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OPTICAL ACTIVITY OF NON-PLANAR CONJUGATED DIENES—IV

INTERACTING CHROMOPHORES IN GLIOTOXIN

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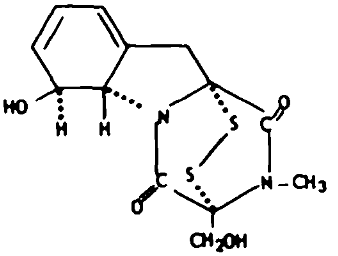
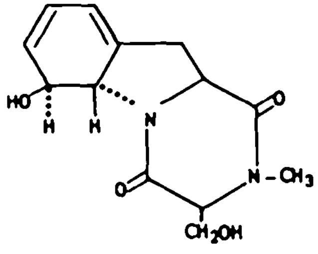
Abstract—The CD of dethiogliotoxin exhibits a negative band at ~ 265 mμ, as predicted from its known chirality. This observation is used to help explain the seeming discrepancy between the optical activity of gliotoxin and its chirality derived from X-ray crystallography.

The apparent anomaly is interpreted as the result of interaction of the diene and disulfide chromophores. The importance of such interactions of chromophores in interpreting optical activity data is stressed. The UV spectrum of gliotoxin is discussed, and the measurement of the rotatory dispersion of gliotoxin in KBr discs is reported.

RECENTLY Mathieson *et al.*[1] determined the absolute stereochemistry of the antibiotic gliotoxin (I) by X-ray analysis; in an accompanying note, Beecham and Mathieson[2] have discussed the CD of I.



I



II

The X-ray analysis has yielded direct evidence on both the chirality of the non-planar diene group present in I, and on the skew angle (14°) of this diene. In view of the scarcity of experimental information on these parameters in conjugated dienes, the study of I is very pertinent to further investigation of the rule which relates the *chirality* of a non-planar cisoid diene with the *sign* of the Cotton effect and CD originating in its absorption band at longest wavelength,[3] and of the theoretical relation[4] connecting the *intensities* of these effects with the skew angle.

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[1] A. F. Beecham, J. Fridrichsons and A. McL. Mathieson, *Tetrahedron Letters* No. 27, 3131 (1966).

[2] A. F. Beecham and A. McL. Mathieson, *Tetrahedron Letters* No. 27, 3139 (1966).

[3] A. Moscowitz, E. Charney, U. Weiss and H. Ziffer, *J. Am. Chem. Soc.* **83**, 4661 (1961).

[4] E. Charney, *Tetrahedron* **21**, 3127 (1965).

From their analysis of the CD of I and of one of its derivatives, Beecham and Mathieson conclude that the CD at 272 mµ *presumably* originating in a transition of the diene chromophore, is *positive*, whereas a cisoid diene with the chirality established by the X-ray analysis should produce a *negative* CD. For this apparent contradiction the authors propose an explanation which is based on the postulated influence of the asymmetric environment of the diene. On this basis they doubt the generality of the "cisoid diene" rule, which is concerned exclusively with the chirality of the diene itself. Their argument suggests that under the influence of asymmetric substituents in the vicinity of the diene system, the symmetry plane, which bisects the dihedral angle of the skewed system in the absence of such substituents, is no longer a bisector. The loci of (+) and (−) rotational strengths therefore take up different aspects with reference to the 4-carbon system. Arguments of this type have given rise to such explanations of optical activity as the octant rule, and are operationally (although not necessarily physically) valid. Schellman[5] has developed the qualitative quantum theory of environmental symmetry effects in considerable detail. While his theory is physically different from that of Beecham and Mathieson, operationally the results could be similar. However, the explanation given by these authors appears to ignore a number of other possible interpretations, which require consideration. The results of several experiments designed to probe alternate explanations are consistent with at least one such alternative.

Possibility of conformational modification by effects of solvents or of the crystal field

In Dreiding models of I with the established[1] absolute stereochemistry, the ring system of I appears rigidly held in single conformation, in which the diene unequivocally shows the M configuration[6] which should produce a negative CD. It does not seem impossible, however, that solvent or crystal forces may distort the molecule in a way which produces an inversion of the skew sense of the diene and might thus be responsible for the apparent anomaly. To test this possibility, we have determined the ORD curve of I in a highly polar solvent (acetonitrile) as well as of the solid in a KBr matrix (Fig. 1). Were the non-polar solvent (dioxan) used in the reported[7] CD measurements responsible for a conformational distortion, changing the solvent might be expected to change the sign of the ORD curve associated with the absorption band due to the diene. The ORD curves of I determined in acetonitrile and as a crystalline solid in a KBr matrix have essentially the same shape and are in agreement as to sign with the previously reported CD curve (in dioxan); a positive Cotton effect appears at about 270 mµ.

These results demonstrate that the conflict cannot be resolved by invoking an effect of the solid crystalline environment.

Effect of the diene chromophore of I; *CD of dethiogliotoxin*

Since conformational distortion in the crystal lattice can thus not be responsible for the apparent anomalies, their cause must be sought in the molecular structure of I itself, and more particularly in the interplay of the several chromophores present which absorb above ~200 mµ, *viz.* the non-planar disulfide bridge, the likewise

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[5] J. Schellman, *J. Chem. Phys.* **44**, 55 (1966).

[6] R. S. Cahn, Sir C. Ingold and V. Prelog, *Angew. Chem.* Internat. Ed. **78**, 413 (1966).

[7] H. Herrmann, R. Hodges and A. Taylor, *J. Chem. Soc.* 4315 (1964).

non-planar conjugated diene, the piperazinedione ring, and the carbonyl groups of the latter. In the treatment,[2,8] it is implicitly assumed that the CD of such a molecule can be treated as the algebraic sum of the CD's contributed by the individual chromophores. While the literature contains a number of instances[10] where this appears permissible, other examples have been found[11] where this additivity does not hold. The chromophores present in such a molecule can thus interact strongly to give a CD curve not identifiable as the sum of the CD's of the isolated chromophores, may interact weekly, or may not interact to any detectable extent.

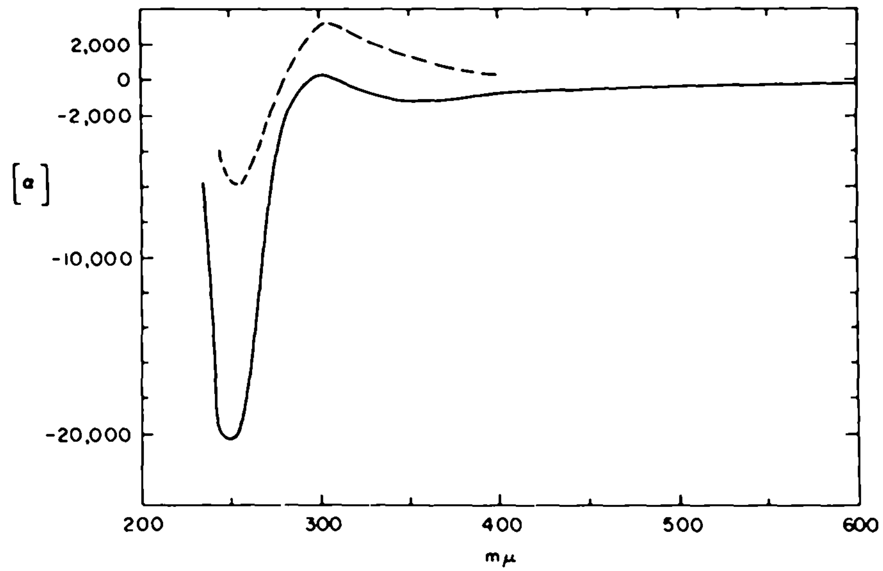

FIG. 1. Solid Curve, ORD of Gliotoxin in MeCN. Dotted Curve, ORD of Gliotoxin in transparent KBr disc. Note that the magnitude of the observed molar rotation in the KBr may be considerably in error, because of possible inhomogeneity of the KBr disc.

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[8] Beecham and Mathieson[2] find that the difference curve of the CD's of I and dehydrogliotoxin has a positive maximum at about 260 mμ and conclude from this that the contribution of the diene is likewise positive. Dehydrogliotoxin, however, still retains four major chromophores, the change from I being conversion of the diene to a phenolic ring. As the authors themselves point out, this chromophore might produce its own Cotton effect by interaction with the nearest asymmetric center. The substantial Cotton effect of tyrosine[9] which has the same structural relation between phenolic chromophore and asymmetric carbon atom as dehydrogliotoxin, shows that this interaction can be far from negligible even in a conformationally flexible molecule. Perhaps more important, the phenolic ring might also interact with the disulfide to generate a new composite chromophore with a rotational strength whose sign and magnitude is not at present amenable to detailed analysis.

[9] T. M. Hooker, Jr. and C. Tanford, *J. Am. Chem. Soc.* **86**, 4989 (1964); E. Iizuka and Y. T. Yang, *Biochemistry* **3**, 1519 (1964); G. D. Fasman, E. Bodenheimer and C. Linblow, *Ibid.* **3**, 1165; S. Beychok and G. D. Fasman, *Ibid.* **3**, 1675.

[10] [a] For example, see Fig. 14 of K. Mislow, E. Bunnenberg, R. Records and C. Djerassi, *J. Am. Chem. Soc.* **85**, 1342 (1963); [b] C. Djerassi and W. Closson, *J. Am. Chem. Soc.* **78**, 3761 (1956).

[11] cf., inter alia, A. Moscowitz, K. Mislow, M. A. W. Glass and C. Djerassi, *J. Am. Chem. Soc.* **84**, 1945 (1962); also Fig. 7 of Ref 10*b*.

Although it is difficult to predict the effects of such interactions, it is possible to approach the problem experimentally. In the absence of interactions, the CD in the 270 mμ region is likely to be produced mostly by the diene and the disulfide, both of which show absorption bands in this area. Removal of either of these groups would then reveal the CD of the other one (provided that this other chromophore is not altered in the process, and that contributions from the rest of the molecule can be neglected). A suitable compound of this type is dethiogliotoxin (II), in which the disulfide bridge has been replaced by two hydrogen atoms, a change which should not affect the stereochemistry about the dienic system.[12] If the substituents closest to the diene system, i.e. the —OH and —N in allylic position to it, were somehow responsible for the discrepancy between the *negative* sign of the CD at ~270 mμ predicted by the diene rule and the observed *positive* one, then the CD band of II in this region should likewise be positive, since its diene group must be under essentially identical influence of its allylic groups. In fact, however, *the CD curve of* II (Fig. 2) *shows a negative band at about* 265 *mμ in exact agreement with the predictions of the rule*. It thus seems impossible to explain the reversal of sign of the CD of I at ~270 mμ without invoking a significant interaction between the disulfide and diene chromophores.

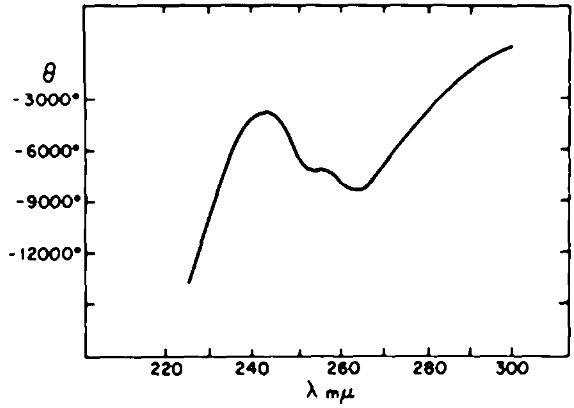

FIG. 2. CD of Dethiogliotoxin in MeCN

It is clear from the foregoing that the CD curve of I must result from some interaction of the chromophores present. Available general knowledge of such interactions is not yet sufficient for a complete analysis; since, however, phenomena of this kind are apt to be encountered, and to play an important role, in the interpretation of ORD and CD, but are hardly ever discussed in any detail, brief exploration of a number of logical possibilities is in order.

Analysis of interactions of chromophores

One such possibility would be that the electronic transitions involving excitation of the non-bonding electrons of the disulfide are pushed well below the $\pi \rightarrow \pi^*$

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[12] Dreiding models show that even the conformation of the piperazinedione system remains essentially unchanged, so that the remote possibility of an influence upon the diene of conformational changes in the heterocyclic part of the molecule can be discounted.

transition of the diene to give rise to the strong optically active transition at about 233 mμ in I. In this case, however, the transition at 272 mμ stays essentially dienic, and thus the supposed discrepancy between diene rule and X-ray results remains unresolved.

Alternatively, the nearly degenerate transitions of the diene (at about 270 mμ) and the disulfide (at about 280 mμ may interact strongly, if the symmetry is appropriate, to push the diene transition to shorter wavelengths. In this case the negative Cotton effect at about 233 mμ would have the sign expected from the known chirality of the diene system, while the smaller positive Cotton effect at 272 mμ would arise from the transition of the disulfide chromophore. Furthermore, the CD band at 233 mμ cannot be ascribed to any second transition of either diene or the disulfide chromophore unless, again, strong interaction is involved. This follows from the fact that the second strong absorption band of an isolated diene system normally occurs at wavelengths considerably shorter than 233 mμ, as does the second absorption band in the disulfide system. For example, in the steroidal compounds, ergosterol, lumisterol, 2,4-cholestadiene and 1,3-cholestadiene, which have long-wavelength bands at 270·5, 271·0, 265·0 and 263·0 mμ, respectively, the second strong $\pi \rightarrow \pi^*$ absorption occurs, respectively, at 209·5, 209·0, 204·5, and 202·0 mμ.[13] Similarly in *trans*-4,5-dihydroxy-*o*-thiane, no absorption with $\varepsilon > 20$ occurs between the 286 mμ band and 190 mμ.[14] Additional support for the foregoing deduction comes from the CD of II,[15] which shows a strong negative contribution which has not yet reached a max at 225 mμ as it approaches shorter wavelengths, while the CD spectrum of I exhibits a strong negative max at 233 mμ. There is, in addition, a possible complication from the two carbonyl groups, which form part of a piperazinedione system, to which Beecham, Fridrichsons and Mathieson attributed the 233 mμ transition. With no interaction, these should contribute only very weak absorption, but possibly with quite strong optical activity in the 260–300 mμ region. Their effects are somewhat easier to see in II than in I. The CD spectrum of II does in fact exhibit two max in this region, at least one (but not necessarily both) of which is certainly the diene transition. There is also an extended tail toward longer wavelengths that probably hides another transition in the 280 to 320 mμ region. In addition, Balasubramanian and Wetlaufer[16] have recently shown the existence of a fairly strong optically active transition in piperazinediones which, from their published ORD curves, appears to be centered at about 212 mμ.[17]

If this transition indeed accounts for the band at 233 mμ in I, then the optically active transition at ~270 280 mμ must be a composite of the disulfide and diene transitions, at present not readily resolveable. However, because of its great strength, we believe that the 233 mμ band contains a large contribution from the long-wavelength ($^1B \leftarrow {}^1A$) diene transition, but this, admittedly, is for the present conjecture.

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[13] U. Weiss, H. Ziffer and E. Charney, *Tetrahedron*, **21**, 3105 (1965).

[14] Unpublished observation of the UV spectrum in MeCN of purified *trans*-4,5-dihydroxy-*o*-thiane, prepared by the procedure given by W. W. Cleland, *Biochemistry* 3, 480 (1964).

[15] We wish to thank Drs. Pierre Witz and Hélène Herrmann, University of Strasbourg, for the CD measurement.

[16] D. Balasubramanian and D. B. Wetlaufer, *J. Am. Chem. Soc.* **88**, 3449 (1966).

[17] This is fairly close to the 233 mμ transition observed in I, but not as close as appears at first sight, since, in more energetically important units, it is 3600 cm^{-1} from the 233 mμ band while the latter is about 6000 cm^{-1} from the nominal 272 mμ transition of the diene.

The foregoing considerations and the relationship between the optical activity of I and II as determined from ORD and CD spectra clearly demonstrate that some interaction between the chromophoric groupings must be taken into account to explain the seeming "discrepancy" between the skew sense of the diene system of I, determined by X-ray crystallography and by CD, respectively. The optical activity of II is in full accord with that predicted from the diene rule, but the rule cannot and should not be applied to complex chromophoric systems such as that of I.[18]

Skew angle of II *and rotational strength*

The availability of precise X-ray data for the skew angle of the diene in I offers an opportunity for a further experimental check of the relationship between this angle and the rotational strength, R, of the diene transitions.[4] Thus far, only one such skew angle, that of lumisterol,[20] has been available from direct observation. Assuming that the skew angle in II is not essentially different from that found by X-ray analysis of I, our observed value for II, obtained from its CD curve, can be compared with the calculated value. In view of the approximations inherent in the theory, the agreement (calc. $-0{\cdot}26 \times 10^{-38}$ c.g.s., obs, $-0{\cdot}25 \times 10^{-38}$ c.g.s.) is surprisingly good.

EXPERIMENTAL

The ORD curves of I were obtained on a Cary Model 60 Spectropolarimeter in acetonitrile: c = 0·0848 g/100 ml, $[\phi]_{360}$ −4308°, $[\phi]_{290}$ 385°, $[\phi]_{250}$ −71,200°.

The KBr pellet was made by conventional methods with 150 mg of a mixture of 0·5 mg compd in 600 mg KBr, pellet thickness 0·5 mm.

The CD curve of II, which was prepared by Dr. J. D. Dutcher following published procedures,[21] was determined on a Jouan Dichrograph in EtOH; $[\theta]_{265}$ −8422. The authors wish to thank Dr. H. Herrmann, Strasbourg, for this measurement, and Dr. J. D. Dutcher for the samples of I and II.

Addendum—After this manuscript was completed, a communication by A. J. McCaffery, S. F. Mason and Miss B. J. Norman appeared describing the similar use of KBr discs to measure CD in the solid state [*Chem. Commun.* 19, 661 (1966)].

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[18] It also appears that another, similar discrepancy observed in the case of the Erythrina alkaloids[19] may well be explicable in an analogous manner.

[19] U. Weiss and H. Ziffer, *Experientia* 19, 108, 660 (1963).

[20] D. C. Hodgkin and D. Sayre, *J. Chem. Soc.* 4561 (1952).

[21] J. D. Dutcher, J. R. Johnson and W. F. Bruce, *J. Am. Chem. Soc.* 67, 1736 (1945).