

2 Part (iii) Optical Rotatory Dispersion and Circular Dichroism

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THE chiroptical techniques, optical rotatory dispersion (o.r.d.) and circular dichroism (c.d.) provide information about molecular dissymmetry and in particular about the absolute configuration of chiral compounds. The maximum differential dichroic absorption ($\Delta\epsilon$) in the c.d. curve occurs at the same wavelength as the corresponding maximum in the absorption curve and should also correspond to the midpoint between the two extrema of the Cotton effect in the o.r.d. curve. The electronic transitions responsible for individual c.d. bands have usually been assigned by comparison with known u.v. spectra but a significant new development is the use of c.d. as a sensitive chiral probe to detect transitions which are not revealed in unpolarised absorption spectra. For example, the c.d. of dialkyldiazenes has been used to explore the relationship between the energy level scheme and the observed electronic transitions,¹ and parallel studies of u.v. and c.d. spectra have been used to analyse the vibrational fine structure of the absorption bands of phenylalanine and its derivatives.²

In a different way, combinations of u.v. spectra and chiroptical methods have been applied to study the chirality induced in symmetrical absorbing molecules by complex formation with non-absorbing chiral molecules. Induced c.d. has been reported for solutions containing cyclo-dextrins and azo-dyes³ and for symmetrical ketones in the presence of chiral, but non-absorbing tetrahydrofuran derivatives⁴ or of (–)-menthol.⁵ Work with thioketones and nitrites⁶ suggests that induced c.d. may be a fairly general phenomenon and that the possibility of hydrogen bonding is not a necessary pre-requisite.⁶

Cotton effects have been reported⁷ which correspond to the charge-transfer bands in the absorption spectrum of an *N*-substituted pyridinium ion.

¹ D. J. Severn and E. M. Kosower, *J. Amer. Chem. Soc.*, 1969, **91**, 1710.

² J. Horwitz, E. H. Strickland, and C. Billups, *J. Amer. Chem. Soc.*, 1969, **91**, 184.

³ K. Sasse and F. Cramer, *Chem. Ber.*, 1969, **102**, 509.

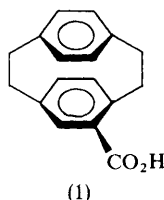
⁴ L. D. Hayward and R. N. Totty, *Chem. Comm.*, 1969, 676.

⁵ K. Noack, *Helv. Chim. Acta*, 1969, **52**, 2501.

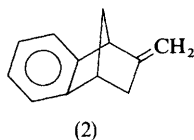
⁶ E. Axelrod, G. Barth, and E. Bunnenberg, *Tetrahedron Letters*, 1969, 5031.

⁷ A. J. de Gee, J. W. Verhoeven, I. P. Dirks, and Th. J. de Boer, *Tetrahedron*, 1969, **25**, 3407.

Inherently Dissymmetric Chromophores.—Weigang and Nugent⁸ have described a semi-empirical exciton theory that enables the absolute configuration of ring-substituted paracyclophanes to be determined from their observed c.d. The theory has been applied⁹ to several compounds including (1) for which the predicted absolute configuration thus assigned is in agreement with that already determined by other methods.



Several groups of compounds have been investigated in which the chromophore is part of a helix. The styrene chromophore which is twisted in a manner comparable to cisoid dienes, gives rise to Cotton effects¹⁰ which are negative and positive for right-handed and left-handed helices respectively. (This 'helicity rule' is opposite to that for dienes; the present work¹⁰ corrects previous statements¹¹). A conformationally rigid homo-conjugated styrene, (+)-2-methylene-5,6-benzonorbornene (2) investigated by Sandman and Mislow¹² has a strong positive Cotton effect centred at 224 nm attributed by the authors to mixing of the ethylenic and benzenoid transitions in the extended π -system. Homoconjugated 1,4-cisoid dienes in the dihydrocarquejol series also behave as single chromophores for which positive dichroism at 200 nm is associated with a right handed helix.¹³ Very large Cotton effects ($\Delta\epsilon \sim 45$ at 221 nm) have been recorded¹⁴ for 1,5-dienes related to jurineolide. This has been attributed to chiral overlap of the π -orbitals of two non-conjugated double bonds in the 10-membered ring, despite their separation by two saturated carbon atoms. O.r.d. and c.d. curves have also been recorded¹⁵ for a large number of santonene derivatives including many types of inherently dissymmetric chromophore.



⁸ O. E. Weigang and M. J. Nugent, *J. Amer. Chem. Soc.*, 1969, **91**, 4555.

⁹ M. J. Nugent and O. E. Weigang, *J. Amer. Chem. Soc.*, 1969, **91**, 4556.

¹⁰ P. Crabbé, *Chem. and Ind.*, 1969, 917.

¹¹ P. Crabbé and W. Klyne, *Tetrahedron*, 1967, **23**, 3449.

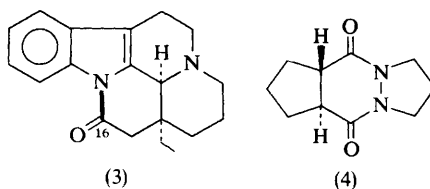
¹² D. J. Sandman and K. Mislow, *J. Amer. Chem. Soc.*, 1969, **91**, 645.

¹³ G. Snatzke, A. F. Thomas, and G. Ohloff, *Helv. Chim. Acta*, 1969, **52**, 1253.

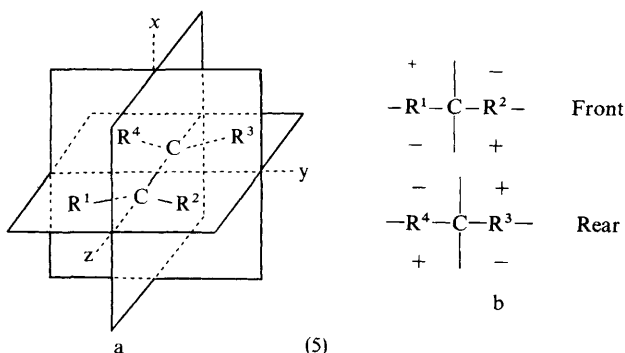
¹⁴ M. Suchý, L. Dolejš, V. Herout, F. Šorm, G. Snatzke, and J. Himmelreich, *Coll. Czech. Chem. Comm.*, 1969, **34**, 229.

¹⁵ L. Bartlett, P. M. Scopes, T. B. H. McMurry, and R. C. Mollan, *J. Chem. Soc. (C)*, 1969, 1088.

Unusually large values of $\Delta\epsilon$ have been recorded for two quite distinct types of compound containing a $-\text{CO}-\text{N}-$ group. Derivatives of (+) jeburnamenine, which are unsaturated at C-16 [with either carbonyl (as 3) or an olefinic double bond] show $\Delta\epsilon$ values much larger than the analogous compounds saturated at C-16.¹⁶ The authors tentatively suggest that the planar indole nucleus and the C-16 double bond form a section of a helix and behave as a single chromophore. Compounds of type (4) which are isomers of diketopiperazines have a single chromophore $-\text{CO}-\text{N}-\text{N}-\text{CO}-$ and also show abnormally large Cotton effects.¹⁷



Regional Rules for Symmetrical Chromophores.—A number of new regional rules have been proposed which relate the sign of the Cotton effect of a symmetrical chromophore to the asymmetry of its surroundings. Scott and Wrixon¹⁸ have proposed an octant rule for olefines (5a, b) and DeAngelis and Wildman¹⁹ a quadrant rule for the aryl chromophore in compounds with an asymmetric benzylic carbon atom. The rules have been tested on an appreciable number of compounds and are in agreement with the predictions from symmetry considerations. Other regional rules have been proposed for dithiocarbamates and dithiourethanes²⁰ and for cyclic thiocarbonates.²¹



¹⁶ K. Bláha, Z. Koblicová, and J. Trojánek, *Coll. Czech. Chem. Comm.*, 1969, **34**, 690.

¹⁷ C. G. Overberger, G. Montaudo, J. Šebenda, and R. A. Veneski, *J. Amer. Chem. Soc.*, 1969, **91**, 1256.

¹⁸ A. I. Scott and A. D. Wrixon, *Chem. Comm.*, 1969, 1182, 1184.

¹⁹ G. G. DeAngelis and W. C. Wildman, *Tetrahedron*, 1969, **25**, 5099.

²⁰ H. Ripperger, *Tetrahedron*, 1969, **25**, 725.

²¹ A. H. Haines and C. S. P. Jenkins, *Chem. Comm.*, 1969, 350.

Detailed studies of benzoates have led to a Sector Rule applicable to the benzoates of cyclic secondary alcohols²² and also to a useful correlation²³ between the configuration of glycol dibenzoates and the sign of the Davydov effect at 230–220 nm.

The precise relationship between molecular geometry and the observed sign of a carboxyl Cotton effect is still not clear. For bridged ring lactones, the sign depends essentially on the chirality of the bridged system²⁴ and the same relationship has now been proposed for bridged lactams.²⁵ The carboxy chromophore has also been studied in an extensive series of Δ^{12} -triterpene-28-carboxylic acids,²⁶ in which the interaction between the carboxy group and the $\gamma\delta$ olefinic bond may be significant. For $\alpha\beta$ -cyclopropyl lactones the sign of the $n-\pi^*$ Cotton effect may be predicted by application of the rule for $\alpha\beta$ -cyclopropyl ketones.²⁷

A theory for calculating the anisotropy factor in optically active ketones has been presented.²⁸

Quite apart from theoretical studies or regional rules, collections of data for related series of compounds can form a satisfactory basis for empirical correlations. Sulphoxide,²⁹ sulphinyl³⁰ and nitryloxy ($R \cdot ONO_2$)³¹ derivatives of steroids have been studied in detail. The last-mentioned show three Cotton effects at about 265–270, 230 and 210 nm respectively, and since the signs of these Cotton effects are characteristic of the position and configuration of the chromophore with respect to the steroid nucleus the nitryloxy group may be a useful ‘chromophoric derivative’ of hydroxy groups, particularly as the c.d. bands can be detected even in the presence of saturated keto groups. Isothiocyanates³² and salicylidene compounds³³ have both been studied as potential chromophoric derivatives of amines, amino acids and amino alcohols, and sugar osazones³⁴ and benzylphenylhydrazones³⁵ as derivatives of carbohydrates. Data have also been reported for various $\alpha\beta$ unsaturated lactones in sesquiterpenes of the guaianolide and related types,³⁶ and the large group of phthalide isoquinoline alkaloids has

²² N. Harada, M. Ohashi, and K. Nakanishi, *J. Amer. Chem. Soc.*, 1968, **90**, 7349; N. Harada and K. Nakanishi, *ibid.*, 7351.

²³ N. Harada and K. Nakanishi, *J. Amer. Chem. Soc.*, 1969, **91**, 3989; N. Harada, K. Nakanishi, and S. Tatsuoka, *ibid.*, 5896.

²⁴ J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 1965, 7229.

²⁵ A. F. Beecham, *Tetrahedron Letters*, 1969, 4897; cf. *Tetrahedron Letters*, 1968, 2355, 3591.

²⁶ J. D. Renwick, P. M. Scopes, and S. Huneck, *J. Chem. Soc. (C)*, 1969, 2544.

²⁷ G. Snatzke and E. Otto, *Tetrahedron*, 1969, **25**, 2041.

²⁸ G. M. Robinson and O. E. Weigang, *J. Amer. Chem. Soc.*, 1969, **91**, 3709.

²⁹ D. N. Jones, M. J. Green, and R. D. Whitehouse, *J. Chem. Soc. (C)*, 1969, 1166; D. N. Jones and W. Higgins, *ibid.*, 2159.

³⁰ D. N. Jones, D. Mundy, and R. D. Whitehouse, *J. Chem. Soc. (C)*, 1969, 1668.

³¹ G. Snatzke, H. Laurent, and R. Wiechert, *Tetrahedron*, 1969, **25**, 761.

³² B. Halpern, W. Patton, and P. Crabbé, *J. Chem. Soc. (B)*, 1969, 1143.

³³ H. Ripperger, K. Schreiber, G. Snatzke, and K. Ponsold, *Tetrahedron*, 1969, **25**, 827.

³⁴ L. Mester, H. El. Khadem, and G. Vass, *Tetrahedron Letters*, 1969, 4135.

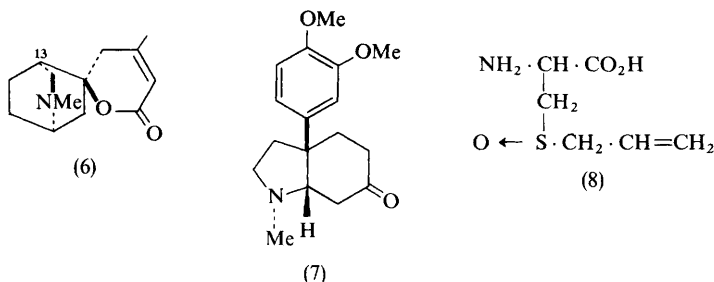
³⁵ W. S. Chilton, *J. Org. Chem.*, 1968, **33**, 4459.

³⁶ T. G. Waddell, W. Stöcklin, and T. A. Geissman, *Tetrahedron Letters*, 1969, 1313.

been reviewed in detail.³⁷ Cotton effects have been observed in the o.r.d. and c.d. curves of a saturated alkyl iodide,³⁸ and in some iodo steroids.³⁹

A report has appeared⁴⁰ of the o.r.d. of some amine derivatives in which the chirality is due entirely to the difference between hydrogen and deuterium. The observed rotations are much greater than any previously recorded for molecules of this type.

Configurational Assignments.—C.d. and o.r.d. data may be used to provide information about either configuration or conformation in a given molecule. It is very rarely possible to determine both together from c.d. and o.r.d. alone; for molecules in which neither configuration nor conformation is known additional evidence is needed from another source, e.g., n.m.r. or X-ray data of relative configuration. The dilemma is illustrated by Beecham's work on dioscorine (6),⁴¹ which exists in two enantiomeric forms each with two possible conformations (C-13 pseudoaxial or pseudo-equatorial with respect to the unsaturated lactone ring). From models it is apparent that Cotton effects of the *same* sign would be predicted for one enantiomer with C-13 equatorial and for the other enantiomer with 3-13 axial. In this case, X-ray measurements show C-13 equatorial and therefore the positive c.d. maximum indicates the absolute configuration (6). In another configuration/conformation problem, n.m.r. evidence has been used with o.r.d. data to allot a revised absolute configuration to the alkaloid mesembrine (7).⁴²



The careful choice of good analogies is essential for empirical comparisons of configuration. This can be illustrated by the work of Mislow⁴³ on alliin (8), (+)-S-allyl-L-cysteine sulfoxide, and related compounds. The authors show that the c.d. curve of alliin is nearly enantiomeric to that of dihydroalliin of the same

³⁷ G. Snatzke, G. Wollenberg, J. Hrbek, F. Šantavý, K. Bláha, W. Klyne, and R. J. Swan, *Tetrahedron*, 1969, **25**, 5059.

³⁸ P. A. Hart and M. P. Tripp, *Chem. Comm.*, 1969, 174.

³⁹ S. Sarel, Y. Shalon, and Y. Yanuka, *Tetrahedron Letters*, 1969, 961.

⁴⁰ W. Meister, R. D. Guthrie, J. L. Maxwell, D. A. Jaeger, and D. J. Cram, *J. Amer. Chem. Soc.*, 1969, **91**, 4452.

⁴¹ A. F. Beecham, H. H. Mills, F. B. Wilson, C. B. Page, and A. R. Pinder, *Tetrahedron Letters*, 1969, 3745.

⁴² P. W. Jeffs, R. L. Hawks, and D. S. Farrier, *J. Amer. Chem. Soc.*, 1969, **91**, 3831.

⁴³ P. D. Henson and K. Mislow, *Chem. Comm.*, 1969, 413.

absolute configuration and is also enantiomeric to the diastereoisomer with the opposite configuration at sulphur but the same configuration at the carboxyl centre. The choice of appropriate analogies is further illustrated by work on pulvilloric acid.⁴⁴ O.r.d. and c.d. data have also been used to allot the absolute configurations to (+)tricyclo[4,4,0]dec-4-ene[(+)-twistene] (9),⁴⁵ [by application of the octant rule to (+)-twistan-4-one], to the alkaloid (R)(-)-multifloramine,⁴⁶ to (-)-transdecahydroquinoline,⁴⁷ to helianthoidin⁴⁸ and to echinulin.⁴⁹ O.r.d. curves have been recorded in the u.v. for about forty carotenoids⁵⁰ and by empirical comparison of curves absolute configurations have been allotted to about fifteen compounds.



(9)

Conformational Studies.—Conflicting reports have appeared in the literature in the past regarding the origin of the c.d. bands in lactic acid. This has been reinvestigated by Djerassi and co-workers⁵¹ with the aid of low temperature measurements and they conclude that the main band at 210 nm and the smaller band at 240 nm have a common origin in the $n-\pi^*$ transition of the carboxy group. At low temperature the 240 nm band disappears and the existence of two bands at room temperature is attributed by the authors to different conformational preferences.

C.d. results have been used with other physical techniques to suggest a solution conformation for erythromycin⁵² and o.r.d. data to deduce the preferred conformation of the seven membered ring in B-homo steroids (C-7-twist chair).⁵³

Solvent Effects.—Much greater attention should be given to the possible existence of solvent effects than has generally been done in the past. A detailed study of arylazosteroids⁵⁴ has shown further good examples where a change of solvent can reverse the sign of a Cotton effect. Compound (10) in mixtures of carbon

⁴⁴ G. C. Barrett, J. F. W. McOmie, S. Nakajima and S. Tanenbaum, *J. Chem. Soc. (C)*, 1969, 1068.

⁴⁵ M. Tichý and J. Sicher, *Tetrahedron Letters*, 1969, 4609.

⁴⁶ A. Brossi, J. O'Brien, and S. Teitel, *Helv. Chim. Acta.*, 1969, **52**, 678.

⁴⁷ H. Ripperger and K. Schreiber, *Tetrahedron*, 1969, **25**, 737.

⁴⁸ R. S. Burden, L. Crombie, and D. A. Whiting, *J. Chem. Soc. (C)*, 1969, 693.

⁴⁹ E. Houghton and J. E. Saxton, *J. Chem. Soc. (C)*, 1969, 1003.

⁵⁰ L. Bartlett, W. Klyne, W. P. Mose, P. M. Scopes, G. Galasko, A. K. Mallams, B. C. L. Weedon, J. Szabolcs, and G. Tóth, *J. Chem. Soc. (C)*, 1969, 2527.

⁵¹ G. Barth, W. Voelter, E. Bunnenberg, and C. Djerassi, *Chem. Comm.*, 1969, 355; cf. R. D. Anand and M. K. Hargreaves, *Chem. Comm.*, 1967, 421.

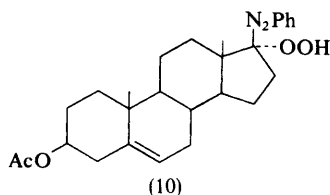
⁵² L. A. Mitscher, B. J. Slater, T. J. Perun, P. H. Jones, and J. R. Martin, *Tetrahedron Letters*, 1969, 4505.

⁵³ L. Kohout and J. Fajkoš, *Coll. Czech. Chem. Comm.*, 1969, **34**, 2439.

⁵⁴ J. Buckingham and R. D. Guthrie, *J. Chem. Soc. (C)*, 1969, 1939.

tetrachloride and dioxan gave a series of curves with the Cotton effect changing from positive to negative; all these curves passed through a common point for which the authors used the name *isorotatory point* (analogous to isosbestic point in adsorption spectra).^{54a}

The solvent-dependent c.d. of *N*-thiobenzoyl-L- α -aminoacids has been used to study the conformation of small peptides in solution.⁵⁵



Macromolecules.—Attention is drawn here to a few leading reviews and papers only; the applications of the chiroptical techniques to proteins⁵⁶ and to nucleic acids⁵⁷ have been reviewed in detail. An important paper by Goodman and his colleagues⁵⁸ describes in detail the o.r.d. and c.d. of some small cyclic lactams as conformationally rigid models for the amide group in proteins and peptides. The o.r.d. of some diastereoisomeric cyclo-hexapeptides has been reported.⁵⁹

Magnetic Circular Dichroism.—Magnetic circular dichroism (m.c.d.) has not previously been detected for simple ketones but improved instrumentation has now enabled Djerassi's school to obtain curves which are physically significant but as yet impossible to interpret.⁶⁰ The m.c.d. Cotton effect corresponding to the normal $n-\pi^*$ transition is of very low intensity and in some cases is split into two maxima of opposite sign. The strength, sign, and relative intensities of these two bands are closely dependent on the structure of the compound concerned.

^{54a} K. Garbett and R. D. Gillard, *J. Chem. Soc. (A)*, 1966, 204.

⁵⁵ G. C. Barrett, *J. Chem. Soc. (C)*, 1969, 1123; cf. G. C. Barrett and A. R. Khokhar, *J. Chem. Soc. (C)*, 1969, 1120.

⁵⁶ 'Optical Rotatory Dispersion of Proteins and Other Macromolecules', by B. Jirgensons. Volume 5 in the series 'Molecular Biology, Biochemistry and Biophysics', published by Springer-Verlag, 1969.

⁵⁷ J. T. Yang and T. Samejima, *Progr. Nucleic Acid Res.*, 1969, **9**, 224.

⁵⁸ M. Goodman, C. Toniolo, and J. Falcetta, *J. Amer. Chem. Soc.*, 1969, **91**, 1816.

⁵⁹ K. Bláha, I. Frič, and J. Rudinger, *Coll. Czech. Chem. Comm.*, 1969, **34**, 3497.

⁶⁰ G. Barth, E. Bunnenberg, and C. Djerassi, *Chem. Comm.*, 1969, 1246.