1211. *Circular Dichroism Studies on Terreic Acid and its Derivatives*

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The circular dichroism spectra of terreic acid and its methyl ether show bands associated with the $n \longrightarrow \pi^*$ transitions of the chromophore. The bands in the spectrum of terreic acid anion have high rotational strengths which are markedly temperature-dependent.

TERREIC ACID [1] (I), the antibiotic from *Aspergillus terreus*, is an interesting example of an optically active compound, in which the asymmetry arises from the unsymmetrical substitution of the double bond in the quinone epoxide ring. Its circular dichroism has been examined in connection with studies on the stereochemistry of mycochrysone derivatives.[2]

The detection of active bands associated with the two $n \longrightarrow \pi^*$ † transitions in the chromophore of terreic acid is possible only if the bands are widely separated, for the rotational strengths of the transitions will be approximately equal but opposite in sign. Separation of the bands, particularly in non-hydroxylic solvents, was expected since the position of the $n \longrightarrow \pi^*$ transition is sensitive to hydrogen bonding,[5] and the 4-carbonyl group is subjected to considerable intramolecular hydrogen bonding from the acidic 3-hydroxyl group. The infrared spectrum [1] shows that the hydroxyl and the chelated carbonyl stretching frequencies are lower by about 300 and 35 cm.$^{-1}$, respectively, than those of non-bonded groups. Thus, since the energy of an $n \longrightarrow \pi^*$ transition increases with the increased bonding on the $2p_y$ electrons of the oxygen, the band associated with the $n \longrightarrow \pi^*$ transition in the 4-carbonyl was expected to be at a lower wavelength than that associated with the 1-carbonyl, and bathochromic shifts of both bands were expected to occur on changing from a hydroxylic to a non-hydroxylic solvent. These differences and changes could not be observed in the ultraviolet spectrum owing to a strong absorption band with a maximum at 315·5 mμ in aqueous methanol.

(I)   (II a)   (II b)
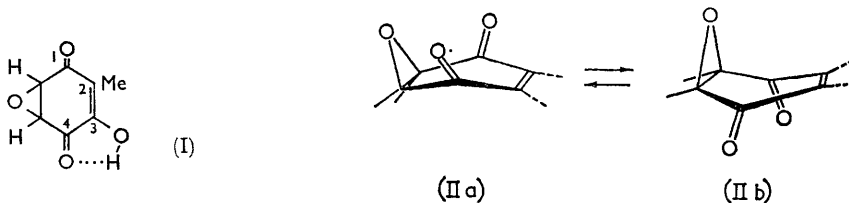
Dreiding models suggest that there are two principal conformers for terreic acid, (IIa) and (IIb), with only a low energy barrier between them. In these the carbonyl oxygen atoms project upwards (*i.e.*, on the same side as the epoxide oxygen) or downwards, respectively. Both are quasi-boat forms in which the dihedral angles between the yz-planes of the carbonyl groups and the yz-plane of the ethylenic bond, taking the direction of the p-bonding orbitals as the x-co-ordinates, are approximately 18°. It might be expected, therefore, that the circular dichroism of terreic acid will be temperature-dependent as a

† In a non-planar $\alpha\beta$-unsaturated ketone the forbidden $n \longrightarrow \pi^*$ transition acquires some allowed $\pi \longrightarrow \pi^*$ transition character, owing to overlap between the π-orbitals of the carbon–carbon double bond and the $2p_y$ non-bonding orbital of the oxygen.[3] Therefore, strictly speaking, the transition should not be referred to as a simple $n \longrightarrow \pi^*$ transition. The octant rule cannot be applied in such cases.[4]

[1] J. C. Sheehan, W. B. Lawson, and R. J. Gaul, *J. Amer. Chem. Soc.*, 1958, **80**, 5536.
[2] G. Read and L. C. Vining, *Chem. and Ind.*, 1963, 1239.
[3] H. Labhart and G. Wagnière, *Helv. Chim. Acta*, 1959, **42**, 2219.
[4] C. Djerassi, R. Records, E. Bunnenberg, K. Mislow, and A. Moscowitz, *J. Amer. Chem. Soc.*, 1962, **84**, 870.
[5] G. J. Brealey and M. Kasha, *J. Amer. Chem. Soc.*, 1955, **77**, 4462.

result of a conformational equilibrium.[6]   The rotational strengths of the $n \longrightarrow \pi^*$ transitions at the two carbonyls will be different for each conformer, and any significant change in the population of each conformer, on changing the temperature, should be reflected in the change of the total rotational strength of each $n \longrightarrow \pi^*$ transition.   However, this will not be observed if the free-energy difference between the two conformers is very small or very large.

The circular dichroism of terreic acid showed two bands in the region associated with $n \longrightarrow \pi^*$ transitions, when examined in 20% aqueous methanol adjusted to pH 3 to reduce the ionisation of the acidic hydroxyl (pK_a 4·5).   These occurred at 313 mμ ([θ] $+6170$) and 351 mμ ([θ] -4420), and were unchanged in position and intensity on cooling the solution from 20 to $-75°$.   Therefore, if a conformational equilibrium is present in terreic acid it cannot be detected by this method.   In cyclohexane the bands were well defined and appeared at 323 mμ ([θ] $+11,800$) and 374 mμ ([θ] -6570), respectively, which clearly shows that they are due to $n \longrightarrow \pi^*$ transitions, while the 51 mμ separation between them indicates that the intramolecular hydrogen-bond strength is about 11·3 kcal./mole in this solvent.   This figure compares with approximately 9·6 kcal./mole for the bond strength based on the infrared data,[1] assuming that the energy of dissociation is approximately that of a phenolic hydroxyl group.[7]   The change in rotational strengths, which accompanied the change in solvent, does not in itself indicate a change in the equilibrium between the conformers.[8]

The circular dichroism of terreic acid methyl ether was examined to ensure that the two bands observed in the case of the parent compound were not due to symmetrical and antisymmetrical combinations of the lone-pair molecular orbitals and the antibonding π-orbitals.   Such combinations occur in diketones [7] and are known to give rise to two absorption bands in the ultraviolet spectrum.   If these combinations had given rise to the two bands in terreic acid, two similar bands should also be observed in the methyl ether whereas the $n \longrightarrow \pi^*$ transitions in this compound would be of approximately equal energy.   When the methyl ether was examined in cyclohexane only one band, at 360 mμ ([θ] $+7690$), was observed, consistent with the overlap of two $n \longrightarrow \pi^*$ transitions of similar energies but differing and opposite rotational strengths.   The positive sign of the band showed that the 4-carbonyl has the greater rotational strength, as was found for terreic acid in cyclohexane.   In aqueous methanol terreic acid methyl ether revealed two bands, at 330 mμ ([θ] -5710) and 371 mμ ([θ] $+6240$), and it is apparent that in this solvent the $n \longrightarrow \pi^*$ transition at the 1-carbonyl has a higer energy than the transition at the 4-carbonyl.   This unexpected finding is attributed to shielding of the 4-carbonyl from the hydroxylic solvent by the juxtaposed methoxyl group.

During these studies it was observed that the ultraviolet spectrum of terreic acid underwent a marked change in weakly alkaline solutions (see Experimental section), which was associated with the formation of the anion rather than a decomposition product since it could be quantitatively reversed on rendering the solutions weakly acid.   The circular dichroism of the anion differed considerably from that of the parent acid.   In aqueous methanol at 20°, only bands at 283 mμ ([θ] $+58,500$) and 315 mμ ([θ] $-32,000$) were observed.   These showed a remarkable temperature-dependence, the circular dichroism rising to [θ] $+175,500$ and [θ] $-125,000$, respectively, at $-75°$.   The changes may reflect a change in the equilibrium between the two conformers analogous to (IIa) and (IIb) but more probably reflect a change in the equilibrium between the solvent and the solvated ions.[8]   In the latter case the number of orientated solvent molecules associated with the ion would be expected to increase as the temperature is lowered.   The transitions responsible for these bands are not known but the band at 283 mμ is in the position at which anions of β-diketones strongly absorb [9] and may be due to a similar transition in the terreic acid anion.

[6] K. M. Wellman, E. Bunnenberg, and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 1870.
[7] J. J. Fox and A. E. Martin, *Proc. Roy. Soc.*, 1937, *A*, **162**, 419.
[8] A. Moscowitz, K. M. Wellman, and C. Djerassi, *Proc. Nat. Acad. Sci. U.S.A.*, 1963, **50**, 799.
[9] B. Eistert, E. Merkel, and W. Reiss, *Chem. Ber.*, 1954, **87**, 1513.

EXPERIMENTAL

The circular dichroism measurements were made on a Roussel-Jouan Dichrograph, using approximately $1\cdot3 \times 10^{-4}$M-solutions in a 2-mm. cell for the studies at ambient temperature. For the low-temperature work a special 1-cm. cell was used, cooled to $-75°$ by a carbon dioxide–acetone bath, and a correction was made for the contraction of the solution. The ultraviolet spectra were recorded on an Optica Spectrophotometer.

Terreic Acid.—The terreic acid used had the following ultraviolet characteristics. $\lambda_{max.}$ $315\cdot5$ mμ (log ε $3\cdot82$) (aqueous methanol pH 3); $\lambda_{max.}$ 307 mμ (log ε $3\cdot82$) (cyclohexane); $\lambda_{max.}$ 254, 311, and 386 mμ (log ε $3\cdot80$, $3\cdot67$, and $3\cdot77$) (aqueous methanol pH $8\cdot5 \pm 0\cdot2$). Sheehan gives $\lambda_{max.}$ 213 and 316 mμ (log ε $4\cdot01$ and $3\cdot79$) (ethanol).

Terreic Acid Methyl Ether.—Terreic acid (*ca.* 6 mg.) was treated with an ethereal solution of excess diazomethane. After 5 min. the ether and excess diazomethane were removed by distillation and the product distilled in an 8-mm. tube at $80°/0\cdot1$ mm. The clear oil obtained solidified on cooling, to give white crystals, m. p. 33—$34°$, $\lambda_{max.}$ 304 mμ (log ε $3\cdot77$) (aqueous methanol), $\lambda_{max.}$ 306 mμ (log ε $3\cdot73$) (cyclohexane), C=O str. 1673 cm.$^{-1}$. Sheehan gives m. p. $41\cdot8$—$42\cdot8°$, $\lambda_{max.}$ 305 mμ (log ε $3\cdot74$) (ethanol).

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