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SOME APPLICATIONS OF THE CONFORMATIONAL DISSYMMETRY RULE

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THE twisted chain of four atoms (I)[1] is not superposable on its mirror image and so is dissymmetric;[2] as such it might be expected to be, of itself, optically active.[3] This optical activity will, of course, be observable only when enantiomeric conformational units are present in unequal amounts because of restraints on rotation about the central bond. Such restraints can be provided by structure (as when the central bond is part of a ring), by steric hindrance (as in the optically active biphenyls) or by a dissymmetric environment which makes one conformational unit more stable than its enantiomer.[4] The concept that conformational dissymmetry may be an important source of optical activity in organic compounds in general has been explicitly employed in many discussions of optical activity, among which may be mentioned those of Kuhn[5], Kirkwood[6], Eyring[7] and Bernstein and Pedersen[8]. Whiffen[9] reduced this

$\Delta[M]_D = +kXY$

I

$$\Delta[M]_D = kXY$$

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[1] This simple chain of four atoms will be referred to as a "conformational unit".

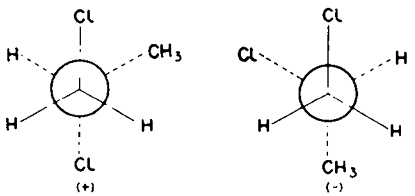
[2] G. W. Wheland, *Advanced Organic Chemistry* (2nd Ed.) p. 151. John Wiley, New York (1949). Properly speaking, this unit is asymmetric only when X and Y are different.

[3] See K. Mislow, *Trans. New York Acad. Sci.* **19**, 298 (1957), for references to some of the early expressions of this idea and for references to examples of optically active conformational enantiomers.

[4] We will confine our attention to cases in which the dissymmetric environment is provided by one or more asymmetric atoms within the molecule containing the conformational unit.

[5] W. Kuhn, *Trans. Faraday Soc.* **26**, 293 (1930); comment on p. 352.

[6] J. G. Kirkwood, *J. Chem. Phys.* **5**, 479 (1937); W. W. Wood, W. Fickett and J. G. Kirkwood, *Ibid.* **20**, 561 (1952). In the latter paper the rotatory properties of 1,2-dichloropropane are considered to be controlled



(+) a (−) b

by the relative prevalence of the dextrorotatory conformation *a* and the levorotatory conformation *b* as influenced by solvent properties and temperature.

[7] See W. J. Kauzmann, J. E. Walter and H. Eyring, *Chem. Rev.* **26**, 338 (1940). This review emphasizes the point that the large rotations of many cyclic compounds reflect the dissymmetry of relatively rigid conformations.

[8] H. J. Bernstein and E. E. Pedersen, *J. Chem. Phys.* **17**, 885 (1949).

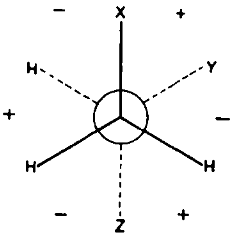
[9] D. H. Whiffen, *Chem. & Ind.* 964 (1956).

principle to a convenient rule which, in modified form,[10] appears to be rather widely applicable. The modified rule, for which the name: "Conformational Dissymmetry Rule" is proposed, can be stated as follows:

(a) The "conformational unit" I is dextrorotatory[11] in the absolute configuration shown.

(b) The magnitude of this rotatory effect is proportional to constants characteristic of the terminal atoms, X and Y:[12]

(c) The rotatory power of a full conformation (as II) is the sum of the rotatory contributions of the six constituent conformational units.



II

$$[M]_D = k(XY - HY - HX + HH) = k(X - H)(Y - H)$$

X	Y	k(X − H)(Y − H)
Br	CH_3	180°
CH_3	CH_3	60
NH_2	CH_3	55
OH	CH_3	50

II

This conformation will be dextrorotatory when X and Y are both more polarizable than hydrogen (compare conformations *a* and *b*[6]). Numerical values for representative full conformations have been obtained empirically;[10] some of these values are shown in II.

Whiffen[9] showed that his form of this rule could be used to predict the sign and magnitude of rotation of the polyhydroxycyclohexanes and the pyranose sugars and pyranosides. The modified rule,[10] using somewhat different constants, permits similar predictions in the carbohydrate series and has been extended to open-chain, saturated carbocyclic, endocyclic unsaturated and deuterium compounds. In certain cases additional effects resulting from gross asymmetry about a carbon atom or from general molecular dissymmetry must also be taken into account. It is the purpose of this

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[10] J. H. Brewster, *J. Amer. Chem. Soc.* **81**, 5475, 5483, 5493 (1959); *Tetrahedron Letters* No. 20, 23 (1959).

[11] This rule is designed for use with rotations measured at the sodium D line. In general, however, a center of optical activity which produces a positive Cotton effect at the wave length of an "optically active absorption band" will produce dextrorotation in longer wave length regions of transparency. Dispersion measurements, even if they produce only plain curves, are therefore recommended as a means of checking up on interpretations made by use of this rule, particularly when a substance may be expected to contain several optically active absorption bands at different wave lengths.

[12] While Whiffen[9] considered this effect to be determined by the terminal atoms, he did not propose this simple proportionality. In consequence, his empirical numerical values could be added and subtracted but not factored; this placed a severe limitation on the extension of his treatment. The empirical numerical values obtained in the present author's treatment roughly follow the expression:

$$\Delta[M]_D = 165 R_x^{1/2} R_y^{1/2}$$

where R_x and R_y are atomic refractions of the terminal atoms. *A priori*, it seems likely that different constants might be needed when the central atoms differ significantly from carbon in polarizability.

paper to illustrate the mechanics of the application of this rule, a clear understanding of this point being necessary if significant tests and criticisms are to be made. Some of the present limitations of this rule will also be pointed out.

Relatively rigid compounds.

The lupine alkaloids. The application of this rule to rigid saturated compounds is straightforward; each bond is examined in turn and its expected rotatory contribution noted, the sum of these contributions being the predicted rotation. We may illustrate the mechanics of this rule, and some of its limitations, by atttempting to predict the absolute configurations of the lupine alkaloids. It should be emphasized that until the limitations of this rule have been defined all such predictions require independent confirmation; we are then, at best, making only tentative assignments of absolute configuration.

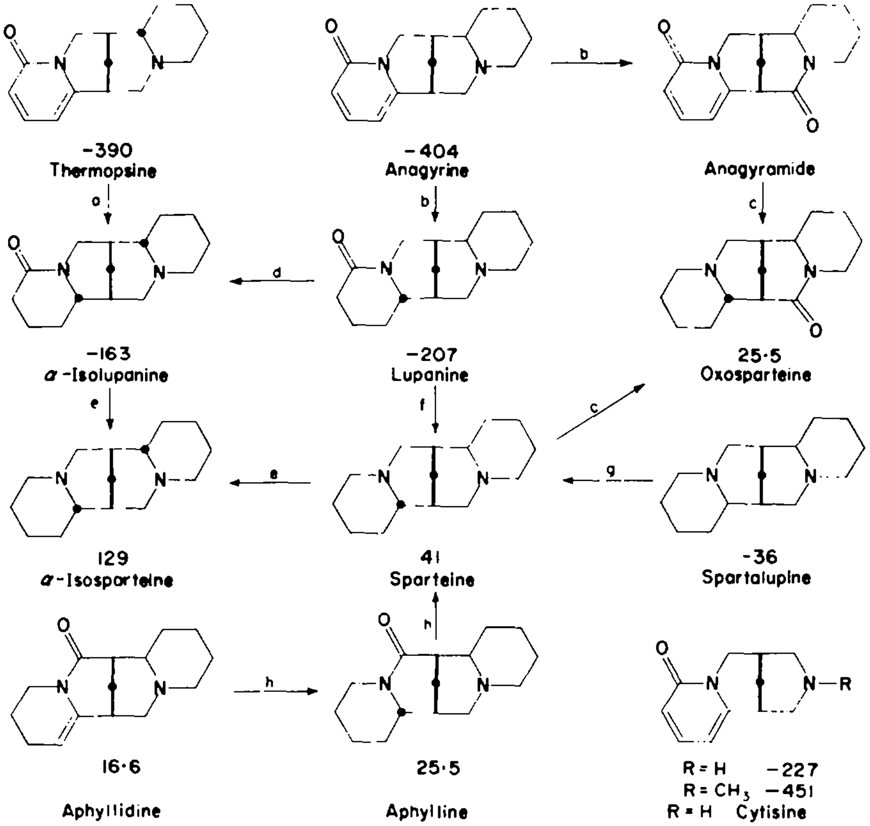

Chart I.

Chart I shows the relative configurations of these alkaloids as deduced by Marion

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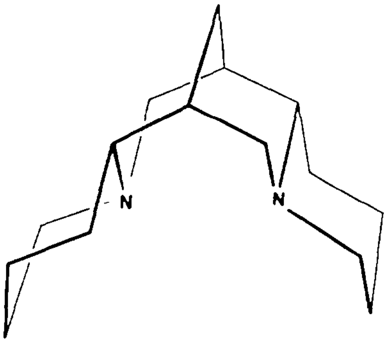
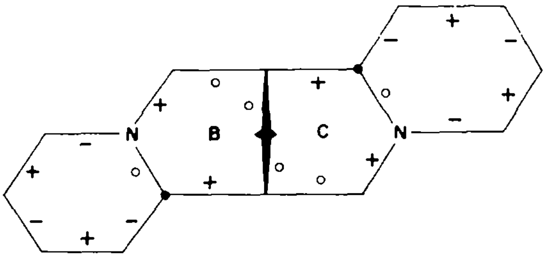
[a] W. F. Cockburn and L. Marion, *Canad. J. Chem.* **29**, 13 (1951)
[b] H. R. Ing, *J. Chem. Soc.* 504 (1933).
[c] F. Galinovsky and E. Stern, *Ber. Dtsch. Chem. Ges.* **76**, 1034 (1943); **77**, 132 (1944).
[d] L. Marion and N. J. Leonard, *Canad. J. Chem.* **29**, 355 (1951).
[e] L. Marion, F. Turcotte and J. Ouellet, *Canad. J. Chem.* **29**, 22 (1951).
[f] G. R. Clemo, R. Raper and C. S. Tenniswood, *J. Chem. Soc.* 429 (1931).
[g] M. Carmack, B. Douglas, E. W. Martin and H. Suss, *J. Amer. Chem. Soc.* **77**, 4435 (1955).
[h] A. Orekhov, *J. Gen. Chem.* (*U.S.S.R.*) **7**, 2048 (1937).

and Leonard[13] and as confirmed by an X-ray diffraction study of α-isosparteine[14](III).



III
α-Isosparteine

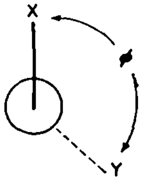
The rotatory effect of each of the bonds of the all-chair form of α-isosparteine is shown in Fig. IV; the molecular rotation predicted for this conformation and configuration is 120°, there being a net excess of two dissymmetric conformations of rotatory power $k(C-H)(C-H)$. The close approach of the two nitrogen atoms in this conformation suggests that rings B and C might adopt boat conformations in each of the epimeric sparteines. These conformations can be analyzed if it be assumed that the conformational unit V has the same rotatory power as I (this would be true if the magnitude of



Ring conformation		Calc $[M]_D$
B	C	
chair	chair	120 (above)
chair	boat	120
boat	chair	120
boat	boat	120

α-Isosparteine

IV



V

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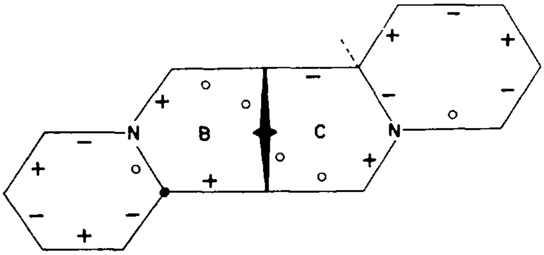
[13] L. Marion and N. J. Leonard, *Canad. J. Chem.* 29, 355 (1951).

[14] M. Przybylska and W. H. Barnes, *Acta Cryst.* 6, 377 (1953).

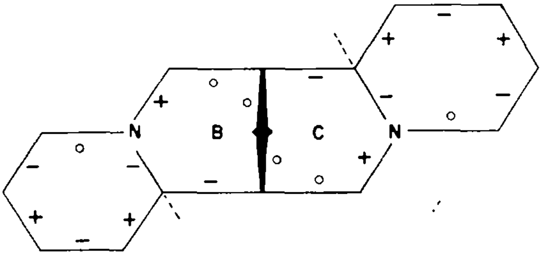
the rotatory effect varied with the sine of the angle ϕ). As seen in the tabulation under Fig. IV, all of the conformations of α-isosparteine are predicted to have the same rotation; this value is in reasonable agreement (in magnitude) with rotations reported for the hydrate, $[M]_D$ 129 (abs. alc.),[15] 141 (methanol).[16]

A similar analysis of conformational dissymmetry in sparteine (VI) and spartalupine (VII) indicates that these epimers should have smaller rotations, with sparteine



Ring conformation		Calc $[M]_D$
B	C	
chair	chair	0 (above)
chair	boat	60
boat	chair	0
boat	boat	60

Sparteine
VI



Ring conformation		Calc $[M]_D$
B	C	
chair	chair	-120 (above)
chair	boat	-60
boat	chair	-60
boat	boat	0

Spartalupine
VII

having the same sign of rotation as α-isosparteine and spartalupine having the opposite sign. The configurationally related alkaloids do, in fact, have rotations of the predicted sign and order of magnitude [sparteine $[M]_D$ 41 (abs. alc.);[15] spartalupine, $[M]_D$ −36 (abs. alc.)][17,18].

This rule is not applicable at present to lactams (as lupanine) or fused ring aromatic compounds (as thermopsine) in part because reliable rotation constants for bonds near highly unsaturated groups are not yet available. Perhaps more important

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[15] L. Marion, F. Turcotte and J. Ouellet, *Canad. J. Chem.* 29, 22 (1951).

[16] N. J. Leonard and R. E. Beyler, *J. Amer. Chem. Soc.* 72, 1316 (1950).

[17] R. Greenhalgh and L. Marion, *Canad. J. Chem.* 34, 456 (1956).

[18] M. Carmack, B. Douglas, E. W. Martin, and H. Suss, *J. Amer. Chem. Soc.* 77, 4435 (1955).

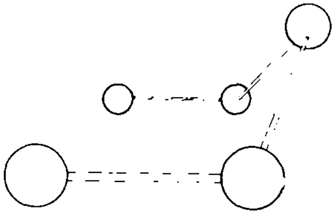
is the likelihood that in these compounds the whole molecule forms a single dissymmetric pattern of polarizability ("permolecular dissymmetry") the rotatory effect of which is dominant. Thus, the alkylation of cytisine (Chart I) produces an enormous rotatory shift which cannot be explained at all by the Conformational Dissymmetry Rule. It is the author's opinion that the approach exemplified by the Octant Rule may be needed to account for such long-range "permolecular" effects in unsaturated compounds; a possible alternative is analysis of such patterns of polarizability as extended dissymmetric conformations.

Flexible compounds

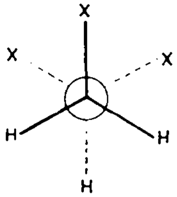
An estimate of the relative prevalence of each possible molecular conformation must be made if the Conformational Dissymmetry Rule is to be applied to a flexible compound. The following rules[10] permit a convenient but approximate conformational analysis of open-chain compounds:

(a) Only staggered conformations are "allowed".

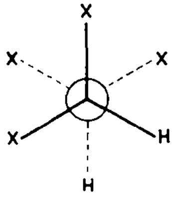
(b) The five atom conformation VIII is "prohibited" when the terminal atoms are larger than hydrogen. The strain in this conformation would be equivalent to that found in the corresponding 1,3-diaxial cyclohexane.



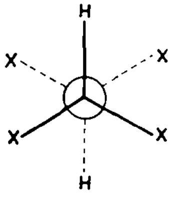
VIII



IX



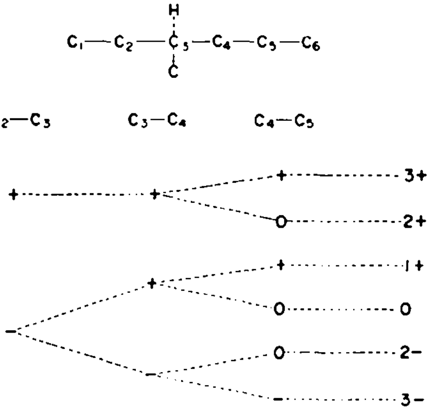
X



XI

(c) The conformation IX is "prohibited". The *cis* conformations of 1,1,2-trichloroethane[19] and of 2-methylbutane[20] are less stable than the corresponding *skew* forms by at least 4 kcal. By the same argument, the two conformations X and XI, which in 1,1,2,2-tetrachloroethane[19] and 2,3-dimethylbutane[20] have almost the same energies, must be "allowed".

(d) All "allowed" conformations are, in the first approximation, equal in energy. This rule is the weakest of the four and, in many cases, can obviously be relaxed; it is really only needed in the conformational analysis of compounds with long flexible chains.



XII

These rules, used systematically, permit a simple, if approximate, conformational analysis of a compound such as (+) 3-methylhexane (XII). Bond C_2—C_3 is "allowed" to have two conformations having rotatory powers of 60° and −60°. When this bond is in the dextrorotatory conformation the only "allowed" conformation of bond C_3—C_4 is also dextrorotatory (rules b and c). When the conformation at C_3—C_4 is dextrorotatory the levorotatory conformation at C_4—C_5 is "prohibited" (rule b), the others being "allowed". (These restraints on rotation at bonds C_3—C_4 and C_4—C_5 are readily seen by use of ball-and-stick models.) For the case when bond C_2—C_3 has its dextrorotatory conformation, there are, then, two molecular conformations having rotatory powers of 180° and 120°. When the conformation at C_2—C_3 is levorotatory the rest of the molecule has greater rotational freedom. Both the dextrorotatory and the levorotatory conformations at C_3—C_4 are "allowed" and for each of these cases two conformations are "allowed" at C_4—C_5. These four molecular conformations have predicted rotations of 60°, 0°, −120° and −180°. This analysis is summarized in a convenient form by the branching diagram shown under XII. Note that if each conformation is considered equally probable the net rotation of the mixture would be 10°; this compares well with the observed value of 9·9°.[21] In effect, the asymmetric atom has provided a dissymmetric environment for the ethyl and propyl groups and prevented

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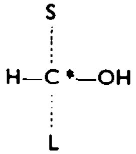
[19] J. R. Thomas and W. D. Gwinn, *J. Amer. Chem. Soc.* 71, 2785 (1949).

[20] D. W. Scott, J. P. McCullough, K. D. Williamson and G. Waddington, *J. Amer. Chem. Soc.* 73, 1707 (1951).

[21] R. E. Marker, *J. Amer. Chem. Soc.* 58, 976 (1936).

them from acting as cylindrically symmetrical substituents. The sign and magnitude of rotation of a large number of simple open-chain compounds can be predicted by this method.[10]

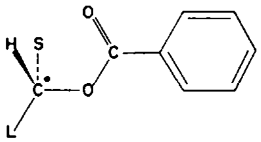
Freudenberg[22] has pointed out that the acid phthalate of a secondary carbinol having the absolute configuration XIII (S is a small alkyl group, L is a large alkyl group) is more dextrorotatory ($[M]_D$) than the parent carbinol. The "Phthalate Rule" can be rationalized by use of the Conformational Dissymmetry Rule; this analysis suggests a more general "Benzoate Rule".



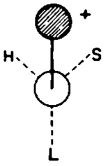
$$\begin{array}{c} S \\ \vdots \\ H-C^{*}-OH \\ \vdots \\ L \end{array}$$

XIII

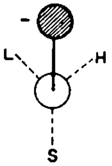
A benzoate ester will tend to adopt the planar conformation XIV in which resonance effects are maximized and steric interactions between the phenyl group and the alkyl group are minimized. The carbonyl oxygen atom has appreciable steric requirements and will tend to align itself so that it is flanked by the two smallest substituents on the carbinol carbon atom. Thus the benzoate of XIII will tend to assume conformation XV about the bond C*—O (the shaded circle represents the 1,4-axis of the benzene ring). This conformation, which is, of course, not found in the parent carbinol, should be strongly dextrorotatory since the alkyl group, S, will be more polarizable than the hydrogen atom. If the steric requirements of L and S are grossly different, conformation XV will be predominant; as the steric requirements of the two groups, L and S, become more nearly alike, more of the levorotatory conformation XVI will be present. Accordingly, if L and S are similar in polarizability, the magnitude of the rotation difference between the benzoate and the carbinol ($\Delta = [M]_{\text{benzoate}} - [M]_{\text{carbinol}}$) will be related to the difference in the steric requirements of the two groups. This will not, however, be a simple relationship since benzoylation will alter the conformational freedom of L and S and so produce additional (but probably small)



XIV



XV



XVI

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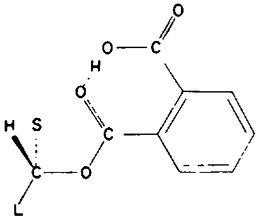
[22] K. Freudenberg, *Stereochemie* p. 696. Deuticke, Leipzig (1933).

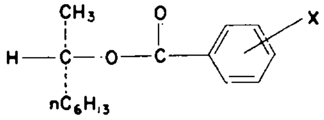
conformational dissymmetry effects. This analysis indicates that similar rotation shifts should be observed when the benzoate group carries *m*- or *p*- substituents. Acid phthalates might be expected to follow this rule because they would probably tend to have the hydrogen-bonded structure XVII, which would reinforce the required rigidity of the benzoyl group. It would not be surprising if other *o*-substituents produced anomalous rotation shifts. This rule would be expected to apply equally well to open-chain and cyclic saturated carbinols.



XVII

As seen in Tables 1 and 2, *m*- and *p*- substituents do not interfere with the operation of this rule; electron-withdrawing *o*-substituents increase the magnitude of the rotatory shifts. There is a regular variation in rotatory shift as a function of the relative steric requirements of the two alkyl groups (Table 3). This effect is also seen in the 2-methylcyclohexanols (XVIII), the borneols (XIX), the cholestanols (XX), the menthols (XXI) and the carvomenthols (XXII). In the last two series the shifts are not always as large as might be expected, perhaps because of conformational mobility of the ring. These regularities suggest that configurational assignments might be based on the occurrence of large rotation shifts of this nature.

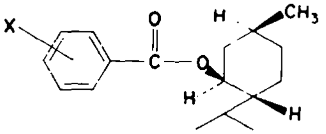
TABLE 1. MOLECULAR ROTATIONS OF BENZOATES OF (+) 2-OCTANOL



X	Temperature	*o*-	*m*-	*p*-
NO_2	20	122[a]	108[a]	
	30			118[a]
	90	115[a]	97[a]	109[a]
OCH_3	20	33[a]	94[a]	113[a]
	90	45[a]	90[a]	109[a]
CO_2H		134 (alc.)[b] 119 (chf.)[b]		
Benzoate			78[c]	

[a] H. G. Rule and A. H. Numbers, *J. Chem. Soc.* 2116 (1926).
[b] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* 99, 45 (1911).
[c] J. Kenyon and R. H. Pickard, *J. Chem. Soc.* 107, 115 (1915).
All rotations positive. Unless otherwise noted all esters in homogeneous state.

TABLE 2. MOLECULAR ROTATIONS OF BENZOATES OF (+) MENTHOL



X	Temperature	o-	m-	p-
NO_2	65	381[a]	250[a]	235[a]
CO_2H	20	332[b]		259[c]
CO_2CH_3	20	265[b]		246[c]
I	20	246[d]	235[d]	241[d]
CH_3	20	231[c]	240[e]	246[e]
Br	20	205[f]	239[f]	239[f]
Cl	20	195[g]	237[g]	237[g]
OCH_3	20	145[c]	247[e]	239[e]
$N(CH_3)_2$	20	206[h] (alc.)		258[e]

Benzoate	236[a]
α-Naphthoate	246[i] (alc.)
β-Naphthoate	283[f] (benz.)

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[a] J. B. Cohen and H. P. Ames, *J. Chem. Soc.* **87**, 1190 (1905).

[b] J. B. Cohen, D. Woodroffe and L. Anderson, *J. Chem. Soc.* **109**, 222 (1916).

[c] J. B. Cohen and H. S. de Pennington, *J. Chem. Soc.* **113**, 57 (1918).

[d] J. B. Cohen and H. S. Raper, *J. Chem. Soc.* **85**, 1271 (1904).

[e] J. B. Cohen and H. W. Dudley, *J. Chem. Soc.* **97**, 1732 (1910).

[f] L. Tschugaeff, *J. Russ. Phys. Chem. Soc.* **34**, 606 (1902).

[g] J. B. Cohen and S. H. C. Briggs, *J. Chem. Soc.* **83**, 1213 (1903).

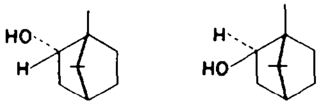
[h] H. G. Rule and W. E. MacGillivray, *J. Chem. Soc.* 401 (1929).

[i] H. Rupe and M. Silberberg, *Liebigs Ann.* **327**, 193 (1903).

Unless otherwise noted all rotations on fused (supercooled) esters; for the most part, these values are not strongly influenced by temperature changes or solvent effects. All of this work was actually done with esters of (−) menthol; the benzoates all have the same sign of rotation as the parent alcohol.

[M]	42 (homog)[23]	15 (homog)[23]
Acid phthalate	166 (benz.)[23]	101 (benz.)[23]
Δ	124	86

XVIII



[M]	58 (toluene)[24]	—33 (toluene)[24]
Acid phthalate	171 (alc)[25]	—234 (alc)[25]

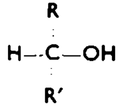
XIX

[23] G. A. C. Gough, H. Hunter and J. Kenyon, *J. Chem. Soc.* 2052 (1926).

[24] A. Haller, *Ann. Chim.*, vi, 27, 392 (1892).

[25] R. H. Pickard and W. O. Littlebury, *J. Chem. Soc.* **91**, 1973 (1907).

TABLE 3. MOLECULAR ROTATIONS OF SATURATED SECONDARY ACYCLIC CARBINOLS AND THEIR ACID PHTHALATES



$$\begin{array}{c} R \\ H\text{—}C\text{—}OH \\ R' \end{array}$$

R′	$R-CH_3$[a]			$R=C_2H_5$[b]			$R-CH(CH_3)_2$[c]			$R=C(CH_3)_3$[d]		
	Carbinol	Acid phthalate	Δ	Carbinol	Acid phthalate	Δ	Carbinol	Acid phthalate	Δ	Carbinol	Acid phthalate	Δ
CH_3	0	0		−10·3	−74·5	−64·2	−4·3	−89·3	−85	−7·8	−160	−152
CH_2CH_3	10·3	74·5	64·2	0	0		15·4	−1·2	−16·6	39	3·3	−36
$(CH_2)_2CH_3$	12·1	87·2	75·1	2·01	10·45	8·4	24·7	20·9	−3·8	55	−8·4	−63
$(CH_2)_3CH_3$	11·8	108·5	96·7	9·4	44	35	33·3	38·7	5·4	60	13	−47
$(CH_2)_4CH_3$	12·0	116	104	10·7	59·7	49	32·9	39·3	6·4			
$(CH_2)_5CH_3$	12·7	120·3	108	11·6	41·2	29·6	33·9	36·1	2·2			
$(CH_2)_6CH_3$	12·9	120·1	107	10·6	38·8	28·2						
$(CH_2)_7CH_3$	13·7	119·3	106	10·7	38·1	27·4	34·5	56·3	21·8			
$(CH_2)_8CH_3$	14·0	119·5	106	11·1	39·5	28·4						
$(CH_2)_9CH_3$	14·5	121·0	107	12·4	44·7	32·3	34·5	50·3	15·8			
$CH(CH_3)_2$	4·3[c]	89·5[c]	85	−15·4[c]	1·2[c]	16·6	0	0		14	0	−14
$C(CH_3)_3$	7·8[d]	160[d]	152	−39[d]	3·3[d]	36	−14[d]	0[d]	14	0	0	

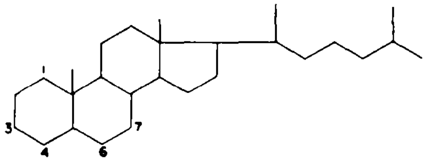
[a] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* **99**, 45 (1911).

[b] *Idem., J. Chem. Soc.* **103**, 1923 (1913).

[c] Idem., *J. Chem. Soc.* **101**, 620 (1912).

[d] W. M. Foley, F. J. Welch, E. M. LaCombe and H. S. Mosher, *J. Amer. Chem. Soc.* **81**, 2779 (1959).

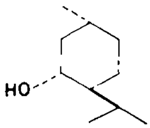
All rotations positive unless otherwise noted. Carbinols homogeneous; acid phthalates in chloroform

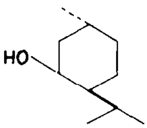


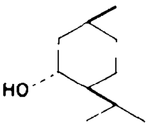
$[M]_D$[26]

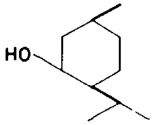
	α—OH			β—OH		
Position	Carbinol	Benzoate	Δ	Carbinol	Benzoate	Δ
1				76	1	−75
3	97	114	17	90	98	8
4	12	−98	−110	113	280	167
6	136	307	171			
7	43	−108	−151	202	428	226

XX







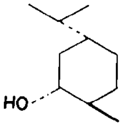


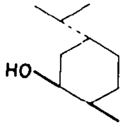
$[M]_D$[27]

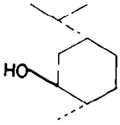
	a	Δ	b	Δ	c	Δ	d	Δ
OH	−77		32		−40		−3·5	
PNB	−232	−155	55	23	−76	−36	16	19·5
DNB	−278	−201	84	52	−95	−53	33	36·5

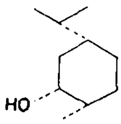
OH, carbinol; PNB, *p*-nitrobenzoate; DNB, 3,5-dinitrobenzoate.

XXI









$[M]_D$[28]

	a	Δ	b	Δ	c	Δ	d	Δ
OH	−43		65		28		54	
PNB	−158	−115	69·5	4·5	83	55	72·5	18·5*
DNB	−185	−142	79	14	94	66	56	2*
APh	−176	−133	148	83				

OH, carbinol; PNB, *p*-nitrobenzoate; DNB, 3,5-dinitrobenzoate; APh, acid phthalate.

* The purity of this isomer, neoisocarvomenthol, is uncertain; these shifts are in a direction opposite to that predicted.

XXII

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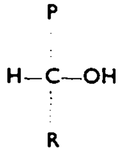
[26] Data cited by J. P. Mathieu and A. Petit in *Tables de Constantes et Donnees Numeriques. 6. Constantes Selectionees. Pouvoir Rotatoire Naturel.* I. *Steroides.* Masson, Paris (1956).

[27] J. Read, W. J. Grubb and D. Malcolm, *J. Chem. Soc.* 170 (1933); J. Read and W. J. Grubb, *J. Chem. Soc.* 313 (1934).

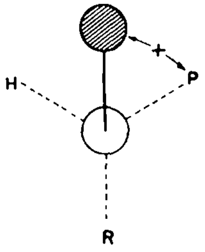
[28] R. G. Johnston and J. Read, *J. Chem. Soc.* 1138 (1935).

A parallel analysis indicates that when the two substituents at the carbinol center have similar steric requirements but differ in polarizability then the carbinol having configuration XXIII (P is the more polarizable group, R is the less polarizable group) will show a dextrorotatory shift (compare XXIV and XXV). Mills[29] has already pointed out that such shifts do indeed occur in the case of allylic alcohols of the terpene and steroid series; the example shown in XXVI is typical.

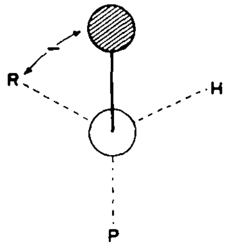


$$\begin{array}{c} \mathrm{P} \\ \vdots \\ \mathrm{H{-}C{-}OH} \\ \vdots \\ \mathrm{R} \end{array}$$

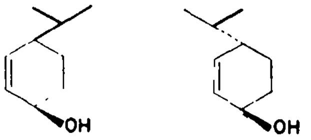
XXIII



XXIV



XXV



$[M]_D$

	a	Δ	b	Δ
OH	104		165	
PNB	540	436	494	329
DNB	518	404	500	335

XXVI

This rule cannot yet be safely applied to the phenyl alkyl carbinol series where the highly polarizable phenyl group is usually also the most bulky substituent. Very large solvent effects are noted in the rotations of the acid phthalates of this series.

Cyclic ketones

We are attempting to establish the limitations of the Conformational Dissymmetry Rule by testing its applicability to groups of conformationally simple compounds of known configuration. The thorough work of Djerassi *et al.*[31] has made it possible

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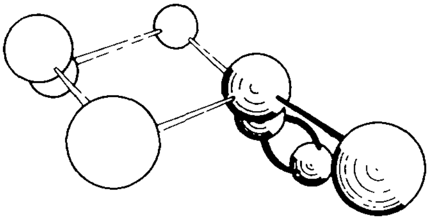
[29] J. A. Mills, *J. Chem. Soc.* 4976 (1952).

[30] D. T. C. Gillespie, A. K. Macbeth and J. A. Mills, *J. Chem. Soc.* 996 (1948).

[31] Reviewed in C. Djerassi, *Optical Rotatory Dispersion.* McGraw-Hill, New York (1960).

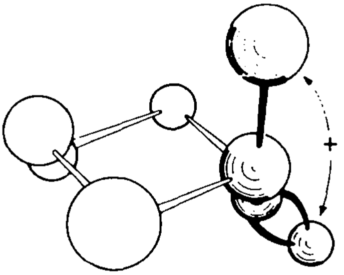
(indeed, necessary) to try out this rule on cyclic ketones. For the most part it gives predictions equivalent[32] to those made by use of the Octant Rule.[33] The cases in which the two rules give opposite predictions are of especial interest as they indicate an area where experimental testing is needed. Although the tests we propose have not yet been made (Jan. 1960) it seems desirable to bring this discrepancy into the open since it indicates a limitation of one or the other of the rules.

An equatorial substituent at position 2 of a cyclohexanone is almost coplanar with the carbonyl group (see the shaded portions of XXVII); this nearly symmetrical conformation would be expected to produce little rotatory effect. An axial substituent at the same position forms a highly dissymmetric conformation with the whole carbonyl group; this particular conformation and configuration has the same geometry as V (let X be the axial substituent and Y the carbonyl oxygen atom) and so should produce a positive Cotton effect at some absorption band of the carbonyl group.[32] This will, of course, only be observable if the axial substituent at position 6 (which is in an enantiomeric conformation) has a lower polarizability. It is to be expected, then, that while alkyl, chloro and bromo groups in the configuration shown in XXVIII will produce



XXVII

Ball-stick model of an equatorial 2-substituted cyclohexane The shaded balls show the nearly symmetrical conformation formed by the equatorial substituent, two ring carbon atoms and the carbonyl oxygen atom



XXVIII

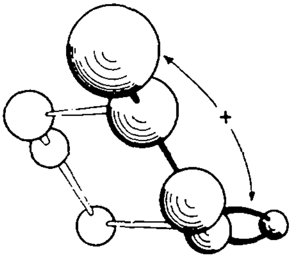
Ball-stick model of an axial 2-substituted cyclohexanone. The shaded balls show the highly dissymmetric conformation formed by the axial substituent, two ring carbon atoms and the carbonyl oxygen atom

[32] This equivalence is rather rough. The Conformational Dissymmetry Rule does not take into account the geometry of electronic transitions and so cannot be used to predict which absorption bands will be optically active. It can only be said that a dextrorotatory effect in the visible will be related to a positive Cotton effect at the wave length corresponding to *some* absorption band of a chromophore that forms a part of a dissymmetric conformation.

[33] See ref. 31, pp. 178-190.

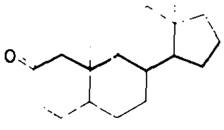
positive Cotton effects, a fluorine atom (less polarizable than hydrogen) will produce a negative Cotton effect; such results have been observed.[34] Thus the two rules appear to give concordant predictions for equatorial and axial substituents at the 2 position.

An equatorial substituent at the 3 position lies in a plane containing the carbonyl carbon atom (position 1) and the carbon atoms at positions 2 and 3. While this plane is *per se*, symmetrical, it is skewed relative to the double bond of the carbonyl group (see the shaded portions of XXIX). The substituent, then extends the dissymmetric conformation about the bond C_1—C_2 and might be expected to have some rotatory effect; this effect would probably be relatively small in the visible since the substituent is at some distance from the carbonyl group but its importance would increase as the optically active absorption band was approached. The direction of this effect, as predicted from XXIX, is in basic accord with the Octant Rule. Further extensions of this conformation should produce larger rotatory effects. Several steroid ketones contain long extended conformations of this sort (see the heavy lines in XXX and XXXI); these

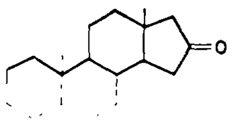


XXIX

Ball-stick model of an equatorial 3-substituted cyclohexanone. The shaded balls show the extended dissymmetric conformation formed by the equatorial substituent, three ring carbon atoms and the carbonyl oxygen atom The equatorial substituent and the three ring atoms lie in a plane.



Positive cotton effect
XXX



Negative cotton effect
XXXI

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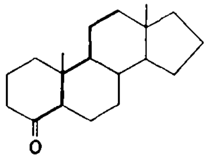
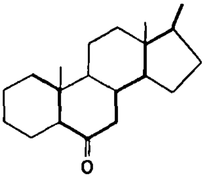
[34] C. Djerassi and W. Klyne, *J. Amer. Chem. Soc.* **79**, 1506 (1957); C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *Ibid.* **80**, 1216 (1958).

ketones show large Cotton effects of the predicted sign.[35] Figures XXXII and XXXIII show that, in this respect, the 4- and 6-ketosteroids have similar dissymmetric conformations and so should give similar negative Cotton effect curves; this is observed.[35] These predictions are similar to those made by use of the Octant Rule.



Negative cotton effect

XXXII



Negative cotton effect

XXXIII

The two rules give different predictions when it comes to axial 3-substituted cyclohexanones. As seen in XXXVI an axial substituent makes a dissymmetric conformation with the carbonyl *carbon atom;* the carbonyl double bond extends this conformation but is not an integral part of it. The relationship between the geometry of the conformation and of the electronic transition is, therefore, different here and we cannot safely predict at which absorption band this conformation will produce its Cotton effect.[32] It is, however, a matter of some interest that if this conformation were to produce a positive Cotton effect at about 300 $m\mu$ then simple explanations would be provided for the dispersion curves shown by (+) isomenthone (XXXV; XXVI) and (+) 3-methylcyclopentanone (XXXVII). Under the Octant Rule, the positive Cotton effect of (+) isomenthone is explained[33] by assuming that the conformer XXXVI, in which the isopropyl group is axial, has the dominant rotatory effect (suggesting that XXXVI is present in larger amount than XXXV). Under the other rule, both conformers would be expected to show positive Cotton effects. In the case of (+) 3-methylcyclopentanone (XXXVII), which shows a large positive Cotton effect, the substituent itself, under the Octant Rule, would be expected to produce a negative Cotton effect. It becomes necessary, then, to assume that the substituent favors a particular mode of ring-puckering and that it is this twisted ring structure which produces the large Cotton effect. Under the Conformational Dissymmetry Rule the substituent has the proper orientation for producing a positive Cotton effect[32] even if all puckered forms of the ring were equally probable (in which case the time-average conformation of the ring would be effectively planar, as would the bulk-average conformation).

The Octant Rule interpretations of the dispersion curves of these two compounds are not unreasonable and may well be correct; the author is not aware of published

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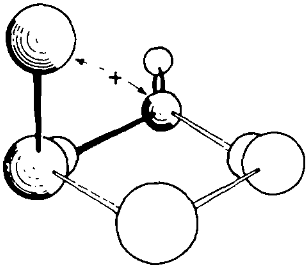
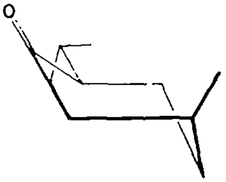
[35] Ref. 31, pp. 42–49.

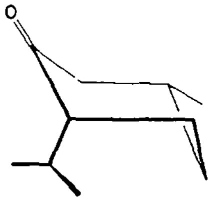


XXXIV

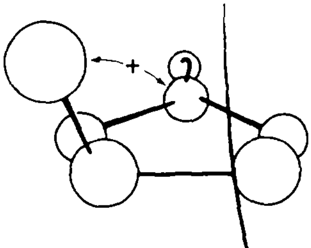
Ball-stick model of an axial 3-substituted cyclohexanone. The shaded balls show the dissymmetric conformation formed by the axial substituent and three ring atoms (including the carbonyl carbon atom).



XXXV



XXXVI



XXXVII

Ball-stick model of the planar conformation of a 3-substituted cyclopentane. This should approximate to the time-average conformation if ring puckering is not influenced by the presence of the substituent

data which unequivocally establish this point. The alternative explanations, using the Conformational Dissymmetry Rule, seem simpler but must be regarded with caution because, in the relevant conformations, the carbonyl group plays a role different from that it does in the other cases. It is, thus, possible that the predicted positive rotatory effect of XXXIV is in fact associated with a shorter wave length absorption band of the carbonyl group.[32] These are, clearly, points to be settled by experiment rather than words. If this discussion, by calling attention to this disagreement, leads to the finding of facts which define the limitations of these two rules it will have served its purpose.

Note added in proof (*Jan.* 1961): Preliminary results of our tests of this point indicate that the Octant Rule does, indeed, give correct predictions of the sign of the rotatory effects of axial β-alkyl groups.