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CIRCULAR DICHROISM OF α-HYDROXY-2-THIENYLACETIC ACID, α-HYDROXY-3-THIENYLACETIC ACID AND MANDELIC ACID

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Abstract—The CD spectra of α-hydroxy-2-thienylacetic acid **1** and the corresponding 3-isomer **2** in various solvents are compared with those of mandelic acid **3**. Two Cotton effects at 190–210 nm, previously not reported, were observed in the later spectra.

Circular dichroism (CD) spectra of various 3,3′-bithienyls have been extensively studied in these laboratories.[1-6] The heterohelicenes investigated by Wynberg and Groen[7-9] constitute other examples of optically active thiophen compounds, for which optical rotatory dispersion (ORD) or CD spectra have been presented. However, scant data are available on chiroptical properties of simple thiophens with a chiral centre in a side chain. In 1967, Verbit, Pfeil and Becker[10] published the ORD spectra of (*S*)-(−)-β-(2-thienyl)ethanolamine and the corresponding furyl derivative in three solvents (acetonitrile, 2-propanol and 0.1 N hydrochloric acid). They observed a positive Cotton effect, corresponding to the 234 nm absorption band of the thiophen chromophore, situated on a negative background rotation with extrema below 200 nm.

The electronic properties of the benzene chromophore are rather well understood, but there is lack of agreement on the theoretical interpretation of the absorbance spectrum of thiophen.[11] (For more recent treatments of thiophen, see, e.g. Skancke and Skancke.[12]) CD investigations of thiophens with a chiral centre in a side chain may be of great interest for many reasons; (a) the possibilities of alternating signs and different relative intensities in CD compared with UV spectra might reveal hidden and obscure absorption bands, (b) comparisons of the CD spectra of related benzene and thiophen compounds would increase the understanding of the electronic and chiroptical properties of both chromophores, (c) a study of the CD spectra of simple thiophens might increase the understanding of the CD spectra of the 3,3′-bithienyls, and (d) the relations between the absolute configuration or conformation and the CD spectra of compounds of any kind are always of interest.

In this paper we present the CD spectra of α-hydroxy-2-thienyl-acetic acid **1** and α-hydroxy-3-thienylacetic acid **2**, the thiophen analogues of mandelic acid **3**, with which comparisons are made with respect to CD.

RESULTS AND DISCUSSION

The results obtained are summarized in Figs. 1–3. The hydroxy acids were investigated in acetonitrile, ethanol, and 0.01N sodium hydroxide. Compound **1** was also studied in n-hexane (see below). The three enantiomeric forms discussed are chirally related (they all belong to the D-series despite the different chirality symbol for **1**).

The isotropic absorption spectra of the thiophen compounds exhibit a band near 235 nm. Bands below 190–195 nm are indicated, but no maximima are reached with the available instruments. The shape of the curve of **2** in acetonitrile at 210–230 nm (Fig. 2) indicates the presence of further band(s), in addition to that at 234 nm. In the UV spectrum of the anion of **2** a small band is obvious at 210 nm. The UV as well as the CD spectrum of **1** is shifted to longer wavelengths relative to those of **2**.

The UV spectrum of mandelic acid in acetonitrile exhibits a long wavelength band, termed the ^1L_b band in the Platt notation, at 258 nm. Another absorption, which may be the ^1L_a band, is observed at 205 nm, and the $^1B_{a,b}$ band is situated below 190 nm. An isotropic absorption band was assigned to the 215–225 nm region by Korver,[13] and such a band may be observed as a shoulder for example in Fig. 1 in a paper by Verbit and Heffron.[14] These authors probably obtained data for a partly ionized sample in water.[15] We could detect no band or shoulder in this interval in the acetonitrile solution spectrum, but in the sodium hydroxide solution spectrum, a weak shoulder is observed at 216 nm and another at 209 nm, whereas the 205 nm peak is less intense (Fig. 3).

The CD spectra of the acidic forms of **1**-**3** all exhibit two negative effects or a negative band with a shoulder between 200 and 250 nm, and a positive band is situated at shorter wavelengths. Compounds **1** and **3** have in addition positive bands at longer wavelengths, that of **3** exhibiting vibrational splitting. The maxima of the isotropic absorption band corresponds to the minima rather than the maxima of the CD band at 250–270 nm (Fig. 3). However, the wavelengths found by us agree well with those given by Korver (methanol) for both bands.[13] The 260 and 220 nm bands of **3** have been observed previously by several authors.[13,14,16-22] To our knowledge, the bands at 197 nm and at *ca.* 205 nm have not been reported previously.

The spectra of the anions in 0.01 N sodium hydroxide are different from those of the corresponding acidic forms in all three cases. In the spectrum of **1**, the long wavelength positive band has increased in magnitude, whereas the 230 nm band has decreased and is obvious only as a shoulder on the now relatively strong negative effect at 205 nm. In the case of **2**, the short wavelength bands appear to have changed signs for the salt, whereas in Fig. 3 the effect at 205 nm may have retained its sign (see below), but in any case the intensity has increased.

The similarities of the CD spectra of the acidic forms of the thiophen compounds **1** and **2** may have been expected

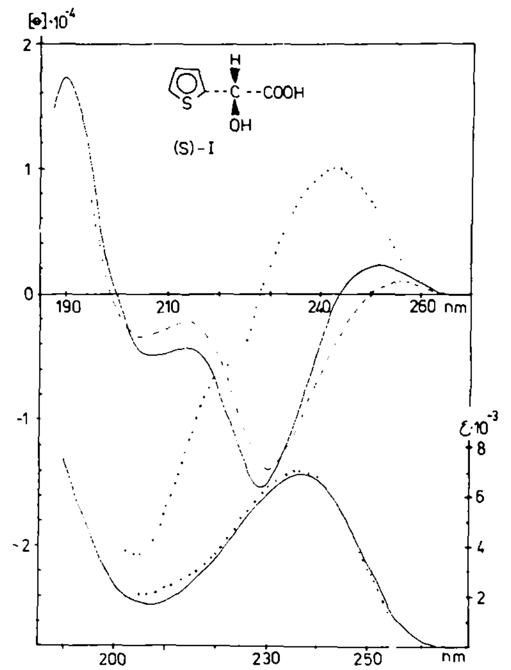

Fig. 1. CD and UV spectra of (*S*)-(−)-α-hydroxy-2-thienylacetic acid in acetonitrile (——), in ethanol (– – –), and in 0.01 N sodium hydroxide (· · ·).

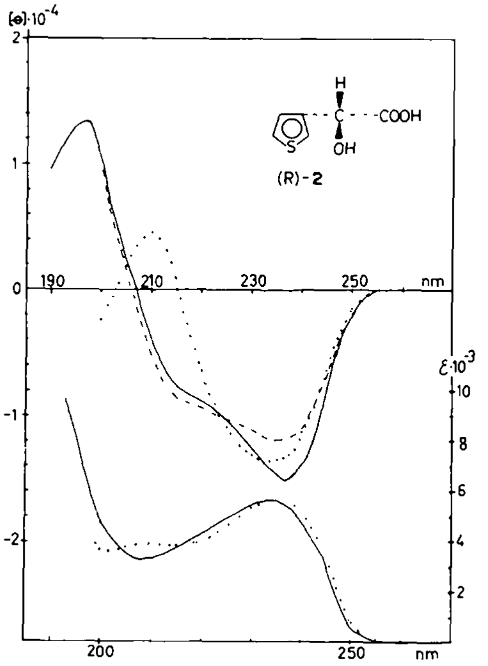

Fig. 2. CD and UV spectra of (*R*)-(−)-α-hydroxy-3-thienylacetic acid in acetonitrile (——), in ethanol (– – –), and in 0.01 N sodium hydroxide (· · ·).

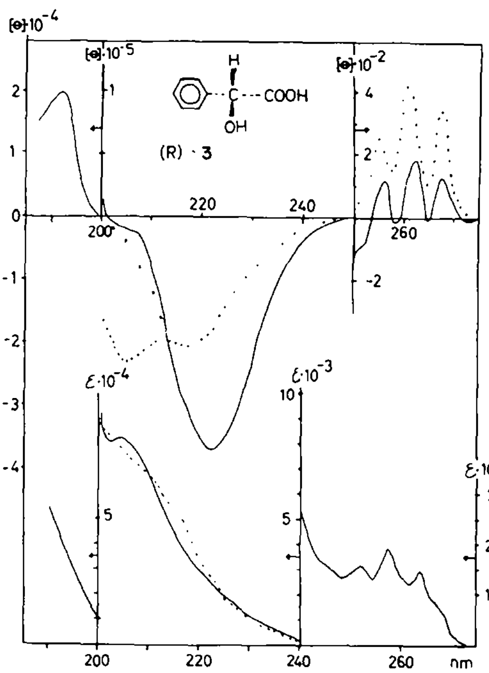

Fig. 3. CD and UV spectra of (*R*)-(−)-mandelic acid in acetonitrile (——) and in 0.01 N sodium hydroxide (· · ·). The ethanol and acetonitrile solution spectra are similar; $[\theta]_{223} - 40\,000$ in ethanol.

from the UV spectra and from the nearly identical chromophores. The spectra of the anions, however, are quite different. Very interesting are the striking similarities of the CD spectra of the thienyl and phenyl compounds despite the large differences between the UV spectra of **3** on the one hand and **1** and **2** on the other. (Note the different scales for the CD curves of **1**-**3**.) However, great care should be taken in making any far-reaching conclusions from these few spectra. More extensive work is necessary before a closer analysis and comparison can be made, and the influence of the carboxylic group has to be evaluated. Such investigations are in progress. In this paper we will simply make some comments on the spectra.

The long wavelength Cotton effects in the spectra of **1** and **3** are certainly not related. The 250–260 nm band of **1** most probably arises from a conformer different from that or those giving rise to the 230 nm band, although the presence of two separate bands of different origin in this interval cannot be completely excluded. For example, by linear dichroism measurements, Nordén[23] found two bands at 235 and 245 nm with mutual perpendicular polarisation in 2,5-dimethylthiophen, which has an absorption spectrum similar to that of **1** and **2**, although red shifted. In addition, a weak band at 260 nm was indicated.[23] However, in Fig. 1 a solvent effect is obvious. For the salt, the positive band dominates the spectrum above 210 nm. In ethanol, the long wavelength effect is smaller than in acetonitrile. In hexane, the positive band has almost disappeared, and in addition the 205 nm band seems to have changed sign. (This spectrum is not reproduced here. Due to the low solubility of **1** in hexane, the concentration of the solution used was not determined. In a 1 cm cell it gave a band at 231 nm with about the same pen deflection as observed for a solution of 5 mg of **1** in 10 ml of ethanol in a 0.1 cm cell. **2** and **3** were less soluble in hexane, which excluded investigations of them in CD.)

Several rotamers may be present in solutions of the hydroxy acids discussed. They are interconverted chiefly by rotation around two bonds: that between the carboxylic carbon and the chiral centre (C_1–C_2 torsion) and that between the chiral centre and the aromatic ring (C_2–C_r torsion). Not much is known about preferred conformations determined by the latter torsion. With respect to the C_1–C_2 torsion angle, α-hydroxy acids are considered to attain a preferred conformation shown in formulas 4-5, where the hydroxy group is eclipsed with the carbonyl part of the carboxyl group and in which hydrogen bonds between these two groups may be formed.[13,24,25] These bonds should be best developed in an apolar aprotic solvent such as hexane, in which the long wavelength positive band is weak.

A second proposed relatively stable conformer is one in which the carbonyl group and the C_2–C_3 (C_2–C_r) bond are eclipsed, provided that the substituent associated with C_3 is not too bulky.[26–32] In the present case, the aromatic ring might attain a conformation in which the ring plane is perpendicular to the plane of the carboxylic group **6**, which strongly reduces their steric interaction (cf Craig *et al.*[33]). Coplanarity of the two groups is highly improbable since in the case of **1** with the sulphur atom in a cisoid position relative to the carboxyl group (cf. formula **6**) the O . . . S distance is only about 2 Å, which is considerably less than the sum of the van der Waal's radii (S1.85 Å and O 1.40 Å[34]). The corresponding transoid coplanar conformation of **1** or coplanar conformations of **2** are even less favourable due to the hydrogens adjacent to the C_2–C_r bond. Conformations with the carbonyl group and the α-hydrogen eclipsed are not considered favorable, but those with the carboxylic C–OH bond and the α-hydroxy group or the C_2–C_3 bond eclipsed have been discussed.[27–32]

Probably not only the character of the aromatic ring but also the α-hydroxy group influences the CD spectrum of **1**. Preliminary investigations of the O-methyl derivative of **1** reveal a CD spectrum similar to that of **1** in acentronitrile, which is not especially solvent dependent. No dramatic effect of salt formation is observed in this case, the details of which will be published elsewhere.

The 220 nm band of mandelic acid has been suggested to originate primarily from the n-π* transition of the carboxyl group.[13,20,22] However, a corresponding band can sometimes be observed in spectra of structurally similar compounds lacking the carboxyl group, which has been taken as evidence for assigning the band to the aromatic ^1L_a transition.[14] The effect of substitution in the benzene ring on the 220 nm band of **3** seems to have been overlooked. Korver[13] found the following CD data for methanol solutions: **3**, $[\theta]_{221}-40\ 280$; 4-Cl-**3**, $[\theta]_{228}-43\ 160$; 4-Br-**3**, $[\theta]_{230}-38\ 580$; 4-OCH_3-**3**, $[\theta]_{236}-22\ 450$. Corresponding red shifts are observed for the ^1L_b band Cotton effects and the obvious conclusion from the above may be that the 220 nm band of **3** is associated with an aromatic transition rather than a carboxylic one. In any case, the negative effects at 230–240 nm in Figs. 1 and 2 are certainly associated with aromatic transitions in the thiophen chromophore. It may be fortuitous that bands of comparable magnitudes are observed at nearly the same wavelengths in thiophen compounds **1-2** and the electron-rich benzene derivative α-hydroxy-(4-methoxyphenyl)-acetic acid mentioned above.

It is interesting that in all spectra effects are observed at 200–215 nm, that is in the interval where the n-π* transition of the carboxyl group may be expected (for example, (*S*)-lactic acid: $[\theta]_{212}+2727$ in ethanol.[35]) Curve shapes similar to those in Figs. 1–3 have been observed for α-alkylphenylacetic acids[33] and for related α-amino acids.[30] In the latter case, it was pointed out that curve types such as those between 200 and 245 nm in Fig. 1 may be interpreted as being composed of two Gaussian curves of the same sign, or alternatively by two curves of opposite signs. The latter interpretation would mean a *positive* effect situated at 210–215 nm in Fig. 1 (acidic forms) which might rather well agree with the presence of a *negative* effect at the same wavelengths, giving rise to the shoulder in the spectra of the acidic form of **2** (Fig. 2). Further, this would imply a blue shift and a reversal of the sign of the band discussed on salt formation of both **1** and **2**.

A closer inspection of Fig. 3 reveals that the short wavelength part of the negative 220 nm band (acetonitrile) is not symmetric with respect to the long wavelength part (a symmetric curve should follow the crosses at 200–213 nm.) This might be due to a small positive effect near 210 nm, and again this might imply a blue shift and a reversal of sign of an eventual band on salt formation.

In any case, ionization of the carboxylic group has an evident effect on the 200–220 nm interval of the spectra of **1-3**, the CD as well as the UV spectra. It has been suggested[36] that the n-π* transition of the carboxylic group moves to higher energy upon ionization. Therefore, it is not excluded that the 210 nm bands discussed above are associated with the carboxyl group. The magnitudes of the effects for organic solvents would also be consistent with carboxylic transitions. We hope to obtain further information from work in progress.

EXPERIMENTAL

(*R*)-(+)-Mandelic acid was commercially available. (*S*)-(−)-α-Hydroxy(2-thienyl)acetic acid[37] and the corresponding (*R*)-(−)-3-isomer[38] were available in these labratories. The former compound, which is very unstable, was stored as the cinchonidine salt.

The CD spectra were obtained with a Cary 60 spectropolarimeter, equipped with a circular dichroism accessory. The UV spectra were recorded on a Cary 15 or a Cary 118 spectrophotometer.

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