violet, but showing bands in the infrared at 6.05 and 11.2 μ in chloroform solution typical of an exomethylene function. Elution of the column with benzene afforded the cyclopropyl ketone V (see below) followed by mixtures of the cyclopropyl ketone V[14] and the 16-methyl-$\pm^{16}$-20-ketone III.[14]

Reaction of the Exomethylene Ketone IV with Potassium Hydroxide.—A solution of 10 mg. of IV in 15 ml. of 5% potassium hydroxide in methanol was refluxed for 2 hours. The solvent was removed *in vacuo*, the residue triturated with water and the crystalline product, after recrystallization from acetone, was identical in all respects with an authentic sample of 3α-hydroxy-16-methyl-16-pregnene-11,20-dione.

Reaction of the Exomethylene Ketone IV with Osmium Tetroxide.—A solution of the exomethylene ketone IV, 90 mg., in 10 ml. of dry dioxane was treated with 90 mg. of osmium tetroxide in 10 ml. of dioxane and allowed to stand at room temperature for 24 hours. The resultant black reaction product was treated with a stream of hydrogen sulfide for 2 hours and then filtered through Celite. Concentration of the filtrate *in vacuo* and crystallization of the residue from ether afforded the furanoid derivative IX, m.p. 204–207°, $E_{222\ \mathrm{m}\mu}$ 6,000; $\lambda\lambda_{\max}^{\text{chf}}$ 5.78, 5.82, 6.0, 6.24 and 9.05 μ. The nuclear magnetic resonance spectrum[13] was in conformity with the assigned structure showing resonances at T = 2.96 (furan olefinic hydrogen) and 7.74 $(\underset{\substack{|\\ \mathrm{O}-}}{\mathrm{C}}\mathrm{H_3C{=}C-})$.

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.96; H, 8.39. Found: C, 75.17; H, 8.49.

Maleic Anhydride Adduct X.—A solution of the above furanoid derivative IX, 100 mg. in 10 ml. of benzene, was treated with 80 mg. of maleic anhydride and refluxed for 2 hours. After concentration *in vacuo* the residue was triturated several times with boiling ether and crystalline product, 100 mg., was isolated by filtration. Crystallization from acetone–ether gave the maleic anhydride adduct X as fine needles, m.p. 201–203°; $\lambda\lambda_{\max}^{\text{chf}}$ 5.40, 5.65, 5.80 and 5.88 μ.

Anal. Calcd. for $C_{28}H_{34}O_7$: C, 69.71; H, 7.10. Found: C, 69.58; H, 7.25.

The maleic anhydride adduct X, 15 mg., was sublimed at 190–195° and 0.05 mm. to give the furan IX.

16,17-Methylenepregnane-3α-ol-11,20-dione Acetate (V).—To a solution of 8.0 g. of mother liquors from the crystallization of III in 100 ml. of dry dioxane was added 6.0 g. of osmium tetroxide in dry dioxane and the reaction mixture was allowed to stand at room temperature for 20 hours. The resultant black solution was treated with a stream of hydrogen sulfide for 2 hours and then filtered. The filtrate was concentrated *in vacuo* and chromatographed on 300 g. of neutral alumina. From the fractions corresponding to 1:1 benzene–petroleum ether through benzene there was obtained, after crystallization from acetone–ether, 950 mg. of the furan compound,[15] m.p. 202–205°. Further elution of the column with benzene through 9:1 benzene–chloroform gave, on concentration and crystallization from acetone–ether, 16,17-methylenepregnane-3α-ol-11,20-dione acetate (V) as mica-like plates, m.p. 171–173°; $\lambda\lambda_{\max}^{\text{chf}}$ 5.78, 5.83 and 5.93 μ.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.46; H, 8.68.

Oxidation of 3α-Acetoxy-16-methyl-16-pregnane-11,20-dione with Potassium Permanganate.—A solution of 1 g. of III in 30 cc. of acetone was treated portionwise with 1.1 g. of potassium permanganate and allowed to stir at room temperature for 2 hours. The reaction mixture was evaporated to dryness, water added andd acidified with sulfuric acid. The excess permanganate and manganese dioxide were discharged with saturated sodium bisulfite. The solution and the acid component were extracted with potassium bicarbonate. The amorphous acid obtained weighed 460 mg. The amorphous acid was identical in the infrared with a sample of acid prepared from the diosphenol VIII by similar oxidation. Treatment of this acid in alkaline solution with a solution of iodine in potassium iodide produced an immediate precipitation of iodofuran.

Oxidation of the Diosphenol VIII to the Acid VII.—A 200-mg. sample of diosphenol VIII in 20 cc. of acetone was oxidized with 261 mg. of potassium permanganate in the manner described above for the oxidation of III. There was obtained 180 mg. of amorphous acid exhibiting the same infrared spectrum as that found for the acid formed from the oxidation of III.

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(14) In the interest of efficient isolation of the cyclopropyl ketone the preferred method is to osmylate the mother liquor first before chromatography (see later experiment above). In this way all unsaturated components are altered in polarity sufficiently to enable easy separation of the desired component.

(15) This represents the preferred method of preparation of the furan IX.

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A Useful Model of Optical Activity. I. Open Chain Compounds

BY JAMES H. BREWSTER

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It is suggested that a center of optical activity can usefully be described as a screw pattern of electron polarizability. Patterns which can be described as left-handed screws are dextrorotatory (in the visible), the magnitude of rotation ($[M]_D$) being related to the refractions of the atoms making up the patterns. Empirical rules for predicting the rotatory effects of asymmetric atoms and conformations are presented. A simple method for the conformational analysis of flexible compounds is described; this, together with the empirical rules, allows prediction of the sign and magnitude of rotation of many open-chain compounds.

The establishment of the absolute configuration of tartaric acid,[1] the definitive correlation of configurations in the "carbinyl" series (HCXRR)′ with those in the "methine" series (HCRR′R″)[2] and the large body of stereochemical correlations within these two series[3] make feasible an attempt empirically to relate sign of rotation[4] to structure,

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(1) J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, *Nature*, **168**, 271 (1951).

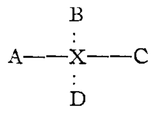
(2) (a) A. Fredga, *Arkiv. Kemi Mineral. Geol.*, **15B**, No. 23 (1942); (b) K. Freudenberg and J. Geiger, *Ann.*, **575**, 145 (1952); K. Freudenberg and W. Hohmann, *ibid.*, **584**, 54 (1953); (c) D. S. Noyce and D. B. Denney, THIS JOURNAL, **74**, 5912 (1952); **76**, 768 (1954); D. S. Noyce and J. H. Canfield, *ibid.*, **76**, 3630 (1954); (d) J. Trommel, *Proc. Acad. Sci. Amsterdam*, **B57**, 364 (1954); J. Trommel and J. M. Bijvoet, Acta Cryst., **7**, 703 (1954).

(3) For a summary, with many references, see J. A. Mills and W. Klyne in W. Klyne "Progress in Stereochemistry," Vol. I, Butterworths Scientific Publications, London, 1954, pp. 172-222. Most of the configurational assignments used here are discussed in this review.

(4) In the first three papers attention is confined to $[M]_D$ values, in part because, for many compounds of interest, no other data are yet available. It is recognized that dispersion measurements which show *experimentally* the location, sign and magnitude of the Cotton effect furnish the most direct method for identifying the rotatory contributions of individual centers of optical activity[7] and should be of value in testing, refining and extending the principles developed here. We are here concerned, however, chiefly with saturated and mono-olefinic compounds, most of which are transparent in the accessible

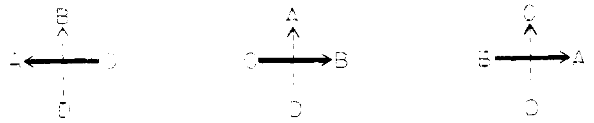
conformation and absolute configuration.[5] It has been found that this can be done for many compounds by use of two general rules, a simple method of conformational analysis, and a limited number of empirical rotation constants. Indeed, in many cases, the magnitude of rotation can also be predicted. The general rules are empirical elaborations of the following hypothesis[6] which underlies the whole treatment used here: *A center of optical activity[7] can usefully be described as an asymmetric screw[8] pattern of polarizability.*[9]

This hypothesis will be useful[6] only if centers of optical activity[7] can be described in such a way that there is, empirically, a correlation between assigned screw handedness and observed sign of rotation[4] and also a correlation between the amount of polarizability distributed in a screw sense and the magnitude of rotatory contribution. The empirical rules developed to meet these requirements are presented in this paper. The application of these rules to open-chain compounds is also described; their application to cyclic compounds is described in the following papers.



$$\begin{array}{c} B \\ \vdots \\ A\text{---}X\text{---}C \\ \vdots \\ D \end{array}$$

I, A>B>C>D



a b c

II

Atomic Asymmetry.—The tetrahedral system, xABCD, can be described as a left-handed screw pattern of polarizability when it has the absolute configuration shown in the Fischer projection I and when A > B > C > D in polarizability.[10] If

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regions of the spectrum, so that Cotton effect data are not available. The present treatment represents an attempt at accommodation to the present scarcity of Cotton effect data. It is felt that any method which is successful in disentangling contributions to $[M]_D$ will be of present utility; if soundly based, such a method should ultimately permit prediction of at least the main features of rotatory dispersion curves and be useful in their interpretation.

As a basis for this potential application of the present treatment we assume, *for purposes of analysis*, that the rotatory contribution of an individual center of optical activity[7] can be described (for regions of transparency) by a single term Drude equation

$$[M] = k/(\lambda^2 - \lambda_0^2)$$

where λ_0 is the wave length of the "optically active absorption band" of a chromophore forming an integral part of the center of optical activity.[7] If so, this center will produce a rotatory effect of one sign at wave lengths greater than λ_0 and of the opposite sign at lower wave lengths; the simplest dispersion curve must, then, show a Cotton effect (near λ_0) of the same sign as the long wave length rotation. More complex cases (including that in which a given chromophore shows several "optically active absorption bands") can be handled analytically by considering that any dispersion curve can be expressed as a summation of a number of simple dispersion curves.

A more detailed consideration of these points will be deferred until the implications of the present, more limited, treatment have been more thoroughly explored.

(5) Solvent effects can be expected to be important when the solvent interacts with a chromophore, affecting a significant electronic transition, or when the solvent influences the relative stability of molecular conformations; these solvent effects could be sensitive to temperature changes. In some cases an increase in temperature, by increasing the flexibility of a chain compound, could produce important rotatory changes. For the present we will focus attention on simple monofunctional compounds, in which these effects are usually minor, to permit an orderly development of the basic principles of the present treatment.

(6) In the empirical approach to this problem it is necessary to set up some hypothesis, in terms of which a unit of molecular structure can be classified as being *geometrically* "right-" or "left-" handed and in terms of which the magnitude of its rotatory effect can be estimated. Such a hypothesis necessarily constitutes, explicitly or implicitly, a proposed model of the phenomenon of optical activity and may properly be compared with theoretical models. The value of the hypothesis does not, however, depend on the extent to which it is consistent with a particular theory but on the extent to which it is useful in leading to methods for predicting sign and magnitude of rotation. Inconsistency with theory or experimental results may point to a flaw in the hypothesis, or the theory, or the observations, the correction of which would be useful. The author has tried to show, in these papers, that the present treatment is widely applicable. He is aware that he has not covered the whole field of stereochemistry and makes no claim to a complete or final solution of all problems of optical activity; he trusts that the reader will recognize that some refinements of this treatment may well prove necessary.

(7) A center of optical activity will be defined as being the smallest unit of molecular structure that can be said to make a particular characteristic and independent contribution to the rotatory properties of the compounds in which it occurs. Such a center could be as small as a single atom or as large as an entire molecule. It is important to note that this concept is artificial and is justified only by its utility in the analysis of complex systems. Thus, in some cases, it is convenient to speak of overlapping, or even of independent but coextensive, centers of optical activity.

(8) A screw pattern need not possess a fully developed helical structure; a fraction of a turn of a helix can adequately be described by reference to the handedness, pitch and radius of the full helix. In the present work particular attention is paid to screw handedness and its relation to sign of rotation.[4] For this purpose a right-handed screw will be defined as one which, when turned clockwise, would advance away from the observer.

(9) This hypothesis is, broadly speaking, consistent[6] with the classical theory of A. Fresnel, *Ann. chim. phys.*, [2] **28**, 147 (1825); *cf.* J. R. Partington, "An Advanced Treatise on Physical Chemistry," Longmans Green and Co., London, 1953, Vol. IV, pp. 333-340. In this theory, optical activity is considered to result when a substance shows a difference in refractive index for right and left circular polarized light, the sign and magnitude of rotation being related to the sign and magnitude of the term: $(n_L - n_R)$. This difference in refractive index can be expressed as a difference in electron polarizability toward the two forms of circular polarized light. A molecule constitutes a three dimensional pattern of atoms; for the present purposes the relevant property of these atoms, in terms of which this pattern can be described, is electron polarizability (which is taken to be proportional to atomic refraction as measured with visible light). It is reasonable to assume that the more fully asymmetric this pattern the more selective it would be in its interaction with the two circular polarized forms of light and, thus, the larger its rotatory effect. Since the asymmetry of circular polarized light is most simply expressed in terms of screw-handedness it would seem most profitable to try to describe the asymmetry of molecular patterns of polarizability in screw terms as well.

(10) A set of Cartesian axes can be established by drawing three lines, each of which bisects a pair of opposite edges of the regular tetrahedron ABCD. The figures IIa-c correspond to projections of I along these axes; taken together, they define the geometry of a single molecule of I (taken in the round) and, so, of a collection of randomly oriented molecules of I. In figure IIa the edges AC and BD would be encountered in succession by a ray of light passing down the projection axis (which is perpendicular to the plane of the paper). To such a ray of light, IIa displays a pattern having the character of a quarter-turn of a right-handed screw. This is most easily seen by imagining a "thread" connecting the high polarizability ends (A and B) of the two edges; if a screw so threaded were to be turned clockwise it would advance away from the observer making it, by definition, right-handed.[8] The contributions of atoms A and C to the screw distribution of polarizability in this pattern are clearly opposed; their net contribution can most simply be expressed as being proportional to the difference $(A - C)$. Here the terms A and C are functions of the polarizabilities such that the difference is zero when the polarizabilities of A and C are the same and such that the sign of the difference is reversed when C is more polarizable than A; in the simplest expression, A and C are the polarizabilities of A and C. This net contribution must also be proportional to some function expressing the imbalance in polarizability of the other edge, most simply the fraction: $(B - D)/(B + D)$, which ranges in value from +1 (when $D = 0$) through 0

our working hypothesis is really useful, then, we may expect all asymmetric atoms having configuration I to make rotatory contributions of the same sign[4]; this statement is operationally meaningless, however, until we can develop some standard method for assigning polarizability rank to the substituents A, B, C and D.[11] It is found that an empirical sequence of polarizabilities (Table I) can be established by noting the sign of $[M]_D$ of configurationally related compounds *which can reasonably be expected to show essentially pure atomic asymmetry*[12] (Table II).[13] It is clear from the position of the phenyl group in Table I that priority cannot be assigned on the basis of the polarizability (refraction) of the *entire* substituent.[11] The position of the carbon sequence suggests that priority could be assigned on the basis of the polarizability of attachment atoms[11] (as the carbon atom of a methyl group) provided unsaturation is taken into account.[14] We obtain, thus, the empirical atomic asymmetry rule: *An asymmetric atom in the absolute configuration I is dextrorotatory*[4] *when the polarizabilities of the substituent attachment atoms*[14] *decrease in the order: A > B > C > D.*[15] Under this rule, a formally asymmetric atom carrying two or more alkyl groups will be considered to be, *per se*, optically inactive although it may provide a sterically asymmetric environment conducive to the development of conformational asymmetry (below).

TABLE I

ROTATIONAL RANK OF COMMON SUBSTITUENTS

		Conformational rotatory powers $k(C-H)(A-H)$	
Substituent (A)	R_D of attachment atom[14]	Obsd.[a]	Calcd.[b]
I	13.954	250	268
Br	8.741	180	192
SH	7.729	No data	174
Cl	5.844	170	139
CN	3.580 (5.459)[c]	160	87 (131)[c]
C_6H_5	3.379 (6.757)[c]	140	82 (158)[c]
CO_2H	3.379 (4.680)[c]	90	82 (114)[c]
CH_3	2.591	60	60
NH_2	2.382	55	53
OH	1.518	50	23
H	1.028	0	0
D	1.004[d]	No data	
F	0.81	No data	−10

[a] Except for the value for NH_2, these values are rounded to the nearest ten degrees. [b] Calculated from the expression: $160(R_C^{1/2} - R_H^{1/2})(R_A^{1/2} - R_H^{1/2})$ (see text below[18]). [c] Value for the entire two atom unsaturated unit ($C{\equiv}N$; $>C{=}C<$; $>C{=}O$). [d] From the data of C. K. Ingold, C. G. Raisin and C. L. Wilson, *J. Chem. Soc.*, 915 (1936); C_6D_6 has a molecular rotation 0.144 lower than C_6H_6.

A number of acids which, at first sight, might have seemed appropriate for inclusion in Table II have been placed in Table III because they carry α-substituents which could hydrogen-bond to the carboxy group (perhaps through the intervention of a molecule of solvent),[5] producing cyclic structures.[12] This, as will be seen in the accompanying papers, would allow the incursion of large con-

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(when $B = D$) to -1 (when $B = 0$). On this basis, the contribution of A and C is

$$k(A - C)\frac{(B - D)}{(B + D)}$$

while that of B and D is

$$k(B - D)\frac{(A - C)}{(A + C)}$$

The total contribution of the four substituents, A, B, C and D to a screw distribution of polarizability in the pattern IIa is, then

$$+ k(A + B + C + D)\frac{(A - C)(B - D)}{(A + C)(B + D)}$$

Here we employ the convention that a right-handed screw pattern will be described as being positive. Patterns IIb and IIc are coextensive with IIa; the contributions of A, B, C and D to screw distributions of polarizability in these *left*-handed patterns are

$$-k(A + B + C + D)\frac{(A - D)(B - C)}{(A + D)(B + C)} \quad \text{(IIb)}$$

$$-k(A + B + C + D)\frac{(A - B)(C - D)}{(A + B)(C + D)} \quad \text{(IIc)}$$

It is a simple matter to show that I has *over-all* a left-handed screw character since the sum of the three expressions is

$$-k(A + B + C + D) + \frac{(A - B)(A - C)(A - D)(B - C)(B - D)(C - D)}{(A + B)(A + C)(A + D)(B + C)(B + D)(C + D)}$$

which must be negative when A > B > C > D. This treatment is, of course, valid only when the three patterns have equal statistical weight.

(11) Two extreme *a priori* criteria could be used. Polarizability rank could be assigned on the basis of the *total* polarizability of the substituent or on the basis of the polarizability of the atom directly attached to the asymmetric center; in principle, rank could be assigned on some intermediate basis as well. In the present work this problem is solved empirically by noting the polarizability rank which must be assigned to substituents if configuration I is to be dextrorotatory (see below) in suitable compounds[12]; an inspection of the sequence so obtained suggests that the polarizability of attachment atoms is a useful criterion for the assignment of rank.

It is to be noted that the sign of rotational effect[4] corresponding to left-handedness cannot be predicted *a priori* under this treatment. It is assumed that the Fischer-Rosanoff convention for D-glucose is correct[1] and absolute configurations are assigned on that basis.[3] (Accordingly, the validity of the present rules could be maintained by simple inversion should that convention prove incorrect.) Again, this problem is solved empirically. In a number of cases, the polarizabilities of attachment atoms[14] almost certainly fall in the same sequence as do the polarizabilities of the whole substituents. Consideration of such cases indicates that the absolute configuration I is associated with dextrorotation[4] (given the correctness of the Fischer-Rosanoff convention[1]).

(12) That is, compounds in which the asymmetric atom is not part of a ring or flexible chain. Such compounds will be as nearly free of conformational asymmetry effects as is possible *unless two of the substituents can interact by hydrogen bonding* (in effect, forming a ring); on this ground, hydroxy and amino acids are considered separately (Table III).

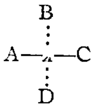
(13) Taken alone, the data in Table II do not permit a unique empirical assignment of priority to the hetero substituents (I, Br, SH, NH_2 or OH) though each must rank higher than the carbon sequence ($CN > C_6H_5 > CO_2H > CH_3$) or between that sequence and hydrogen. The priority of chlorine is established by noting the configuration of (+)α-chloro-α-phenylpropionic acid and of (+)α-phenylethyl chloride. If polarizability is to be taken as the criterion of rank, the following sequences are to be expected: I > Br > Cl; SH > Cl; $CH_3 > NH_2 > OH > H > D > F$, whence we obtain the sequence shown in Table I.

(14) The refraction values for saturated atoms are those given by A. I. Vogel, *J. Chem. Soc.*, 1833 (1948). A fully consistent scheme of atomic refractions would take unsaturation into account by assigning different refraction values to saturated and unsaturated atoms. On this basis, the double bonded carbon atom would be assigned half the value for the unit: $>C{=}C<$ (6.757/2 = 3.379) and the triple bonded carbon atom half the value for $-C{\equiv}C-$ (7.159/2 = 3.580); these values lead to the polarizability sequence: $Cl > CN > C_6H_5 \sim CO_2H > CH_3$ which is essentially that obtained empirically. Even a minute contribution of atoms more distant from the asymmetric center would make the phenyl group outrank the carboxy group, in accord with the empirical sequence.

(15) It is to be recognized that this is the simplest (and so, at present, the most useful) form of this rule. Second order effects, involving more distant atoms, are to be expected but, to judge from the case of the phenyl group, these effects are small. *For the present* it will be assumed that they can be ignored in saturated substituents.

TABLE II

COMPOUNDS SHOWING PURE ATOMIC ASYMMETRY

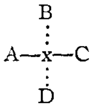


	A	B	C	D	$[M]_D$	Solvent	Ref.
1	Br	C_6H_5	CO_2H	H	+319	Benzene	*a*
2	Cl	C_6H_5	CO_2H	H	+327	Benzene	*b*
3	Cl	C_6H_5	CO_2H	CH_3	+ 48	Benzene	*c*
4	Br	C_6H_5	CH_3	H	+178	None	*d*
5	SH	C_6H_5	CH_3	H	+146	None	*e*
6	SO_3H	C_6H_5	CH_3	H	+ 27	Water (K salt)	*f*
7	Cl	C_6H_5	CH_3	H	+144; +170	None	*g*
8	CN	C_6H_5	CH_3	H	+ 9	None	*h*
9	CN	C_6H_5	OH	H	+ 62	Ether-hexane	*i*
10	C_6H_5	CO_2H	CH_3	H	+122	Ethanol	*j*
11	C_6H_5	CH_3	NH_2	H	+ 49	None	*k*
12	C_6H_5	CH_3	OH	H	+ 53	None	*l*
13	C_6H_5	CH_3	H	D	+ 0.3	None	*m*
14	I	CO_2H	CH_3	H	+100	Ether	*n*
15	Br	CO_2H	CH_3	H	+ 47^{aa}	None	*o*
16	Cl	CO_2H	CH_3	H	+ 17^{aa}	None	*p*
17	Br	CN	CH_3	H	+ 10	None	*q*
18	CN	CH_3	NH_2	H	+ 18	Water	*r*

[aa] λ = 5780 Å. [a] Resolved sample; A. McKenzie and I. A. Smith, *J. Chem. Soc.*, **125**, 1582 (1924). [b] Resolved sample; A. Darapsky, *J. prakt. Chem.*, [2] **99**, 179 (1919). [c] From (+)-hydroxy acid with thionyl chloride (retention *probable*); A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **97**, 1016 (1910). [d] C. L. Arcus and G. V. Boyd, *ibid.*, 1580 (1951). [e] B. Holmberg, *Arkiv. Kemi. Mineral. Geol.*, **13A**. No. 8 (1939); P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **70**, 365 (1926); S. Siegel and A. F. Graefe, THIS JOURNAL, **75**, 4521 (1953). [f] B. Holmberg (*e*); E. B. Evans, E. E. Mabbott and E. E. Turner, *J. Chem. Soc.*, 1159 (1927). [g] R. L. Burwell, A. D. Shields and H. Hart, THIS JOURNAL, **76**, 908 (1954). [h] P. A. Levene, L. A. Mikeska and K. Passoth, *J. Biol. Chem.*, **88**, 27 (1930). [i] K. Freudenberg and H. Biller, *Ann.*, **510**, 230 (1934). [j] H. S. Raper, *J. Chem. Soc.*, **123**, 2557 (1923). [k] W. Leithe, *Monatsh.*, **51**, 385 (1929). [l] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **97**, 379 (1932). [m] E. L. Eliel, THIS JOURNAL, **71**, 3970 (1949). [n] E. Hannerz, *Ber.*, **59**, 1367 (1926). [o] K. Freudenberg and L. Markert, *ibid.*, **60**, 2447 (1927). [p] K. Freudenberg, W. Kuhn and I. Bumann, *ibid.*, **63**, 2380 (1930). [q] K. L. Berry and J. M. Sturtevant, THIS JOURNAL, **63**, 2679 (1941). [r] H. Reihlen, E. Weinbrenner and G. von Hessling, *Ann.*, **494**, 143 (1932).

TABLE III

COMPOUNDS TWO SUBSTITUENTS OF WHICH MAY INTERACT



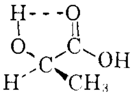
	A	B	C	D	$[M]_D$	Solvent	Ref.
1	SH	C_6H_5	CO_2H	H	+120	Ether	*a*
2	SO_3H	C_6H_5	CO_2H	H	+ 52	Water	*b*
3	C_6H_5	CO_2H	NH_3^+	H	+254	5NHCl	*c*
4	C_6H_5	CO_2H	OH	H	+243	Water	*d*
5	C_6H_5	CO_2H	CH_3	OH	− 89	Water	*e*
6	SH	CO_2H	CH_3	H	+ 59	None	*f,a*
7	SO_3H	CO_2H	CH_3	H	+ 49	Water	*g*
8	CO_2H	CH_3	NH_3^+	H	− 13	5NHCl	*c*
9	CO_2H	CH_3	OH	H	− 3	Water	*h*

[a] Prepared from the (−)bromo analog with KHS (*probable* inversion); P. A. Levene, T. Mori and L. A. Mikeska, *J. Biol. Chem.*, **75**, 337 (1927). [b] Prepared by oxidation of (+)-thiol (*a*): value for resolved sample; J. Brust, *Rec. trav. chim.*, **47**, 153 (1928). [c] Resolved sample; *cf.* J. P. Greenstein, "Advances in Protein Chemistry," Vol. IX, Academic Press, Inc., New York, N. Y., 1954, p. 184. [d] Resolved sample; J. Lewkowitsch, *Ber.*, **16**, 1568 (1883). [e] Resolved sample; A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **97**, 1016 (1910). [f] Prepared from (−)bromo compound *via* xanthyl derivative (*probable* inversion); P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **63**, 85 (1925). [g] Prepared by oxidation of (+)-thiol; a resolved sample; A. P. N. Franchimont and H. J. Backer, *Verslag Akad. Wetenschappen*, **23**, 648 (1914) [*C.A.*, **9**, 1768 (1915)]. [h] E. Jungfleisch and M. Godchot, *Compt. rend.*, **140**, 719 (1905).

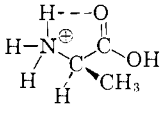
formational asymmetry effects. It will be seen in part III that the ring structure IIIa will be levorotatory (and IIIb dextrorotatory) when A > B in terms of Table I. If the interactions in question take the form shown in IV–VIII (all compounds shown in absolute configuration I) we would expect lactic acid (IV), alanine (V) and atrolactic acid (VI) to show the effects of opposed atomic and conformational asymmetry by having relatively small rotations of unpredictable sign. Mandelic acid (VII) and phenylglycine (VIII), on the other hand, should be strongly dextrorotatory since the atomic and conformational effects will both work in the same direction. The observed rotatory properties of these compounds suggest that the conformational effect is the larger of the two. Smaller conformational effects are to be expected with the mercapto acids and sulfo acids; in these cases the sign of rotation corresponds to the sign of the atomic asymmetry effect (Table III).


(−) (+)

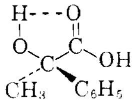
a III b



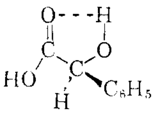
IV, $[M]_D$ −3



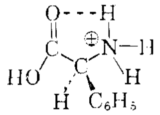
V, $[M]_D$ −13



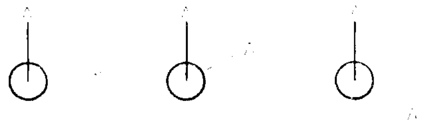
VI, $[M]_D$ −89



VII, $[M]_D$ +243



VIII, $[M]_D$ +254


a b c

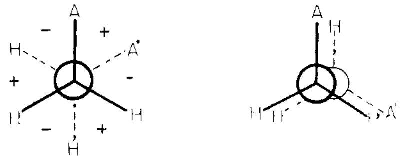
IX

Conformational Asymmetry.—A twisted chain of four atoms, A–C–C–A′, displays its asymmetry most clearly when it is viewed along the C–C bond, as in the Newman projections IX; the conformational asymmetry of a complex structure is most conveniently analyzed by systematic inspection of all bonds for units of this nature. It is found empirically that *the conformational units IXb and IXc can be considered to be dextrorotatory*[4,16] *in the absolute configurations shown*[11] *and to make contributions to* [M]D *which can be expressed mathematically*[17]

$$\Delta[M] = +k\cdot A\cdot A'$$

where A and A' are *functions* of the polarizabilities of the terminal atoms[18] and k a constant which appears to be the same for IXb and IXc.[18] It is of interest that this dextrorotatory conformational unit can be described as a left-handed screw pattern of polarizability[19] (compare the asymmetric atom, above). It is to be expected that the magnitude of the rotatory effect of one of these conformational units would be increased if one (or both) of the terminal bonds were multiple. The basic rule of conformational asymmetry is made operational by the assumption that the rotatory effects of conformational units are additive in full conformations, as Xa ("staggered") and Xb ("eclipsed") which, on this basis, have the rotatory power

$$\begin{aligned}[M] &= +k(A\cdot A' - A\cdot H - A'H + H\cdot H)\\ &= +k(A - H)(A' - H)\end{aligned}$$



a X b

It is found empirically that rotatory powers[4] can be assigned to the full conformations (Xa) (Table I) which, used in conjunction with a simple method of conformational analysis (below), permit predictions of the sign and magnitude of rotation of simple open-chain compounds (this paper). It is shown in part II that these same rotation constants can be used with saturated cyclic compounds, *where this method of conformational analysis is not needed.* It will be noted (Table I) that these rotatory values fall into a sequence paralleling the empirical polarizability sequence found for compounds showing pure atomic asymmetry; it has already been pointed out that these values can roughly be calculated from refractions by use of an empirical equation.[18]

The working rules of the simple method of conformational analysis used here are: (1) Only conformations corresponding to energy minima will be prevalent enough to produce appreciable rotatory effects. (2) The five atom conformation XI is "prohibited" when the terminal atoms are *both* larger than hydrogen, the strain here being comparable to that found in a 1,3-diaxially substituted cyclohexane. (3) The conformation XII is "prohibited" when the atoms A, B and C are *all* larger than hydrogen.[20] (4) *In the first approximation,* all allowed conformations are considered equally probable. This rule cannot be justified theoretically but is necessary for a simple analysis of flexible compounds; it may well be that it works because there is some compensation of errors in the method.

In addition to these rules, it is assumed that the rotatory contributions of individual conformations are additive.

The use of these rules can be illustrated for the case of 3-methylhexane (XIII), where the significant bonds will be designated: C_2–C_3 = I, C_3–C_4 = A, C_4–C_5 = B. The three staggered conformations of bond A are shown in XIV, with C_3, the asym-

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[16] This conclusion, as it applies to IXb, was reached earlier by D. H. Whiffen, *Chemistry & Industry*, 964 (1956), in an empirical study of the rotatory properties of the cyclitols and pyranose sugars. The author wishes to acknowledge the importance of Whiffen's work in the development of the present treatment and to emphasize that no disparagement of his work is intended in discussions of ways in which his treatment can be made more general and more useful.

[17] Whiffen[16] used superficially similar expressions *as a notation* which was formal and without mathematical significance. In the present work these expressions are given mathematical significance. This feature of the present work is the key to most of the improvements made in Whiffen's treatment: it allows comparison of diverse conformations and, incidentally, provides a simpler notation than that used by Whiffen.

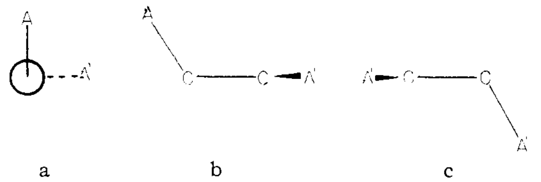
[18] It is of interest that if this expression be given the form

$$\Delta[M] = +160\cdot R_A{}^{1/2}\cdot R_{A'}{}^{1/2}$$

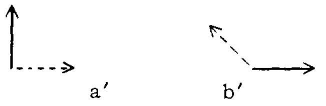
where R is atomic refraction, then calculations of the rotatory powers of full conformations (below) can be made; the calculated values are in rough agreement with those found empirically (Table I). The constant k can be expected to depend on the angular separation of A and A'. It is found, empirically, that rotation values for staggered and eclipsed full conformations are roughly comparable in magnitude.

[19] The geometric analysis of IXa is simpler than, but parallel to, that of IXb or IXc. This analysis brings out the geometric similarities of the three patterns and suggests a basis for the empirically observed significance of the terminal atoms.

We may establish a set of Cartesian coördinates for IXa so that one axis coincides with the C–C bond while the other two bisect that bond in such a way that A and A' lie in planes formed by two of the axes. The three projections along these axes (a, b, c) completely define the geometry of this system taken in the round; the projection axes are perpendicular to the paper.

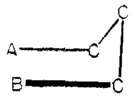


A ray of light passing downward along the projection axis of a encounters first the off-center polarizability of A and then that of A', the polarizability of the central atoms being symmetrically distributed. The pattern of polarizability found in a has the character of a quarter turn of a right-handed screw (a'); its rotatory effect should depend almost wholly on the polarizabilities of the terminal atoms since the system would be *functionally* symmetrical if A or A' had zero polarizability.

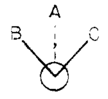


In passing down the projection axis of b a ray of light encounters first the off-center polarizability of A' and then that of A, the two carbon atoms making equal and opposite contributions. The pattern found here (b') has the character of roughly one third of a turn of a left-handed screw. A comparable pattern is found in c. All of these patterns should be roughly comparable in magnitude of rotatory effect, on which basis the two left-handed patterns (b and c) will outweigh the right-handed pattern (a). Small changes in the angular separation of A and A' (to form IXb and IXc) will not appreciably alter this picture.

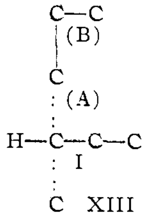
[20] The staggered *cis* form of 1,1,2-trichloroethane (XII, A = B = C = Cl) is less stable than the staggered *skew* forms by at least 4 kcal.; J. R. Thomas and W. D. Gwinn, THIS JOURNAL, **71**, 2785 (1949). A similar situation exists in 2-methylbutane; D. W. Scott, J. P. McCullough, K. D. Williamson and G. Waddington, *ibid.*, **73**, 1707 (1951).



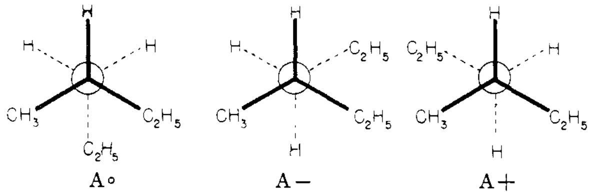
XI



XII



XIII



	A°	A−	A+
[M]	0	$-k(\mathrm{C-H})^2$	$+k(\mathrm{C-H})^2$
	a	b	c

XIV

metric center, forward. One of these conformations (A°, XIVa) is prohibited by rule 3 (above); the other two conformations have equal and opposite rotations (from Table I, ±60°). Inspection of models reveals that the combinations $A^+ B^-$, $A^- B^+$ and $A^- I^+$ are prohibited by rule 2 (I° is prohibited by rule 3). There are, then, only the six molecular conformations shown in Table IV (perhaps seen more clearly in the branching diagram XV); these conformations are equal in probability (rule 4) so that the predicted rotation of a collection of these molecules will be the average of that produced by these six conformations, or

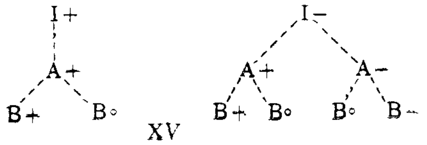
TABLE IV

MOLECULAR CONFORMATIONS OF 3-METHYLHEXANE IN CONFIGURATION XIII

Bond conformation			[M]
I	A	B	
+	+	+	$+3\,k(\mathrm{C-H})^2$
+	+	0	$+2\,k(\mathrm{C-H})^2$
−	+	+	$+1\,k(\mathrm{C-H})^2$
−	+	0	$0\,k(\mathrm{C-H})^2$
−	−	0	$-2\,k(\mathrm{C-H})^2$
−	−	−	$-3\,k(\mathrm{C-H})^2$

$$[M] = \frac{+k(\mathrm{C-H})^2}{6} = +10.0$$

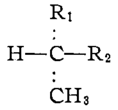
The observed value (Table V) for 3-methylhexane in this configuration[3] is +9.9°. Rotations have been predicted in this way for fourteen optically active paraffins of known absolute configuration (Table V); the observed molecular rotations (bold face) are, in every case, of the correct sign and in reasonably good numerical agreement.



XV

TABLE V

CALCULATED MOLECULAR ROTATIONS OF OPTICALLY ACTIVE PARAFFINS[a]



$$\begin{array}{c} \mathrm{R_1} \\ \vdots \\ \mathrm{H{-}C{-}R_2} \\ \vdots \\ \mathrm{CH_3} \end{array}$$

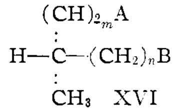
	$[M]_D$			
	R_2			
R_1	$-CH_2CH_3$	$-(CH_2)_2-CH_3$	$-(CH_2)_3-CH_3$	$-(CH_2)_4-CH_3$
$-(CH_2)_2CH_3$	10, **9.9**			
$-(CH_2)_3CH_3$	12, **11.4**	2, **1.7**		
$-(CH_2)_4CH_3$	13.3, **12.5**	3.3, **2.4**	1.3, **0.8**	
$-CH_2CH(CH_3)_2$	20, **21.3**	10, **14.9**	8, **11.9**	6.7, **9.3**
$-(CH_2)_2CH(CH_3)_2$	13.3, **11.9**	3.3, **3.5**	1.3, **1.5**	0, **0.2**

[a] All values are positive; figures in bold face are observed rotations; R. E. Marker, THIS JOURNAL, **58**, 976 (1936).

It is a useful consequence of the rules of conformational analysis given above that the molecular rotation of a compound having the structure and configuration shown in XVI can be expressed as a difference of radical rotations

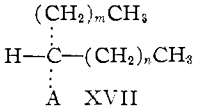
$$[M]_{\mathrm{XVI}} = \Delta M_{(\mathrm{CH_2})_m\mathrm{A}} - \Delta M_{(\mathrm{CH_2})_n\mathrm{B}}$$

provided only that A and B do not interact (as by hydrogen bonding). It is a further consequence of



$$\begin{array}{c} \mathrm{(CH)_{2m}A} \\ \vdots \\ \mathrm{H{-}C{-}(CH_2)_nB} \\ \vdots \\ \mathrm{CH_3} \end{array}$$

XVI



$$\begin{array}{c} \mathrm{(CH_2)_mCH_3} \\ \vdots \\ \mathrm{H{-}C{-}(CH_2)_nCH_3} \\ \vdots \\ \mathrm{A} \end{array}$$

XVII

these rules that the radical rotations can be expressed as shown in Table VI, these values becoming almost constant when m is larger than 4 or 5. Numerical values for the radical rotations can be

TABLE VI

RADICAL ROTATIONS FOR $-(CH_2)_mA$

m	$\Delta[M]_{(CH_2)_mA}$	$\Delta[M]_{(CH_2)_mCH(CH_3)_2}$[a]
1	$\frac{k(\mathrm{C-H})(\mathrm{A-H})}{3}$	$\frac{2k(\mathrm{C-H})^2}{3}$
2	$\frac{2k(\mathrm{C-H})^2 + k(\mathrm{C-H})(\mathrm{A-H})}{6}$	$\frac{5k(\mathrm{C-H})^2}{9}$
3	$\frac{7k(\mathrm{C-H})^2 + k(\mathrm{C-H})(\mathrm{A-H})}{15}$	$\frac{12k(\mathrm{C-H})^2}{21}$
4	$\frac{19k(\mathrm{C-H})^2 + k(\mathrm{C-H})(\mathrm{A-H})}{36}$	$\frac{29k(\mathrm{C-H})^2}{51}$
5	$\frac{48k(\mathrm{C-H})^2 + k(\mathrm{C-H})(\mathrm{A-H})}{87}$	$\frac{70k(\mathrm{C-H})^2}{123}$

[a] Identical values should be obtained for terminal cycloalkyl groups, if they are symmetrical.

TABLE VII

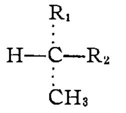
RADICAL ROTATIONS: $\Delta M(CH_2)_mA$[a]

A	CH_2A	$(CH_2)_2A$	$(CH_2)_3A$	$(CH_2)_4A$
Br	60	50, **49.5**	40, **40.5**	36.7, **37.5**
CO_2H	30	35.0, **35.5**	34.0, **34.0**	34.2
CH_3	20, **21.5**	30, **30**	32, **32**	33.3, **33.3**
NH_2	18.3	29.2, **30**	31.7	33.2
OH	16.7	28.3, **28**	31.3, **31**	33.0, **32**
$CH(CH_3)_2$	40, **44**	33.3, **33.5**	34.3	34.1

[a] Bold face values are empirical radical rotations which, in some cases, give better agreement with available data. Unless otherwise specified, the calculated radical rotations are used throughout this paper. It should be noted that if these groups are arranged in descending order of magnitude of radical rotation they fall in essentially the order found empirically by R. E. Marker, THIS JOURNAL, **58**, 976 (1936). Such differences in order as do exist are trivial since they lead to divergent predictions only for compounds expected to have very small rotations.

TABLE VIII

CALCULATED MOLECULAR ROTATIONS OF COMPOUNDS WITH TWO FLEXIBLE CHAINS[a]



$H—\overset{R_1}{\underset{CH_3}{C}}—R_2$

	[M]D			
	R₂			
R_1	$-CH_2CH_3$	$-(CH_2)_2CH_3$	$-(CH_2)_3CH_3$	$-(CH_2)_4CH_3$
$-(CH_2)_2Br$	30, **38.8**	20, **21.3**	18, **16.8**	16.7, **14.7**
$-(CH_2)_3Br$	20, 21.9	10, **14.5**	8, **8.3**	6.7, **6.2**
$-(CH_2)_4Br$	16.7, 14.9	6.7, **7.8**	4.7, **5.3**	3.4, **4.0**
$-CH_2CO_2H$	10, **10.3**	0, **−3.6**	−2, **−6.1**	−4.1, **−8.1**
$-(CH_2)_2CO_2H$	15, **13.6**	5, **6.9**	3, 4.1	1.7, **1.9**
$-(CH_2)_3CO_2H$	14, 11.1	4, **3.7**	2, **1.7**	0.7, **0.8**
$-(CH_2)_2NH_2$	9.2, **10.6**	−0.8, **−0.4**	−2.8, **−1.9**	−4.1, **−3.6**
$-CH_2OH$	−3.3, **−5.2**	−13.3, **−6.8**	−15.3, **−7.9**	−16.6
$-(CH_2)_2OH$	8.3, **9.0**	−1.7, **−2.1**	−3.7, **−4.0**	−5.0, **−6.1**
$-(CH_2)_3OH$	11.3, **11.9**	−1.3.0	−0.7, **−0.7**	−2.0, **−2.6**
$-(CH_2)_4OH$	13.0, **12.0**	3.0, **1.7**	1.0, **0**	−0.3, **−1.9**

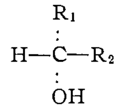
[a] Bold face values are homogeneous molecular rotations reported by R. E. Marker, THIS JOURNAL, **58**, 976 (1936); values are positive unless otherwise indicated. See also P. A. Levene and A. Rothen, *J. Org. Chem.* 1, 76 (1936).

calculated from these expressions by use of the values in Table I (see Table VII); empirical radical rotations, obtained by accepting values for the alkyl groups and using the difference formula, are shown in bold face. These values in turn can be used to predict the sign and magnitude of rotation of the forty-three compounds of known configuration shown in Table VIII. In a simple extension of this treatment, it is found that the rotations of compounds of the series XVII should follow the difference rule, provided that the substituent A is appreciably larger than hydrogen

$$[M]_{XVII} = \Delta M_{(CH_2)_mCH_3} - \Delta M_{(CH_2)_nCH_3}$$

TABLE IX

CALCULATED MOLECULAR ROTATIONS OF SECONDARY CARBINOLS WITH TWO FLEXIBLE CHAINS

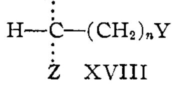


$H—\overset{R_1}{\underset{OH}{C}}—R_2$

	R₂		
R_1	$-C_2H_5$	$-n-C_3H_7$	$-CH_2CH(CH_3)_2$[a]
$-C_2H_5$	0	−10, **−5**	−24, **−24.6**
$-n-C_3H_7$	+10, **+5**	0	−14, **−16.3**
$-n-C_4H_9$	+12, +9.4	+2, +1	−12, **−13.8**
$-n-C_5H_{11}$	+13.3, **+10.7**	+3.3	−10.7, **−11.3**

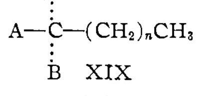
[a] Empirical radical rotation of 44 used instead of calculated rotation of 40; rotations and configurations as in K. Freudenberg "Stereochemie," Deuticke, Leipzig, 1933, opp. p. 696; observed values in bold face.

While data suitable for checking this prediction are scarce, the values for secondary carbinols shown in Table IX are in good agreement. The present treatment indicates that the difference rule should also apply to compounds of the series XVIII *provided that m* and *n* are both larger than



$H—\overset{(CH_2)_mX}{\underset{Z}{C}}—(CH_2)_nY$

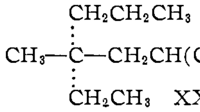
XVIII



$A—\overset{(CH_2)_mCH_3}{\underset{B}{C}}—(CH_2)_nCH_3$

XIX

unity, that there is no appreciable interaction among the substituents X, Y and Z, and that Z is (roughly) the size of a methyl group. Pursuing this analysis further, it is to be expected that compounds of the series XIX will be essentially optically inactive if the substituents A and B have similar steric requirements, but that when B > A (in size) and *m* > *n* then configuration XIX will be dextrorotatory. Data required for checking these predictions do not appear to be available. A paraffin with three or four flexible chains at the asymmetric center should, by this analysis, be almost completely optically inactive; in accord with this prediction, the tetraalkylmethane XX (of unknown absolute configuration) shows a rotation of [M]D − 0.05 ± 0.03[21] (calculated for optically pure material from the rotation of a sample of 25% optical purity).



$CH_3—\overset{CH_2CH_2CH_3}{\underset{CH_2CH_3}{C}}—CH_2CH(CH_3)_2$

XX

Compounds containing only one flexible chain show a particularly simple form of conformational asymmetry. Under the rules of conformational analysis used above, the compound XXI possesses two conformations about bond C_2–C_3 (XXIIa and XXIIb) which, *in the first approximation*, are equal in energy (conformational analysis rule 4 above). If the substituent A is roughly equal in size to the methyl group the chain R is in a sterically symmetrical environment and makes no further contribution to optical activity. Accordingly, it is predicted that the rotation of XXI will be

$$[M] = \frac{k(A - H)(C - H) - k(C - H)^2}{2}$$

It is seen, in Table X, that, except for the alcohols and amines, the sign of rotation is correctly predicted in this way and that there is, in many cases, reasonable agreement between predicted and observed magnitudes of rotation. Now, it has been pointed out above that the assumption that all "allowed" conformations will be equal in energy can only be true to a first approximation. In the case of the alcohols and amines, the hetero substituents are appreciably smaller than the methyl group

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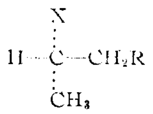
[21] A. Streitwieser, Jr., and T. R. Thomson, THIS JOURNAL, **77**, 3921 (1955).

TABLE X

MOLECULAR ROTATIONS OF 2-SUBSTITUTED ALKANES[aa]



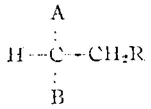
$$\begin{array}{c} X \\ \vdots \\ H\text{—}C\text{—}CH_2R \\ \vdots \\ CH_3 \end{array}$$

X =	I	Br	Cl	CN	C_6H_5	CO_2H	OH	NH_2	NH_3^+
					$[M]_D$				
$[M]^{bb}$calcd.	95	60	55	50	40	15	− 5	−3	− 3
R = CH_3	59^a	36^c	36^f	25^e	37^g	18^g	10^a	$+5^j$	-1^j
C_2H_5	92^b	63^b	46^b	49^e	38^h	21^g	$+12^a$		
n-C_3H_7	81^a			51^e	39^h	24^g	$+12^a$	$+5^k$	-3^k
n-C_4H_9				43^i		26^i	$+12^a$		
n-C_5H_{11}	115^b	$75^{b,d}$	54^b				$+13^a$	$+7^k$	-10^k
n-C_6H_{13}				40^l		27^g	$+13^a$		

[aa] All compounds except the amine salts are dextrorotatory; all rotations in homogeneous state except amine salts (water). [bb] Calculated on assumption that equal amounts of XXIIa and XXIIb are present (see text). [a] R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911). [b] D. H. Brauns, *Rec. trav. chim.*, **65**, 799 (1946). [c] Minimum value; R. L. Letsinger, THIS JOURNAL, **70**, 406 (1948). [d] W. Gerrard, *J. Chem. Soc.*, 741 (1946). [e] P. A. Levene, A. Rothen and R. E. Marker, *J. Biol. Chem.*, **115**, 253 (1936). [f] Upper limit; R. L. Letsinger, L. G. Maury and R. L. Burwell, Jr., THIS JOURNAL, **73**, 2373 (1951). [g] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **100**, 685 (1933). [h] Data of Levene, *et al.*, cited by R. E. Marker, THIS JOURNAL, **58**, 976 (1936). [i] P. A. Levene and M. Kuna, *J. Biol. Chem.*, **140**, 255 (1941). [j] L. G. Thomé, *Ber.*, **36**, 582 (1903). [k] P. A. Levene, A. Rothen and R. E. Marker, *J. Biol. Chem.*, **120**, 759 (1937). [l] Calcd for optical purity from data of P. A. Levene and L. A. Mikeska, *ibid.*, **84**, 571 (1929).

TABLE XI

MOLECULAR ROTATIONS OF COMPOUNDS WITH ONE FLEXIBLE CHAIN

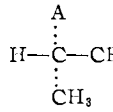


$$\begin{array}{c} A \\ \vdots \\ H\text{—}C\text{—}CH_2R \\ \vdots \\ B \end{array}$$

A	B	$[M]_D$ R = $-CH_3$	R = $-C_2H_5$	R = n-C_3H_7
		A > B > CH_3		
Br	C_6H_5	$+140^a$	$+160^a$	
Cl	C_6H_5	$+78^b$	$+45^b$	$+25^b$
CN	C_6H_5	$+40^c$	$+11^c$	
Br	CO_2H	$+66^d$	$+37^e$	$+82^d$
SH	CO_2H	$+21^e$	$+20^e$	$+24^e$
C_6H_5	CO_2H	$+149^f$	$+58^f$	$+83^f$
		A > CH_3 > B		
C_6H_5	NH_2	-6.17^g	-3.40^g	
C_6H_5	OH^{aa}	$-40,^l$ -54^h	$-69^{i,f}$	-28^l
CO_2H	NH_3^+	$+21^j$	$+28^j$	$+32^j$
CO_2H	OH	-3.1^k		-2.1^r

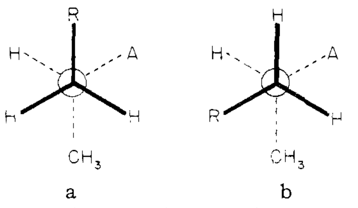
[aa] Only these values are to be as maximum values. [a] P. A. Levene and A. Rothen, *J. Biol. Chem.*, **127**, 237 (1939); rotations in benzene; λ = 5780 Å. [b] P. A. Levene and L. A. Mikeska, *ibid.*, **70**, 355 (1926); *cf.* W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman and A. D. Scott, *J. Chem. Soc.*, 1252 (1937); no solvent. [c] P. A. Levene, L. A. Mikeska and K. Passoth, *J. Biol. Chem.*, **88**, 27 (1930). [d] P. A. Levene and M. Kuna, *ibid.*, **141**, 391 (1941); ether solvent. [e] P. A. Levene, T. Mori and L. A. Mikeska, *ibid.*, **75**, 337 (1927); *probable* configurations; no solvent. [f] K. Mislow and C. L. Hamermesh, THIS JOURNAL, **77**, 1590 (1955). [g] P. A. Levene, A. Rothen and M. Kuna, *J. Biol. Chem.*, **120**, 777 (1937). [h] R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **105**, 1115 (1914); benzene solvent. [i] J. Kenyon and S. M. Partridge, *ibid.*, 128 (1936). [j] J. P. Greenstein in "Advances in Protein Chemistry," Vol. IX, Academic Press, Inc., New York, N. Y., 1954, p. 184; solvent, 5 *N* HCl. [k] D. H. S. Horn and Y. Y. Pretorius, *J. Chem. Soc.*, 1460 (1954); solvent, water. [l] P. A. Levene and A. Rothen, *J. Org. Chem.*, **1**, 76 (1936).

since in conformation XXIIa they can turn their hydrogen atoms away from the R group and present it a bare face. On this basis it is to be expected that conformation XXIIa (which is dextrorotatory) will predominate. For the amines, a 50% excess of XXIIa over XXIIb (corresponding to an energy difference of about 0.2 kcal.) would give rotations of +3° while for the alcohols, a 100% excess (an energy difference of about 0.4 kcal.) would give rotations of +13°. It is to be expected, if this *post facto* interpretation is correct, that the ammonium salts (where the substituent and the methyl group are equal in size) would have rotations of about −2.5°; this, very roughly, is the case.



$$\begin{array}{c} A \\ \vdots \\ H\text{—}C\text{—}CH_2R \\ \vdots \\ CH_3 \end{array}$$

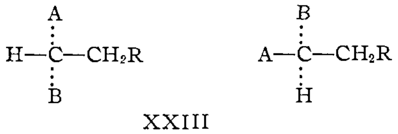
XXI



$+k(A - H)(R - H)$ $\quad -k(C - H)(R - H)$

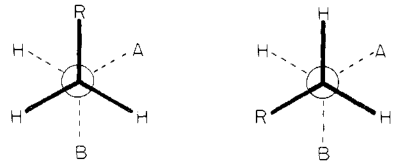
XXII

In compounds of the type XXIII both atomic and conformational asymmetry come into play. When the substituents are ranked (see Table I): A > B > CH_3, the asymmetric atom will be dextrorotatory and should have the same rotatory power as in the methyl compound (R = H) (see Table II). The dextrorotatory conformation XXIVa will have a greater rotatory power than the levo-conformation XXIVb. Such compounds should be, unequivocally, dextrorotatory (as they are, see Table XI). When the substituents are ranked: A > CH_3 > B (when B is hydroxy or amino) the asymmetric atom is levorotatory. For the case where A is phenyl it is readily seen that the presence of equal amounts of conformations XXIVa and XXIVb will produce a dextrorotatory effect nearly equal to that produced by the levorotatory asymmetric atom. Arguing, as above, that the hydroxy and amino groups will be smaller than the phenyl group, we can predict that more molecules will be in conformation XXIVb than in XXIVa; this will make the conformational asymmetry effect less dextrorotatory, on which basis the alcohols and amines of this series should be levorotatory in configuration XXIII (A = $-C_6H_5$; B = $-OH$, $-NH_2$) (see Table XI). For the case where A is carboxy, atomic asymmetry will be levorotatory in effect, conformational asymmetry (in terms of XXIVa and XXIVb) dextrorotatory—but possibly weakly so—and ring asymmetry (in analogy with IV and V) dextrorotatory; such systems are (for the present anyway) too complex for predictions to be made.



$$\begin{array}{c} A \\ \vdots \\ H\text{—}C\text{—}CH_2R \\ \vdots \\ B \end{array} \qquad \begin{array}{c} B \\ \vdots \\ A\text{—}C\text{—}CH_2R \\ \vdots \\ H \end{array}$$

XXIII



$+k(A - H)(R - H)$ $-k(B - H)(R - H)$

a b

XXIV

Permolecular Asymmetry.—It is to be recognized that additional kinds of screw patterns of polarizability will be possible. Optically active allenes, spiranes and biphenyls show such patterns when viewed along their axes of asymmetry. These screw patterns, in effect, run *through the molecule* and will be called permolecular patterns; such patterns may be important in rigid and cyclic compounds. It is found necessary to invoke this concept in the treatment of carbohydrates (part II).

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LAFAYETTE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Optical Activity of Saturated Cyclic Compounds[1]

BY JAMES H. BREWSTER

RECEIVED SEPTEMBER 2, 1958

It is shown that the principles of conformational asymmetry and the empirical constants used in estimating the sign and magnitude of rotation of acyclic compounds (part I) can also be used in estimating the sign and magnitude of rotation of saturated cyclic compounds.

A flexible chain compound will generally have a relatively small rotation because its molecules can assume many conformations with different and opposed rotatory powers. It was shown in part I that the rotations of many open-chain compounds of known absolute configuration can be estimated by use of a simple system of conformational analysis and a series of empirical rotation constants for asymmetric conformations about individual bonds; this treatment provides an explanation for the regularities observed in the rotations of acyclic compounds.[2] The relatively large rotations of ring compounds can, then, be ascribed to their near rigidity which allows a display of the full rotatory powers of their asymmetric conformations.[3] We may, accordingly, test the rotation constants obtained in part I by determining whether they can be used in estimating the sign and magnitude of rotation of cyclic compounds. It is shown in the present paper that these constants can, indeed, be used for this purpose, whence it follows that indirect support for the system of conformational analysis used in part I has been obtained. An important result of this test is the demonstration that, although the Marker Rules[2] cannot be applied *as such* to cyclic compounds,[4] the principles which lead to rules equivalent to those of Marker can be used successfully in the cyclic series so that the apparent lack of correspondence between the cyclic and acyclic series[4] disappears.[5]

Cyclohexane Derivatives.—Each of the ring bonds of the chair form of cyclohexane is asymmetric, alternating dextro (Ia) and levo (Ib); since these rotatory effects cancel completely, the optical activity of cyclohexane derivatives can be ascribed wholly to the asymmetric conformations made by the substituents with ring atoms or with one another.[6] An isolated equatorial substituent, replacing H* in Ia or Ib, has no effect on the conformational asymmetry of any of the bonds; an isolated axial substituent, replacing H in Ia or Ib, causes equal and opposite changes in the asymmetry of the two nearby ring bonds but should have no effect on more distant bonds. Accordingly the epimers IIa and IIb should have essentially the same rotation and this rotation should be close to

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(1) A Useful Model of Optical Activity, Part II; part I, preceding paper, p. 5475.

(2) R. E. Marker, THIS JOURNAL, 58, 976 (1936).

(3) W. J. Kauzmann, J. E. Walter and H. Eyring, *Chem. Revs.*, 26, 338 (1940).

(4) J. A. Mills, *Chemistry & Industry*, 218 (1953).

(5) It should be noted that the present treatment of cyclic compounds was, in many important respects, anticipated by D. H. Whiffen. *ibid.*, 964 (1956), in a discussion of the rotatory properties of the hydroxytetrahydropyrans, the cyclitols and certain of the terpenes. It should also be noted, however, that the present treatment leads to several major simplifications and extensions of Whiffen's work which would have been impossible were *all* of Whiffen's conclusions accepted (see text, below). It is, thus, one of the burdens of this paper to show that the principles presented here and in part I lead to results comparable to those obtained by Whiffen, the net result being to provide a broader justification of the *essential* points of his thesis. The author wishes to make it clear that no part of the present paper is to be regarded as an attack on Whiffen's important pioneering contribution.

(6) Asymmetrically distributed substituents may produce asymmetric distortions of the ring which could make the ring itself optically active. These effects will probably be small but might account for the small rotations observed in compounds otherwise expected to be optically inactive. These possible effects will, for the present, be ignored.