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INVERSE SIGN OF THE CHIRAL-OPTICAL EFFECTS OF NON-PLANAR HETEROANNULAR *CISOID* DIENES

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Abstract—The chiral-optical effects of heteroannular *cisoid* dienes are attributed to the dissymmetry of the skewed diene chromophore as in the case of homoannular *cisoid* dienes and of *transoid* dienes. The sign of these effects for a small number of heteroannular *cisoid* dienes is opposite to that predicted from the "diene rule" (1). This inversion of sign is ascribed to the change in electronic properties of the diene when, as in these compounds, the dihedral angle about the central bond is very large compared to that of the homoannular dienes. Consistent with these observations, recent theoretical treatments of the functional dependence of the rotatory strengths on the dihedral angle demonstrate that the sign of the CD and ORD effects can change at large angles.

EARLIER STUDIES in our laboratory, in cooperation with A. Moscowitz,[1] resulted in a theoretically derived rule connecting the sign of the chiral-optical effect for the optical transition at longest wavelength of 1,3-cyclohexadienes with the chirality of the chromophore. According to this rule, the optical activity of this transition is positive when the four carbon atoms of the diene are skewed in the sense of a right-handed helix. This rule was found to be valid for all of the ~30 compounds investigated[1,2] and has been quantitatively tested by the theoretical calculation using HMO wave-functions of an ORD curve which produced excellent agreement with the observed one.[1] Extension of the treatment to *transoid* dienes has resulted in an analogous rule, likewise confirmed by experiment.[3] We have briefly noted, however, that the applicability of the "cisoid diene" rule is questionable in the case of heteroannular *cisoid* dienes;[2] we now wish to present evidence that the limited number of suitable compounds of this class that have been investigated has given chiral-optical effects with a sign opposite to the one predicted from the stated rule. Burgstahler and Barkhurst[4] have recently published an empirical correlation of the sign of the optical activity of all three types of dienes with the chirality contributions of axial bonds allylic to the chromophore. In doing so the activity is attributed primarily to the influence of the vicinal (allylic) chirality rather than to the inherent dissymmetry of the conjugated chromophore. The purpose of our present paper is to show that the chiral-optical effects associated with the longest wavelength transition of the conjugated chromophore can be formulated in terms of its dissymmetry even in the aforementioned heteroannular compounds.

Only few heteroannular *cisoid* dienes have been available for study so far. To satisfy the stringent requirements of an unequivocal test of the effect of dissymmetry on the optical activity, the substance studied must, in addition to known structure

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and stereochemistry, have complete conformational rigidity, or must show the same skew sense in every conformation suggested by models. *In addition, the compound should be free of groups whose optical transitions or vicinal interactions could appreciably perturb the electronic transition of the diene.* These requirements, in addition to synthetic problems, have limited the number of compounds investigated.

Our findings are given in Table 1. Compound **1** comes closest to meeting the above requirements: conformationally unequivocal skewness shown in Dreiding models, and the absence of possibly perturbing groups in the vicinity of the chromophore. The methyl ester of vanguerolic acid acetate, (**2**), likewise has an unequivocal conformation. However, a possible perturbing influence of the carbomethoxy group allylic to the diene cannot be excluded, especially in view of possible overlap of its electronic transitions with that of the very strongly skewed diene. The closely related **3**, having the same chromophore as **2**, is included because the partial ORD curve given in ref. 5 likewise suggests the same sign as in **2** for the first extremum which, however, could not be reached with the instruments available at the time.

TABLE 1[a]

Compound	λ_{max} (nm) obs.	calc.[b]	$\Delta\nu$ (cm^{-1})	Sign predicted[c]	Observed Sign and Magnitude $\theta(\lambda_{nm})$	$\phi(\lambda_{nm})$
1	243	267	3800	+	−80,400 (240 nm)	[d]
2	227	272	7200	−		+68,000 (248 nm)
						−86,000 (214 nm)
4	243	267	3700		− 4,570 (260 nm)	
					+ 8,970 (248 nm)	
				−	+ 8,620 (240 nm)	
					+ 9,500 (237·5 nm)	
5	250	272·5	3400	+	−52,500 (247 nm)	

[a] We wish to express our appreciation to Prof. G. Ourisson for the earliest measurements of the CD of our compounds taken on the Juoan Dichrograph. The data above are more recent, taken on the Cary Model 60/61 spectropolarimeter in our laboratory. We also wish to acknowledge receipt of samples from Professors D. H. R. Barton, R. M. Moriarity and G. Just.

[b] Calculated as described in text. The 257 nm baseline used for the homoannular *cisoid* dienes is at higher energy then is actually observed in somewhat more constrained compounds. In (+)-*trans*-9-methyl-1,4,9,10-tetrahydronaphthalene it is at 262 nm.[22] Using the latter, values for the frequency shifts would be some 700 to 800 cm^{-1} larger than given in the table.

[c] Predicted on the basis of the simple diene rule[1]

[d] The ORD curve of this compound is presented in ref. 4.

Compound **4** has the same chromophore as **1**, but the presence of an acetoxy group at C-6, *i.e.* in the allylic position, could perturb the diene,* and indeed the CD curve of **4** is much more complex than that of **1** (Fig 1). Finally, the 3-isopropylidene-A-nor-steroid (**5**) described by Moriarty *et al.*[6] appears to be in a class by itself: it is the only compound in which one of the double bonds is not contained in a ring.† As will be discussed below, this feature may be very significant.

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* It is not clear at this time whether the change in sign in going from **1** to **4** is the results of an asymmetric perturbation of the diene chromophore (see Addendum) or of stereochemical influences of hydrogen bonding between the OH at C-5 and the AcO groups.

† A similar diene system is present in compound **6**, described by Ziffer and Robinson.[7] However, models of **6** suggest the existence of two conformations with opposite chiralities, making the substance unsuitable as a test compound.

The results summarized in Table 1 show that in **1**, **2**, **3** and **5** the sign of the CD (in the case of **4** the band at longest wavelength) is *opposite* to the one predicted by the rule for *cisoid* dienes which was found to apply to every one of the homoannular *cisoid* dienes that have been studied. While the observational material is quite inadequate for any generalizations, it is sufficient to show the existence of clear-cut departures from a rule which is based on the treatment of the diene system as a dissymmetric chromophore and which, in two classes of compounds, has stood the test of experimental scrutiny. It is necessary, therefore, to examine the possible reasons for this aberrant behavior of heteroannular *cisoid* dienes or, conversely, to examine whether the limitations of the HMO treatment are exceeded in the case of these compounds.

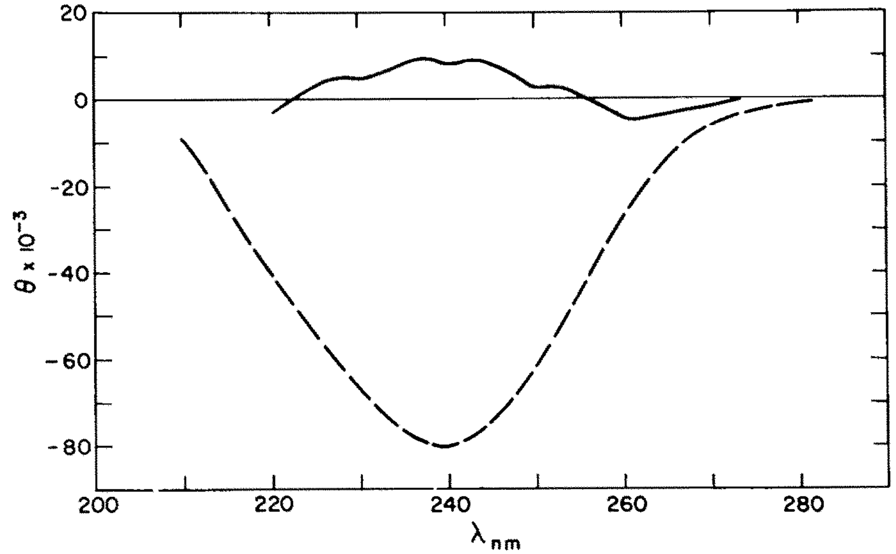
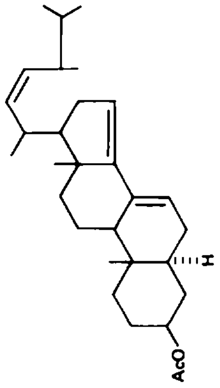


FIG 1. Circular dichroism of (-) compound **4** in isooctane: (----) compound **1** in isooctane.

One factor which distinguishes at least compounds **1**–**4**, perhaps also **5**, from their homoannular analogs is the much larger dihedral skew angle. Dreiding models of 1,3-cyclohexadiene and its analogs usually show angles up to ~20°: experimentally, an angle of 17° has been found for the parent compound (in the gas phase) by electron diffraction,[8,9] and similar values have been measured by X-ray crystallography: 8·3° for lumisterol,[10] 14° for gliotoxin,[11] and 17·3 ± 1° for compound **7**.[12] It seems possible that factors safely neglected at low degrees of non-planarity start playing a role at higher skew angles, and indeed in our previous discussion of the theoretical dependence of the intensity and sign of the CD of non-planar *cisoid* dienes upon the skew angle,[13] the assumed validity of the diene rule was explicitly limited to angles below 25°. Recent X-ray determinations of the absolute stereochemistry of levopimaric acid[14] and **7**[12,15] have confirmed the chirality of the chromophore assigned employing the diene rule.

An examination of the Dreiding models of **1** and **4** show the skew angles to be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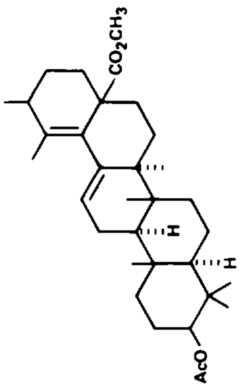
H

1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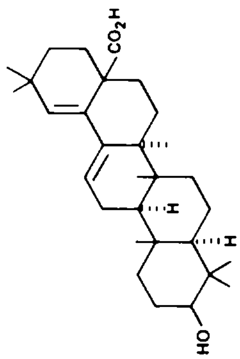
H
H
CO2CH3

2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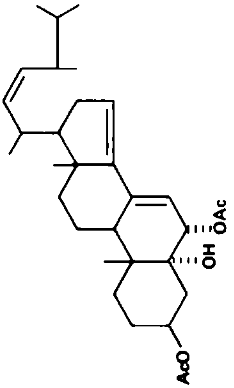
H
CO2H

3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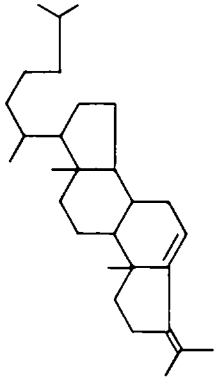
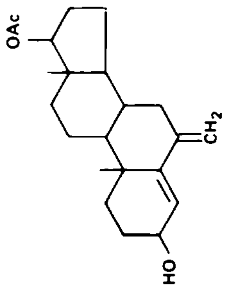
OH
OAc

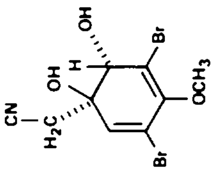
4



5


HO
CH2
OAc

6


CN
H2C
OH
H
OH
Br
OCH3
Br

7

approximately 35–40°, significantly larger than those encountered in the 1,3-cyclohexadienes. A similar examination of models of **2** and **3** shows their skew angles to be 40–45°. Although models suggest only moderate skewness (16°) in **5**, its actual skew angle may be greater as a result of the strong steric interference which must exist between the vinylic hydrogen at C-6 and the Me group *cis* to it.

Effects of the larger skew angles would be expected to appear in the UV absorption spectra of these compounds.[16] As the skew angle becomes larger, the $\pi^* \leftarrow \pi$ transitions have a tendency to shift to higher energies, indicative of a loss of conjugation. In the homoannular *cisoid* dienes, for example, a frequency shift of about 6500 cm^{-1} (from 257 nm to 220 nm) is observed in going from the moderately skewed 1,3-cyclohexadiene to the highly skewed 1,3-cyclononadiene.* A similar difference of about 5100 cm^{-1} (248 nm to 220 nm) is observed between the nearly planar 1,2-dimethylenecyclopentane and the highly skewed 1,2-dimethylenecyclohexane. An extreme case is seen in the *transoid* compounds, where a shift of 10,000 cm^{-1} between the absorption peaks of 2,3-dimethyl-1,3-butadiene and 2,3-di-t-butyl-1,3-butadiene[17] exists. Using 1,3-cyclohexadiene as a baseline and Woodward's Rule of a red shift of 5 nm per alkyl substituent, the blue shifts of compounds **1**–**4** are shown in Table 1. In the case of compounds **5** and **6**, a better approximation of λ_{max} of the basic diene system is given by assuming a value halfway between the absorption maxima of 1,3-cyclohexadiene and 1,2-dimethylenecyclopentane. It will be observed that in all cases there is a blue shift of at least 3400 cm^{-1} from the calculated values, indicative of substantial deviations of the diene chromophore from planarity.

We have already referred to the fact that in compounds having small dihedral angles the slightly modified Hückel treatment was very successful in predicting the optical activity: from this we infer that adjacent asymmetric centers make a relatively small contribution to the optical activity of skewed dienes. Recently, two treatments using more sophisticated approaches[18, 19] have appeared, in which spectroscopic configuration interaction is taken into account in analyzing the effect of skew angle on the rotatory strength of dienes. While the theoretical curves relating skew angle and rotatory strength in the two treatments differ, both analyses indicate that the relationship between skew angle and rotatory strength is not monotonic. In fact, Cheong *et al.*[18] predict that the longest wavelength transition will change in sign in the vicinity of a dihedral angle of 50°; the different rotational strengths in compounds **1** and **4** may cautiously be interpreted as indicative of the sensitivity of this parameter to small changes in geometry in the vicinity where the sign changes. The analysis by Gould and Hoffmann[19] shows the importance of configurational mixing and indicates the possibility of a sign reversal. In addition to configuration interaction, in a more complete treatment it would be necessary to consider specifically transitions to and from the sigma system of butadiene such as has been done for twisted ethylene by Yaris *et al.*[20] Changes in geometry in the excited states may also be important in the highly skewed dienes, a fact to which we have alluded previously.[13] As a result,

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* Of the two intermediate compounds the octadiene fits very well in the series relating the energy of the long wavelength transition to the known dihedral angle, but the heptadiene (λ_{max}) does not. However the electron diffraction data which established the near planarity of the diene chromophore in the heptadiene [P. F. Chiang and S. H. Bauer, *J. Am. Chem. Soc.* **88**, 420 (1966)] also indicate very severe strain in several of the bond angles and perhaps a slight lengthening of the nominal single bond between the ethylene moieties. It is reasonable to expect, therefore, that the transition energy to the first excited state in this molecule should not fit precisely into the correlation of the dihedral angle and the band positions.

in molecules with exocyclic methylene groups, transitions to the excited state, whose symmetry controls the optical activity, may take place predominantly from molecules whose ground state is vibrationally distorted, as in ethylene.[21] This could be the most important factor in determining the sign of the optical activity in compounds **5** and **6** where the exocyclic double bond is not constrained by incorporation in a ring.

It should be apparent that neither our earlier treatment nor the treatment of Cheong *et al.* distinguishes between homoannular and heteroannular dienes, nor between *exo*cyclic methylene and heteroannular groupings. The observation that this sign inversion has thus far been seen only in the heteroannular dienes or those containing exocyclic methylene or isopropylidene groups may simply be indicative of the circumstance that it is primarily in these compounds that a large skew angle is realized.* The definitive theory of the optical activity of skewed dienes has yet to be developed. It is quite clear that in compounds of the type discussed here, the "diene rule" must be modified to accommodate the findings of a sign opposite to that predicted by our slightly modified HMO treatment for molecules in which the dihedral angle is smaller than 25°. The correlation by Burgstahler and Barkhurst[4] of the stereoconfiguration of axial allylic hydrogens in both homoannular and heteroannular dienes with the sign of the optical activity, must also be accommodated in a complete theory either through contributions from the allylic centers or through its connection with the sense of skewness of the diene system. The configuration interaction treatments seem to indicate clearly, however, that even at large skew angles, the dissymmetric chromophore approach is capable of incorporating the diversity of results.

ADDENDUM

Since this paper was prepared for publication, an article by Beecham *et al.*[23] has appeared taking exception to our interpretation of the optical activity of gliotoxin. We do not feel that this is the appropriate place to discuss this problem. However, the supporting material in that paper is significant for the present discussion since it calls attention to a correlation between the sign of the chiroptical effect of a diene and the stereochemistry of an allylic oxygen containing substituent. Two classes of compounds are examined: *transoid* heteroannular dienes in schellhammerine derivatives and cyclohexadienes related to chorismic acid. In neither of these classes of compounds is the nominal diene moiety sufficiently isolated from groups capable of interacting with it, or which extend the conjugation to be treated as a diene chromophore. Thus, in principle, the "diene rule" is not expected to apply. Nevertheless, for the light they indeed throw on the influence of oxygen containing substituents allylic to the unsaturated four-carbon system, we may consider the juxtaposition of the two correlations which have been proposed to replace the treatment of the compounds as inherently dissymmetric chromophores. The correlation proposed by Beecham *et al.* for chorismic acid and its relatives correctly predicts the sign of the optical transition near 270 nm, but is in direct conflict with the correlation with the helicity of the allylic axial substituents as proposed by Burgstahler and Barkhurst. An analogous contradiction occurs in the schellhammerine derivatives

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* Engel and Ruest report a homoannular *cisoid* diene [the reduction product of compound **1** in *Can. J. Chem.* **48**, 3136 (1970)] whose optical activity exhibits a Cotton effect opposite to that predicted by the diene rule. We defer comment until a complete report is available.

when the allylic OH substituent is in the equitorial position; when the allylic OH is axial the two correlations are in agreement. This is further evidence that neither the axial allylic interpretation nor the diene rule may be used with equanimity to interpret the optical activity of compounds with extended or interacting chromophores.

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