Tetrahedron Letters No.27, pp. 3139-3146, 1966. Pergamon Press Ltd.
Printed in Great Britain.

THE CIRCULAR DICHROISM OF GLIOTOXIN

by

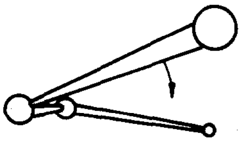
A. F. Beecham and A. McL. Mathieson
Division of Chemical Physics, Chemical Research Laboratories,
C.S.I.R.O., Box 160 P.O., Clayton, Victoria, Australia.

(Received 22 April 1966)

On the basis of a theoretical treatment and a selection of reference compounds, Moscowitz, Charney, Weiss and Ziffer (1) enunciated a rule relating the sign of the circular dichroism associated with cisoid skew dienes to the chirality of these dissymmetric chromophores. The X-ray analysis of gliotoxin (2) has defined absolutely the chirality of a cisoid diene for the first time in a molecule of considerable rigidity. Consideration of the circular dichroism of gliotoxin with allied evidence has led us to conclude that, in this case, the rule is at variance with experimental observation.

The rule states (1): "A strong positive Cotton effect associated with the lowest frequency cisoid diene absorption band (~ 260-280 mμ) means the presence of a cisoid diene chromophore twisted in the sense of a right-handed helix. A strong negative Cotton effect is indicative of the left-handed twist." In gliotoxin, we find a left-handed twist, the dihedral angle ∠ C5C6C7/C6C7C8 being 14° (2). This is associated with a strong positive C.D. peak in the region of lowest frequency cisoid diene absorption.

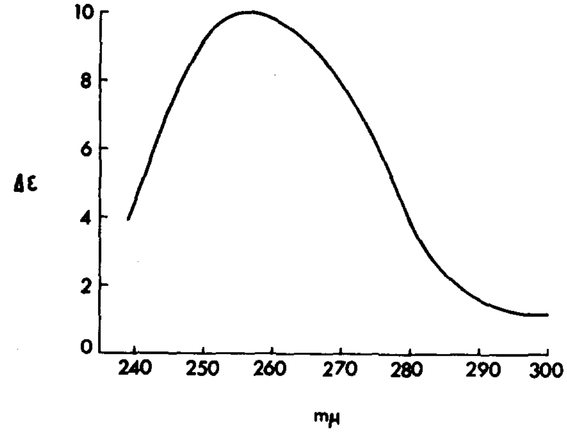
FIG.1



The C.D. curves we have used to derive this result are those recorded in (3). That for gliotoxin has been redetermined on a Roussel-Jouan Dichrograph and accords with the published curve. Its major features are a large negative peak near 233 mμ, a positive peak at _circa_ 270 mμ, a small negative inflection at _circa_ 310 mμ and a negative peak, similarly small, at 340 mμ. The peak at 233 mμ we attribute to transitions associated with the disulphide-bridged piperazinedione system since four other molecules containing this structural element show similar C.D. in this region (2,3). The peak occurs at somewhat longer wavelength than would be expected for absorption due to the peptide groups in a diketopiperazine (4). This may reflect both the special disposition of the two amide groups with respect to each other and the proximity of the disulphide bridge. Again, the true band centre may be at shorter wavelength, the turnover occurring where it does due to contiguity with a positive band of higher frequency.

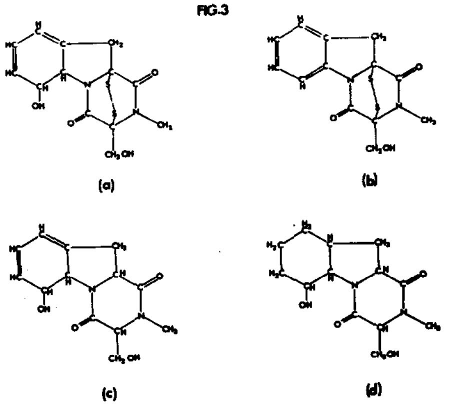
The positive peak near 270 mμ in the C.D. curve of gliotoxin is in the region where the contribution from the lowest energy band of a cisoid skew diene would be expected to occur (1). Transformation of gliotoxin, Fig. 3a, to dehydrogliotoxin, Fig. 3b, involves conversion of the cyclohexadiene ring to an aromatic one. Two centres of asymmetry are destroyed, a hydroxyl group being lost in the process, Figs 3a and 3b, but the disulphide-piperazinedione ring system is not affected. Subtraction of the C.D. data of dehydrogliotoxin from that of gliotoxin should then reveal the contribution of the skew diene, unless this is masked by rotatory effects arising from introduced aromatic bands.

FIG.2



As shown in Fig. 2, such a difference curve contains an isolated positive peak at <u>circa</u> 260 mμ, $\Delta\epsilon = 10$, consistent in position and magnitude with that expected from the diene. U.V. spectra reinforce the belief that this absorption has its origin in the diene system. That of gliotoxin contains a band $\lambda_{max} = 270$ mμ, $\log \epsilon = 3.64$ (5) which is also present in dethiogliotoxin, Fig. 3c, $\lambda_{max} = 268$ mμ, $\log \epsilon = 3.61$ (5). Tetrahydrodethiogliotoxin, Fig. 3d, shows only low general absorption through the same region (6).

FIG.3

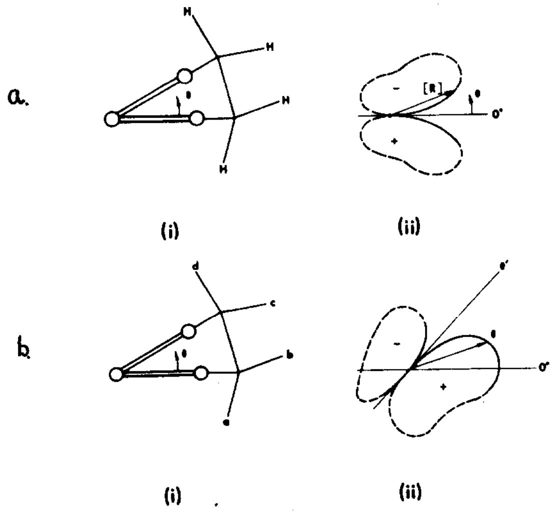


(a) (b) (c) (d)

It is difficult not to ascribe the positive dichroic absorption revealed by the difference curve of Fig. 2 to the left-handed skew diene. This, however, would constitute an infringement of the rule (1). In certain other cases (7), C.D. results have seemed to violate the rule and special effects have been invoked to bring them into line. Because of these examples, we at first explored the possibility of inverting the rule with regard to sign. However, for the cisoid diene at least, it appears to be soundly based theoretically (8) and the majority of experimental observations appear to support its correctness. On the other hand, the result from gliotoxin and the possible existence of other anomalous examples do suggest that the fundamental assumptions underlying the rule warrant examination.

It is convenient and instructive to illustrate the relationship between rotational strength [R] and dihedral angle θ in a dissymmetric chromophore by means of a polar diagram, as in Fig. 4a.

FIG.4



The lobe segments representing the locus of [R] in the figure are intended as descriptive only, but the null line at $\Theta = 0^\circ$ will always be a line of anti-symmetry, as shown, _if_ one assumes with Moscowitz _et al_. (1) that only the inherent dissymmetry of the chromophore need be considered. This viewpoint implies, perhaps, too clear a distinction between the rotatory properties of dissymmetric chlorophores, such as the cisoid diene, and perturbed symmetric chromophores represented by the carbonyl group in ketones. Although it has been stated (9) that "- - - the high degree of dissymmetry of such a chromophore is to be contrasted with the second-order dissymmetry of a carbonyl for which the optical activity is merely induced by its surroundings" in fact, the ranges of rotational strengths of the two classes overlap. It, therefore, seems reasonable to suggest that the presence of substituents a, b, c and d, Fig. 4(b)(i), will modify the dichroic absorption of the diene system, not so drastically as to invert the sign of the lobes in the polar diagram, but sufficiently to rotate the disposition of the lobes relative to $\theta = 0^\circ$,[*] the amount of rotation depending on the nature of a, b, c and d. The null line would then be at $\theta = \theta'$ and no longer a line of exact anti-symmetry. Under these circumstances, a *left-handed* chirality could be associated with a *positive* Cotton effect as illustrated in Fig. 4(b)(ii) and as observed in gliotoxin.

We are aware that if peripheral asymmetry is capable of affecting the rotatory properties of a cisoid diene in the way suggested then the diene rule loses much of its value. The paucity of evidence from X-ray structure analysis for the absolute geometry of compounds in which this has been deduced by circular dichroism is unfortunate. We feel that closer inspection of the anomalous behaviour of α-phellandrene[**] and levopimaric acid (7) is warranted and we intend to carry out an X-ray analysis of the latter. Correlation of C.D. data with detailed absolute structure analyses of other carefully selected compounds would prove most valuable in resolving the uncertainties in this situation.

---

[*] Footnote: A hint as to the possibility of invoking such an explanation resulted from plotting the values of $[\alpha]_D$ *versus* dihedral angle for 1,2-dichloropropane, listed by Kirkwood *et al.* (10) and considering the influence of molecular symmetry on the resulting polar diagram. Asymmetric perturbation of a dissymmetric chromophore will, in general, alter unequally the shapes as well as the angular disposition of the lobes of Fig. 4a.

[**] Footnote: A recent study of the C.D. of α-phellandrene down to −150°C has revealed no change in sign (11). Such might have been expected if, as suggested (12), the observed results at 20–80°C depend on a thermal balance between equatorial and axial conformations.

The Disulphide Chromophore

In the gliotoxin molecule, the group C1-S-S-C3 constitutes a dissymmetric chromophore with a left-handed chirality, the degree of skewness being indicated by the dihedral angle $\angle$ CSS/SSC = 14°. The dominant influence of dihedral angle on the U.V. absorption of the disulphide group is demonstrated by the results of Calvin *et al.* (13), where it is shown that the lowest frequency band of the chromophore moves to longer wavelengths and decreases in magnitude as the angle is reduced from the open chain value of ~100° towards 0°. In gliotoxin, the transition is observed as a barely perceptible shoulder at 340 mμ, ϵ = 200 on the U.V. absorption curve, corresponding to the negative C.D. peak, $\Delta\epsilon$ = 0.4 at 340 mμ. A second negative feature appears as an inflexion, $\Delta\epsilon$ = 0.3, at 310 mμ (14). In gliotoxin, the negative disulphide C.D. in the region of the lowest frequency absorption band is associated with left-handed chirality but whether the sign is dominated by the skew sense remains unclear. Adjacent asymmetric elements within the molecule may well have a perturbing influence on this chromophore as suggested in the case of the cisoid diene. Absolutely determined model compounds would be valuable here also.

References

1. A. Moscowitz, E. Charney, U. Weiss and H. Ziffer, J.A.C.S., **83**, 4661 (1961).
2. A. F. Beecham, J. Fridrichsons and A. McL. Mathieson, Tetrahedron Letters — accompanying paper.
3. H. Herrmann, R. Hodges and A. Taylor, J. Chem. Soc., 4315 (1964).
4. L. J. Saidel, Arch. Biochem. Biophys., **56**, 45 (1955).
5. J. D. Dutcher, J. R. Johnson and W. F. Bruce, J.A.C.S., **67**, 1736 (1945).

6. J. R. Johnson and R. Buchanan, J.A.C.S., 75, 2103 (1953).

7. A. W. Burgstahler, H. Ziffer and U. Weiss, J.A.C.S., 83, 4660 (1961).

8. A. C. Hurley — private communication.

9. P. Crabbe, Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry, Holden-Day, San Francisco (1965), p.180.

10. W. W. Wood, W. Fickett and J. G. Kirkwood, J. Chem. Phys., 20, 561 (1952).

11. G. Horsman and C. A. Emeis, Tetrahedron Letters, No. 34, 3037 (1965).

12. H. Ziffer, E. Charney and U. Weiss, J.A.C.S., 84, 2961 (1962).

13. J. A. Barltrop, P. M. Hayes and M. Calvin, J.A.C.S., 76, 4348 (1954).

14. C. Djerassi, H. Wolf and E. Bunnenberg, J.A.C.S., 84, 4552 (1962) — 6,8-thioctic acid will have a dihedral angle of ~26° (cf. X-ray data on 1,2-dithiolane-4-carboxylic acid, O. Foss and O. Tjomsland, Acta Chem. Scand., 12, 1810 (1958)) and therefore constitutes the nearest available comparison with gliotoxin in this respect.