity, is still visible.[7] The zwitterionic nature of free amino acids explains the absence of the 240 nm band in these compounds, and the reason why this effect has not previously been reported.

Interaction of non-bonding electrons of the hydroxyl group with the carbonyl chromophore in S(−)β-(5-imidazolyl)lactic acid (**4**) also explains satisfactorily the weak negative CD band at 247 nm observed[12] in this compound.

The existence of a conformational equilibrium may thus account for the long-wavelength negative Cotton effect observed in the CD spectra of α-amino esters and of α-hydroxy acids, and it is possible[11] that the positive band at shorter wavelength is due to form I while the long-wavelength negative band is associated with forms II and III, in which coupling of the heteroatom non-bonding orbital with the chromophoric transition of the carbonyl occurs.

TABLE 1. CIRCULAR DICHROISM SPECTRA OF α-HYDROXY ACIDS

	Compound[a]	λ_{max}nm ($[\theta]_{max}$) 212 nm band	240 nm band
1	S(+)Lactic acid	210 (2727)	244 (−17·6)
	S(+)Lactic acid[b]	212 (2157)	246·5 (−17·4)
	S(+)Lactic acid[c]	214 (744)	0
	S(−)Calcium lactate[d]	215 (432)	0
2	S(+)Glyceric acid	210 (1834)	244 (−37·3)
3	S(+)Malic acid	212 (2600)	246 (−47·0)
4	S(−)β-(5-Imidazolyl)lactic acid[12]	214 (2100)	247 (−27)
5	S(−)Methyl lactate	211 (2545)	240 (−66)
6	S(−)Methyl α-methoxysuccinate	216 (2230)	242 (−219)
7	S(−)n-Butyl α-methoxypropionate	212 (1736)	237 (−342)
8	S(+)α-Methylbutyric acid	212 (267)	0
9	S(+)Butyl β-hydroxyisobutyrate	215 (192)	0

[a] In 95% ethanol unless otherwise indicated.
[b] In water at pH 1.
[c] In water at pH 9; π—π^* 190 nm[e] (−3160).
[d] In water at pH 10; π—π^* 198 nm[e] (−3030).
[e] Lowest wavelength recorded.

TABLE 2. CIRCULAR DICHROISM SPECTRA OF α-AMINO ACIDS

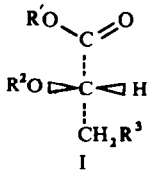
	Compound[a]	λ_{max}nm, ($[\theta]_{max}$) 200 nm band	210 nm band	235 nm band
10	S(+)Alanine[b]	—	209 (1277)	0
	S(+)Alanine[c]	—	211 (1261)	235 (−28)
11	S(+)Alanine methyl ester	199 (3564)	209 (3227)	236 (−395)
	S(+)Alanine methyl ester hydrochloride	0	208 (2987)	0
12	S(−)Proline methyl ester	202 (3788)	209 (2889)	232 (−604)
	S(−)Proline methyl ester hydrochloride	0	208 (3148)	0
13	S(−)N-Methyl proline methyl ester	199 (3593)	209 (1891)	226 (−643)
	S(−)N-Methyl proline methyl ester hydrochloride	0	209 (1722)	0

[a] In 95% ethanol unless otherwise indicated.
[b] In 50% ethanol at pH 1.
[c] In 50% ethanol at pH 11.

The ratio of the amplitudes of the two bands and their separation (17–34 nm), are reminiscent of the reported[13] double Cotton effects resulting from super-position of two adjacent CD maxima of opposite sign, suggesting that the original transitions may actually be located only 10–20 nm apart.

EXPERIMENTAL

CD curves were determined with a JASCO spectropolarimeter at 25°, and maxima are recorded in molecular ellipticity units $[\theta]$.[14]



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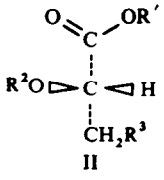
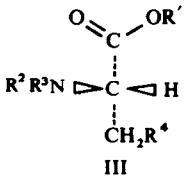


II



III

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