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THE PRINCIPLE OF PAIRWISE INTERACTIONS AS A BASIS FOR AN EMPIRICAL THEORY OF OPTICAL ROTATORY POWER

W. KAUZMANN, F. B. CLOUGH[1] and I. TOBIAS[2]
Frick Chemical Laboratory, Princeton University, Princeton, New Jersey

FEW properties of matter can rival optical rotatory power as a potential means of gaining information about the more subtle aspects of molecular structure. Optical rotation is especially sensitive to such structural factors as the spatial conformation of a hydrocarbon chain in an asymmetric molecule and the existence of a six-membered ring in one or the other of the chair forms or bed forms. It is also easy to measure, it is not affected to any unusual extent by impurities, and the apparatus for measuring it is readily available. Furthermore, the theoretical principles that underlie the phenomenon are well understood in a general way. Rosenfeld's quantum mechanical equation for optical rotation specifies the fundamental molecular quantities responsible for the phenomenon and shows that it is dependent on the properties of the electronic transitions that give rise to visible and ultra-violet spectra. The more detailed models of Kuhn, Kirkwood and Condon and Eyring present us with specific ways in which the rotatory properties are related to molecular structure and conformation. These theories have been useful in the interpretation of rotatory dispersion, circular dichroism the role of weak absorption bands, and the effects of solvents and temperature.

Unfortunately the use of optical rotation has not yet reached the level of importance that it deserves. The principal reason for this is that we do not yet have a sufficiently reliable and detailed understanding of the relationship between the optical rotation and molecular structure—an understanding, that is, which would permit us to predict with confidence the sign and magnitude of the rotation to be expected for a given molecule in a given configuration and conformation. All of the existing theories require such drastic approximations when one attempts to use them to calculate a numerical value of the rotation that one can have little confidence in them for this purpose. Furthermore, there is no reason to expect any great improvement in the current theories in this respect in the near future.

At the present time, therefore, the only hope of success in relating optical rotation to molecular structure seems to lie in a more empirical approach. Such an approach has been attempted by a number of workers with varying and uncertain success. One of the earliest attempts was the van't Hoff principle of superposition, which we now know cannot be valid except in certain limited circumstances. More recently Marker[3] Whiffen[4] and Brewster[5] have given discussions of the signs and magnitudes of optical rotations which are encouraging, although the general validity of the principles that they have proposed still remains to be demonstrated.

[1] Present address: Department of Chemistry, Stevens Institute of Technology, Hoboken, N.J.
[2] Present address: Institute for Molecular Physics, University of Maryland, College Park, Md.
[3] R. E. Marker, *J. Amer. Chem. Soc.* **58**, 976 (1936).
[4] D. H. Whiffen, *Chem. & Ind.* 964 (1956).
[5] J. H. Brewster, *J. Amer. Chem. Soc.* **81**, 5475, 5483, 5493 (1959).

If an empirical approach is to be fruitful, it ought to be set up in a manner consistent with what is known about the general theoretical basis of the phenomenon. In this paper we shall examine these basic requirements. Many theories of optical rotation show that each pair of groups in an optically active molecule can interact to give rise to a contribution to the optical rotation. The contribution by a given pair will in general be affected by the remaining groups in the molecule, but under certain circumstances such disturbances will be small, and it should be a good approximation to express the optical rotation as the sum of contributions arising from all ways of pairing the groups in the molecule (the principle of pair-wise interactions). We shall examine the degree to which this principle may be valid in different types of optically active molecules and we shall show how the principle may be tested further. We shall also show how it may be useful in studying the absolute configurations and conformations of organic molecules.

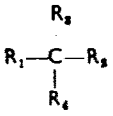
I. ADDITIVITY PRINCIPLES AND THEIR APPLICATION TO OPTICAL ROTATORY POWER

Many empirical theories have been developed which relate the properties of matter to its molecular constitution. Properties which have been successfully dealt with in this way include the molecular volume, the molar energy, the polarizability (and the closely related property of molar refraction), the dipole moment, bond lengths, chemical reactivity (in certain classes of compounds), infrared and ultraviolet absorption spectra, diamagnetic susceptibility and, recently, nuclear magnetic resonance spectra. The empirical theories that are used to predict these properties are invariably based on some form of the principle of additivity: the property in question is given by an aggregate of numbers, each number being characteristic of an atom, or perhaps a group of atoms present in the molecule. (In the case of the dipole moment, vectors rather than numbers must be combined.) At times, however, one encounters substances in which two or more groups interact to give additional effects not observed when either group is present alone. For instance, this is observed in the "exaltation" of the molar refraction of molecules containing conjugated double bonds, or in the increase in the diamagnetic susceptibility of benzene rings as compared with non-cyclic compounds containing three double bonds. Exaltation effects can, however, be included in the additivity principle if appropriate selections are made of the groups of atoms to which group properties are assigned. Thus it is better to consider the benzene ring as a new kind of group rather than as a collection of three double bonds, especially in interpreting the spectra and heats of combustion of compounds containing phenyl groups.

The explanation of the success of these additivity rules is simple: The rules are valid whenever interactions between groups are small. For instance, the contribution of a methyl group to the molar refraction is about the same if the methyl group is adjacent to a carboxyl group as it is when it is adjacent to another methyl group or a phenyl group or a chlorine atom. The displacement of the electrons in a methyl group when it is placed in an electric field (which is what determines the molar refraction) is about the same, no matter what the neighbors of the methyl group might be.

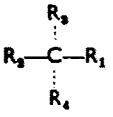
In view of the success of simple additivity rules with other properties, one might be encouraged to construct an empirical theory of optical rotation on the basis of the same type of rule. It is easy to see, however, that (except under certain circumstances which

happen to be found in the sterols; see Klyne[6]) such an approach is theoretically unsound. Consider the asymmetric molecule



(ID)

and its mirror image



(IL)

in which R_1, R_2, R_3 and R_4 are simple, optically inactive groups such as —H, —Cl, —CH_3, —COOH, and —C_6H_5. Suppose that we write the optical rotation of compound *ID* as the sum of "partial rotations" assigned to each of its groups, proceeding as though the optical rotation were a property like the heat of combustion:

$$[M]_{ID} = M_1 + M_2 + M_3 + M_4 + M_C$$

where M_1 is the contribution of R_1, M_C is the contribution of the asymmetric carbon atom, and so on. Now let us express the optical rotation of IL by the same procedure. The rotations of ID and IL are equal in magnitude but opposite in sign, so

$$[M]_{IL} = -M_1 - M_2 - M_3 - M_4 - M_C$$

Thus, in some compounds R_1 will have a positive contribution to the rotation, and in others it will have a negative contribution. The decision as to the sign that is to be given to M_1 cannot, however, be based on any property inherent in R_1 because R_1 is assumed to be optically inactive when it stands by itself, so it is not changed when it is replaced by its mirror image. It is clear that the position of each group relative to other groups in the molecule would have to be known in order to be able to give a sign to its contribution. This means that groups in an optically active molecule cannot be considered to be acting independently in contributing to the optical rotation; the contribution by each group is determined by the presence of the other groups. In short no principle of the additivity of independent contributions by groups can serve as a sound basis for a general empirical theory relating structure to optical rotation.

The coupled oscillator theories of Kuhn and Kirkwood and the one electron theory of Eyring and Condon suggest a better procedure for constructing an empirical theory of optical rotation. All of these theories assume that in a molecule such as ID or IL the interactions between the groups, R_1, R_2, R_3 and R_4 affect the motions that the electrons in the groups undergo when the molecule is exposed to light. The optical rotation arises, according to these theories, not from the way in which the electrons move in the isolated groups, but from the way in which these motions are modified because of the presence of other groups in their vicinity. The different theories do not agree in the detailed descriptions of these so-called "vicinal interactions", but this need not concern us. The important point is that all of these theories postulate that the rotation

[6] W. Klyne, *Determination of Organic Structure by Physical Methods.* (Edited by E. A. Braude and F. C. Nachod) p. 108 ff. Academic Press, New York (1955).

comes, not from the sum of contributions by isolated groups, but from the sum of interaction effects between groups.*

This suggests that an empirical theory of optical rotation might be based on the concept of the addition of interactions. As a first approximation we may assume that the important interactions are those that exist between pairs of groups, so that we may write for the optical rotation of compound ID

$$[M]_{ID} = m_{12} + m_{13} + m_{14} + m_{23} + m_{24} + m_{34} + m_{1C} + m_{2C} + m_{3C} + m_{4C} \quad (1)$$

where m_{12} is the optical rotation that would be observed in a hypothetical molecule containing only the two groups R_1 and R_2 located in exactly the same relative spatial positions that they have in compound ID. Similarly m_{1C} is the optical rotation that would be observed if only R_1 and the asymmetric carbon atom were present, and so on for m_{13}, m_{14}, etc. To this approximation the optical rotation of ID is the sum of the pairwise interactions of all of the groups present in the molecule. This assumption will be called *the principle of pairwise interactions.*

Since it has been assumed that group R_3 has some influence on each of the groups R_1 and R_2, it is obvious that the interaction term m_{12} between R_1 and R_2 that would be observed if the group R_3 were not present cannot be quite the same as the interaction between these same two groups when R_3 is present. Similarly, the interaction m_{23} between R_2 and R_3 must be affected by R_1 and the interaction m_{13} between R_1 and R_3 must be affected by R_2. Let us denote by $m_{12.3}$ the change in m_{12} that is caused by the presence of the group R_3. Similarly we may use the symbol $m_{23.1}$ to denote the change in m_{23} that is caused by R_1, and the symbol $m_{13.2}$ to denote the change in m_{13} caused by R_2. Let us next define a "three-way interaction term,"

$$m_{123} = m_{12.3} + m_{23.1} + m_{13.2}$$

Three-way interactions m_{124}, m_{134}, m_{234}, m_{12C}, etc. between other triplets of groups can be defined in a similar fashion. It is evident that if we write

$$[M]_{ID} = m_{12} + m_{13} + m_{14} + m_{1C} + m_{23} + m_{24} + m_{2C} + m_{34} + m_{3C} + m_{4C}$$
$$+ m_{123} + m_{124} + m_{12C} + m_{134} + m_{13C} + m_{14C} + m_{234} + m_{23C} + m_{24C} + m_{34C} \quad (2)$$

* One often sees statements seeming to imply that asymmetric centres in a molecule make contributions to the optical rotation through some unspecified inherent ability to interact with polarized light. The following quotations indicate this: "A full treatment [of the magnitude of the optical rotatory power] should include both asymmetric centers and asymmetric bond arrangements". "In a compound with two or more asymmetric carbon atoms the optical activities of the individual atoms can be added algebraically." Since all physical theories of optical rotation agree that the phenomenon arises exclusively from interactions of one kind or another between groups, it is misleading and fundamentally unsound to base a general empirical approach on any concept of the independent contributions by "centers" to the rotation. (There are, however, special circumstances where this concept may be useful, particularly where two or more asymmetric centers are so far apart in the molecule that the groups about one center do not interact appreciably with the groups about another center. This explains the success of such an approach with the steroids.[6])

It cannot be too strongly emphasized that the role of the asymmetric carbon atom in giving rise to optical rotation is exclusively a structural one. It provides the chromophoric electrons in the molecule with an environment that is not superimposable on its mirror image, and which can be converted into its mirror image only by a rearrangement of chemical bonds—a process requiring a high activation energy and therefore having a low rate. The consequence is that the vicinal actions between groups (taken two at a time if we are concerned with pairwise interactions, or three or four at a time if we wish to consider higher order interactions) fail either to vanish or to cancel one another. The asymmetric carbon atom is, however, only one of a number of ways of introducing a high energy barrier between the enantiomorphs of a compound. (Another way of obtaining such a barrier is through steric hindrance to the rotation of the benzene rings in ortho-substituted diphenyls.) The physical factors that lead to the high energy barrier are entirely different from the physical factors that rotate the plane of polarized light. It is unfortunate that they are so often confused.

we shall obtain a closer approximation to the optical rotation of compound ID than would be given by expression (1). In this approximation the "pairwise interaction terms", m_{12}, etc. are defined in exactly the same way as they are in expression (1) (i.e., m_{12} is still the rotation that would arise if only groups R_1 and R_2 were present). The "three-way interaction term" m_{123} is the correction that would have to be added to $m_{12} + m_{13} + m_{23}$ in order to obtain the optical rotation that would actually be observed if the three groups, R_1, R_2 and R_3, and these three groups alone, were present. The rest of the three-way interactions terms, m_{134}, m_{234}, etc., have similar meanings.

We could, if necessary, go one step further and set up "four-way interactions terms", such as m_{1234}, which would denote the correction that must be added to $m_{123} + m_{134} + m_{124} + m_{234}$ in order to obtain the correct rotation when groups R_1, R_2, R_3 and R_4 (but not the asymmetric carbon) are present. Terms of the type m_{1234}, m_{123C} etc., when added to expression (2) would give a still better approximation to the actual optical rotation of compound ID. Finally, a "five-way interaction term", m_{1234C} could be introduced which would take care of all the interactions that were not included in the four-way terms; inclusion of this term would, by definition, have to give the correct value for the optical rotation of ID.

One of the most important problems that faces the current theories of optical rotation is to determine how many of these interaction terms must be included in order to obtain a reasonably good quantitative theory of optical rotation. The empirical approach faces the same problem. In general, the interactions that lead to the pairwise interaction terms, m_{12}, etc., are quite small. The three-way interaction terms, m_{123}, etc., result from the compounding of the effect of one small interaction on another small interaction. This leads us to expect that the three-way terms will be much smaller than the two-way terms. We should like to know, however, just how small they are, and under what conditions one can expect to obtain good results by including only the pairwise terms.

The present paper has two principal objectives. The first objective is to examine the conditions under which the principle of pairwise interactions is valid. We shall do this by an empirical approach, looking for molecules in which the pairwise interactions must vanish, so that all of the rotation must come from three-way and higher interactions. The magnitudes of the rotations observed for such molecules will give us some idea of the errors that might be expected if only pairwise interactions are taken into account. The second objective of this paper is to show that if the principle of pairwise interactions is valid it may be used to predict useful and interesting quantitative relationships between the optical rotations of certain compounds. Unfortunately the data necessary for a rigorous test of most of these predictions are not now at hand, but when they become available they will obviously have an important bearing on the basic question of the adequacy of the pairwise interaction principle—a basic assumption common to most of the current theories of optical rotation.

It should be pointed out that in practice the "interactions" of which we speak here may be rather complex. They will, of course, include the direct vicinal actions that are computed by theories of optical rotation. They may also include other kinds of interactions which influence the optical rotation less directly. For instance, the solvation of a group may be influenced by other near-by groups. (The hydration of a carbonyl group in an aqueous solution of a ketone may be changed if a hydroxyl group is attached to a carbon atom close to the carbonyl.) The vicinal actions between a

given pair of groups (call them A and B) will certainly be affected by the manner in which the two groups are solvated. Suppose that a group C changes the solvation of A or B when it is placed next to one of them. Then the group C may have a significant indirect effect on the contribution of the A—B interaction to the optical rotation, even though the three-way optical interactions of A, B and C are small. In general, therefore, it is desirable to apply and test the principle of pairwise interactions in inert solvents if this is possible. It would be even more desirable if optical rotations could be measured in the vapor, but this is unfortunately difficult to do.

Interactions between a pair of groups will also be significantly changed if a third group is added which can resonate with one member of the pair. Steric interactions between groups may also be responsible for an apparent failure of the principle of pairwise interactions. Thus, in a compound such as 3-ethylcyclopentanone the contribution of the interaction between the ethyl group and the carbonyl group will depend on the spatial position of the ethyl group, especially with respect to rotation of the group about the bond that joins it to the ring. Substitution of a bulky group, such as a phenyl, at position 4 in the ring in a *cis* relationship to the ethyl group would undoubtedly have an influence on the spatial position of the ethyl group. Thus the phenyl group may have a large effect on the contribution to the optical rotation arising from the ethyl-carbonyl interaction, even though the optical interactions of the phenyl group with these two groups happened to be small.

It should be stressed that all of the considerations to be discussed in this paper will apply to optical rotations measured at any wavelength. If we happen to restrict our discussion to measurements made at only one wavelength, this is no sense an inherent limitation of the approach that we are taking.

II. SOME EXPERIMENTAL TESTS OF THE PRINCIPLE OF PAIRWISE INTERACTION

A. *Molecules in which the groups attached to the asymmetric carbon atom have axial symmetry.* Consider the optical rotation of α-bromo-propionitrile, CH_3—CHBr—CN, in terms of the principle of pairwise interactions. According to this principle the molecular rotation should be given by

$$[M] = m_{MeBr} + m_{MeH} + m_{MeCN} + m_{MeC\bullet} + m_{HBr} + m_{HCN} + m_{HC\bullet} + m_{BrCN} + m_{BrC\bullet} + m_{C\bullet CN}$$

where m_{MeBr} is the contribution to the optical rotation arising from the interaction of the methyl group with the bromine, $m_{C\bullet CN}$ is the contribution of the interaction between the asymmetric carbon atom and the nitrile group, and so on. It is easy to see that all of these pairwise interactions are identically equal to zero. For instance, m_{MeBr} is defined as the optical rotation of the molecular fragment containing only the methyl group and the bromine atom (Fig. 1) This fragment is superimposable on its mirror image, so it can give rise to no optical rotation. Similarly, all of the other fragments shown in Fig. 1 are superimposable on their mirror images and can have no optical rotation. Therefore the rather large optical rotation that is observed for this substance ($[M]_D = 21°$ for the pure liquid, Berry and Sturtevant[7]) must arise entirely from three-way and higher interactions.

[7] K. L. Berry and J. M. Sturtevant, *J. Amer. Chem. Soc.* **61**, 3583 (1939).

In general *the contribution of pairwise interactions to the optical rotation must vanish for any molecule in which all of the groups attached to the asymmetric carbon atom have axial symmetry about the bond joining them to the asymmetric carbon atom* (Kauzmann and Eyring,[8]). Two other compounds are known having axially symmetric groups of this kind: CH_3—$CH(NH_3^+)$—CN, with $[M]_D = 13°$ in water, (Delepine[9]) and Cl—CHI—SO_3^-, with $[M]_D = 36°$ in water (Read and McMath[10]). The

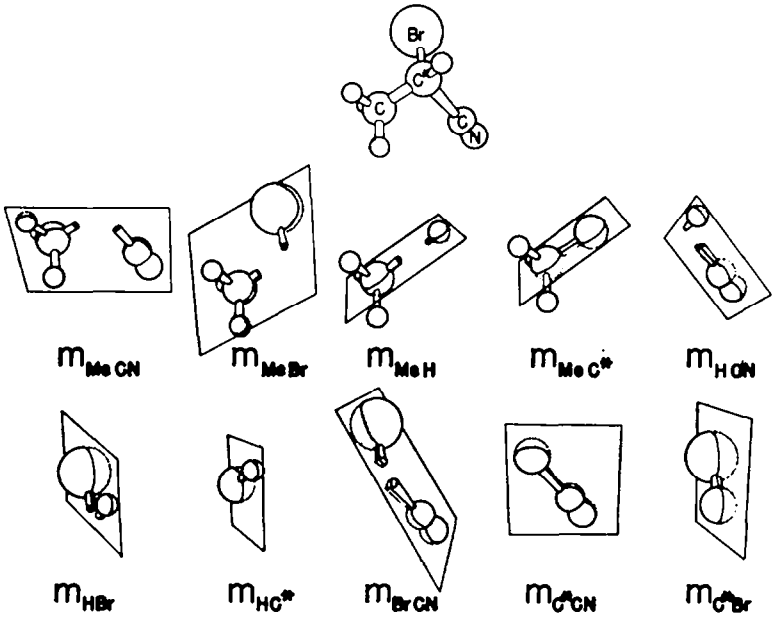


FIG. 1. Cancellation of pairwise interactions in α-bromopropionitrile. If any two groups are considered apart from the rest of the molecule, a plane of symmetry may be passed through them. Therefore pairwise interactions in this molecule cannot give rise to optical rotation.

relatively large rotations of these two substances must also come entirely from three-way and higher interactions.

These examples show that the higher order interactions can lead to optical rotations of sodium D light as large as 20° or 30° or more. It must be realized, however, that in the three examples cited especially large interactions would be expected between the groups attached to the asymmetric carbon atom. At least two of the groups are strongly polar in each of the three examples, so they must have relatively large effects on each other. Furthermore, the interacting groups are all very close together and the measurements were all made in strongly polar solvents, so the indirect effects of groups on each other's solvation may well be pronounced. These rotations must, therefore, be taken as an indication of the upper limit to the magnitudes of three way interactions. The contributions of higher order interactions should be smaller in molecules in which the groups attached to the asymmetric carbon atom are less polar and in compounds in which the polar groups are not so close together; they may also be smaller if the rotations are measured in less polar solvents.

[8] W. Kauzmann and H. Eyring, *J. Chem. Phys.* **9**, 41 (1941).
[9] M. Delepine, *Bull. Soc. Chim. Fr.* (3) **29**, 1195 (1903).
[10] J. Read and A. M. McMath, *J. Chem. Soc.* 2723 (1932).

B. *Molecules in which rotation is possible about the bonds attached to the asymmetric carbon atom.* Consider next the optical rotation of secondary butyl bromide, C_2H_5—CHBr—CH_3. Taking into account the threefold energy barrier that restricts rotation about the carbon-carbon bond joining the ethyl group to the asymmetric carbon atom, this molecule should exist predominantly in the three conformations, A, B and C, shown in Fig. 2. Now let us remove, in our minds, the methyl group and the secondary hydrogen atom from the asymmetric carbon atom, leaving the fragment C_2H_5—C—Br. It will be seen that in forms A and C the conformations assumed by this fragment are mirror images of one another. This means that the contribution to the optical rotation

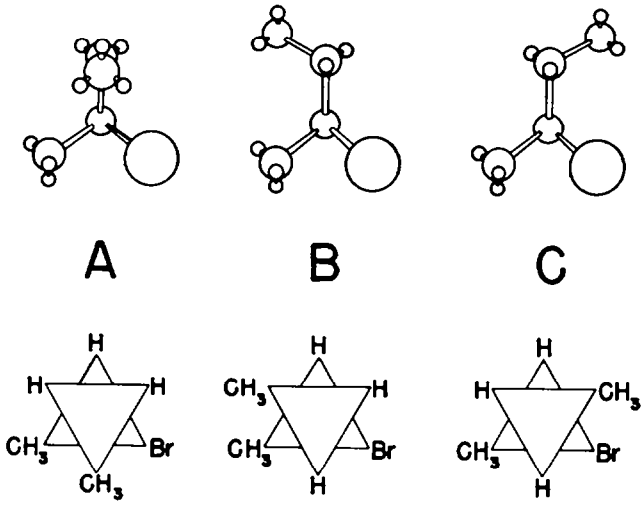


FIG. 2. Conformations of secondary butyl bromide.

arising from the pairwise interaction of the ethyl group and the bromine atom must be equal and opposite in sign in forms A and C. Furthermore, in form B this same fragment is superimposable on its mirror image, so that the contribution of the interaction between the ethyl group and the bromine atom must vanish. The same reasoning will show that the contribution from the pairwise interaction between the ethyl and methyl groups attached to the asymmetric carbon will vanish in form C and will be equal and opposite in sign in forms A and B, and that the contribution of the interaction of the ethyl group and the secondary hydrogen on the asymmetric carbon atom will vanish in A and be equal and opposite in sign in B and C. The contributions of all of the pairwise interactions between the secondary hydrogen atom and the methyl group and the bromine atom vanish in each of the three forms, since the fragments formed from any two of these groups are all superimposable on their mirror images.

It is evident that if secondary butyl bromide existed in equal amounts in the three forms A, B and C, all of the pairwise interactions between its groups would vanish, and the entire rotation would have to arise from higher order interactions. Since higher order interactions generally give smaller optical rotations than pairwise interactions, any forces which cause the three forms to exist in unequal amounts will tend to make the optical rotation larger.

The groups attached to the asymmetric carbon atoms of an optically active molecule will normally be expected to occur in several equilibrium positions which are

symmetrically disposed about the single bond joining the groups to the asymmetric atoms. The arguments presented above are quite general and lead us to expect that *whenever some factor is present which causes these groups to spend unequal amounts of time in the different equilibrium positions, the optical rotation will usually become larger.* We may note by allowing the ethyl group in secondary butyl bromide to occupy its three equilibrium positions to equal extents we have, in effect, given this group an axis of symmetry about the bond that joins it to the asymmetric carbon atom. In a similar fashion it is possible to confer an effective axial symmetry on a propyl or a butyl group (or, indeed, on any group not containing an asymmetric carbon atom that is a member of a ring) by equalizing the populations present in the equilibrium positions about each single bond in the group—including, of course, the single bond between the group and the asymmetric carbon atom. Therefore, this rule is really a corollary of the rule formulated in Section A, above.

The experimental evidence which supports this rule has been presented elsewhere, (Kauzmann and Eyring[8]; Kauzmann, *et al*,[11]) and need not detain us. We shall however, find it instructive to examine the rotations of some compounds in which the groups attached to asymmetric carbon atoms may be expected to attain effective axial symmetry. This will permit us to make some additional estimates of the order of magnitude of the contributions of three-way interactions to the optical rotation in some typical optically active molecules.

(1) *Evidence from the comparison of the rotations of open chain and ring compounds.* The most effective way in which to prevent equalization of the populations in the three positions of equilibrium about the single bonds that are in the vicinity of asymmetric carbon atoms is to make the asymmetric carbon a member of a ring. Organic chemists have known for a long time that ring closure usually brings about a marked increase in the magnitude of the optical rotation, and numerous examples may be cited (Kauzmann and Eyring[8]). Perhaps the most striking examples are to be found in the comparison of the optical rotations of the open chain sugar alcohols with the optical rotations of the cyclitols. Table 1A gives the optical rotations of sugar alcohols of the general formula $H(CHOH)_nH$ and Table 1B gives the rotations of some hydroxylated cyclohexanes. It is seen that the formation of a ring in these chemically quite similar compounds tends to increase the magnitude of the optical rotation by a factor of something like ten.

These two tables force us to the somewhat surprising conclusion that there must be almost complete equalization of the populations in the three equilibrium positions about all of the carbon-carbon bonds in the sugar alcohols of the formula $H(CHOH)_nH$. Table 1B also demonstrates that for the kinds of groups present in these molecules pairwise interactions must be capable of giving optical rotations for sodium D light that may be of the order of 50° to 100°. Finally, Table 1A indicates that the higher order interactions in these compounds must result in optical rotations of less than about 5°. (We cannot say how much less than 5° they are because we do not know how much of of the rotation that is observed for the sugar alcohols is caused by uncompensated pairwise interactions from slight deviations from complete equalization of the populations in the three equilibrium positions about the single bonds. Hydration effects are also undoubtedly large in these compounds because all of the rotations were

[11] W. Kauzmann, J. Walter and H. Eyring, *Chem. Rev.* **26**, 339 (1940).

measured in aqueous solution. These would tend to make the higher order interactions larger than otherwise.)

The conclusion that all conformations of the sugar alcohols are equally likely may come as something of a shock to organic chemists who are concerned with conformational analysis. If one constructs models of these alcohols, and if one follows the usual dictates of conformational analysis in rejecting conformations which tend to bring groups into close proximity, many of the conformations of the open chain sugars

TABLE 1. OPTICAL ROTATIONS OF HYDROXYLATED COMPOUNDS

Substance	Formula	Configurations of hydroxyls*	$[M]_D$ in water†
A. *Fully hydroxylated open chain compounds*			
D-threitol	$HOCH_2(CHOH)_2CH_2OH$	DL	+5·25
D-arabitol	$HOCH_2(CHOH)_3CH_2OH$	DDL	0
D-talitol	$HOCH_2(CHOH)_4CH_2OH$	DLLL	+5·8
D-mannitol	$HOCH_2(CHOH)_4CH_2OH$	DDLL	−3·8
D-sorbitol	$HOCH_2(CHOH)_4CH_2OH$	DDLD	−3·5
D-iditol	$HOCH_2(CHOH)_4CH_2OH$	DLDL	+6·4
D-glycero-L-glucoheptitol	$HOCH_2(CHOH)_5CH_2OH$	DLLDL	+5·1
D-glycero-D-glucoheptitol	$HOCH_2(CHOH)_5CH_2OH$	DDDLD	−1·6
D-glycero-D-idoheptitol	$HOCH_2(CHOH)_5CH_2OH$	DDLDL	+1·5
D-glycero-D-mannoheptitol	$HOCH_2(CHOH)_5CH_2OH$	DDDLL	+4·2
D-glycero-D-altroheptitol	$HOCH_2(CHOH)_5CH_2OH$	DDDDL	−0·6
D-erythro-L-talooctitol	$HOCH_2(CHOH)_6CH_2OH$	DDLDDD	−1·9
D-erythro-L-galaoctitol	$HOCH_2(CHOH)_6CH_2OH$	DDLDDL	+5·8
D-threo-L-galactooctitol	$HOCH_2(CHOH)_6CH_2OH$	DLLDDL	0·0
ααα-D-gluconitol	$HOCH_2(CHOH)_7CH_2OH$	DDLDDL(L?)	+4·1
αααα-D-glucodecitol	$HOCH_2(CHOH)_8CH_2OH$	DDLDDL(L?D?)	+3·6
B. *Hydroxylated cyclohexane derivatives* (cyclitols)			
Viboquercitol	$C_6H_7(OH)_5$	1,2,4/3,5	−90
Protoquercitol	$C_6H_7(OH)_5$	1,4/2,3,5	+42
Epiquercitol	$C_6H_7(OH)_5$	1,2,3,5/4	−9
Inositol	$C_6H_6(OH)_6$	1,2,5/3,4,6	+117

* For the open chain compounds, the chain is written vertically. Starting at the bottom, the hydroxyls that are attached to asymmetric carbon atoms are labeled in succession, D if they lie on the right hand side of the chain and L if they lie on the left hand side. For the cyclohexane derivatives the ring is assumed to be flattened out in the plane of the page and the ring atoms are numbered from 1 to 6 moving clockwise around the ring. The hydroxyl groups that lie above the plane of the paper appear before the slash (/) and those that lie below the plane of the paper appear after the slash.

† Data from Pigman[13] and Angyal and Anderson.[13]

would have to be rejected. Yet the small rotations of these compounds clearly indicate that all of the conformations must be nearly equal in energy. On the other hand Sheppard and Szasz[14] and Scott, McCullough *et al.*[15] have shown that there is a difference of less than 100 cals between the three rotational trans and gauche conformers of 2,3-dimethyl butane (that is, the conformers that result from rotation about

[13] W. W. Pigman, *The Carbohydrates: Chemistry, Biochemistry, Physiology.* Academic Press, New York (1957).

[13] S. J. Angyal and L. Anderson, *Advanc. Carbohyd. Chem.* **14**, 191 (1959).

[14] N. Sheppard and G. J. Szasz, *J. Chem. Phys.* **18**, 145 (1950).

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

the single bond joining carbon atoms 2 and 3). The three conformers of 2,3-dimethyl butane are therefore present in very nearly equal amounts at ordinary temperatures. Since the steric interactions of two methyl groups on adjacent carbon atoms may not be greatly different from the steric interactions of a pair of hydroxyl groups, and since nearly all of the carbon-carbon bonds of the sugar alcohols are disubstituted at either end with carbon and oxygen atoms (and thus resemble the 2,3 bond in 2,3-dimethyl butane) equal energies for the three positions about each bond in the sugar alcohols might not be too unreasonable. It is interesting in this connection to notice that the

TABLE 2. OPTICAL ROTATIONS OF PARTIALLY HYDROXYLATED OPEN CHAIN COMPOUNDS

Substance	Formula	Configurations of hydroxyls*	$[M]_D$ in water†
1,6-di-deoxy D-mannitol	$CH_3(CHOH)_4CH_3$	DDLL	−31.
D-lyxohexanetetrol-1,2,3,4	$CH_3CH_2(CHOH)_3CH_2OH$	DLL	+6·5
2-deoxy D-sorbitol	$HOCH_2CH_2(CHOH)_3CH_2OH$	DLL	+27.
1-deoxy L-sorbitol	$CH_3(CHOH)_4CH_2OH$	DLDD	−7.
D-rhamnitol	$CH_3(CHOH)_4CH_2OH$	DDLL	−20.
2-deoxy D-allitol	$HOCH_2(CHOH)_3CH_2CH_2OH$	DDD	−31·5 (in methanol)
L-idomethylitol	$CH_3(CHOH)_4CH_2OH$	DLDL	+4·3
D-rhodeitol	$CH_3(CHOH)_4CH_2OH$	DDDD	−2·4
D-isorhodeitol	$CH_3(CHOH)_4CH_2OH$	DDLD	−16.
6-deoxy D-talitol	$CH_3(CHOH)_4CH_2OH$	DLLL	−3·8

* Notation same as in Table 1, with right hand carbon atom toward the top of the page.
† Data from Beilstein and Vogel and Georg[16].

optical rotations of alcohols in which some of the CHOH groups of the sugar alcohols are replaced by CH_2 groups often tend to be several times as large as those of the sugar alcohols themselves. (See Table 2.) In these substances a greater proportion of the carbon-carbon bonds are not disubstituted at both ends.

(2) *Evidence from the effect of temperature on the optical rotation of simple open chain compounds.* One of the most effective means of equalizing the populations in the equilibrium positions about carbon-carbon single bonds is to raise the temperature. Unfortunately the effect of temperature on the optical rotation has not been as widely studied as one could wish for this purpose, but we do have the extensive data of Pickard, Kenyon and their co-workers, who made systematic investigations of temperature effects on many aliphatic and aromatic carbinols, their esters and their ethers over a wide range of temperatures (20°C to 150°C or more in many instances). All of these studies were performed on the homogeneous compounds, so that "solvent effects" (here, the effects of the optically active molecules on each other) are a variable factor impossible to separate from intramolecular conformational effects. Nevertheless the studies throw an interesting light on the question of the relative magnitudes of pairwise interactions and higher order interactions, and they also lead to interesting conclusions about the conformations of alkyl chains in simple molecules at room temperature.

Before considering the measurements of Pickard and Kenyon, it is necessary to discuss a correction caused by the variation of the internal field with the temperature, because it produces an indirect effect on the optical rotation that is of no interest here.

[16] H. Vogel and A. Georg, *Tabellen der Zucker und ihrer Derivate.* Springer, Berlin (1931).

All theories of optical rotation show that a general solvent effect exists due to this internal field. If the internal field can be given by the equation derived by Lorentz (and this is generally believed to be a reasonable assumption, especially under the present circumstances) then it is found that the optical rotation of a substance dissolved in a solvent of refractive index n is

$$[M] = \frac{n^2 + 2}{3}[M]^\circ$$

where $[M]^\circ$ is the optical rotation that the substance would have if its molecules were maintained in the same conformations that they have in the solvent, but if they were surrounded by a vacuum (i.e. if the solvent had an index of refraction of unity). Since the refractive index changes with the temperature, the rotation, [M], may therefore depend on the temperature even though the molecular conformations do not change with temperature. (This factor has been discussed by Beckmann and Cohen[17,18], Rule and Chambers,[19] Kauzmann, *et al.*[11] and Schellman.[20]) In order to avoid this extraneous effect, it is better to consider the temperature variation of the quantity

$$[M]^\circ = \frac{3}{n^2 + 2}[M]$$

rather than of [M]. Unfortunately measurements of the index of refraction are not commonly available over a range of temperatures, but if the Lorentz-Lorenz relation is valid,

$$\frac{n^2 - 1}{n^2 + 2}\frac{1}{d} = K$$

where d is the density and K is a constant for any substance or solution, then it is found that

$$\frac{3}{n^2 + 2} = 1 - Kd$$

so that

$$[M]^\circ = [M](1 - Kd)$$

Thus if one knows the index of refraction at one temperature, and if the densities are known as a function of the temperature, it is an easy matter to find K, and from this the temperature dependence of the Lorentz field factor, $3/(n^2 + 2)$. The correction is often not very great, but it is safer to make it, and in most of what follows it has been made. The constant K is usually around 0·3 cm^3/gm and between 20° and 150°C the density of the carbinols and their derivatives change, typically, from 0·83 to 0·71. Therefore the Lorentz factor changes from about 0·751 at 20° to 0·787 at 150°—a total variation of about 5 per cent. In many instances this is an appreciable fraction of the total change of the optical rotation in this temperature range.

The variation of $[M]_D^\circ$ with temperature for a number of simple aliphatic carbinols is shown in Fig. 3. In most instances, but not all, the magnitude of $[M]_D^\circ$ decreases with temperature, in accordance with what we should expect if raising the temperature has

[17] C. O. Beckman and K. Cohen, *J. Chem. Phys.* **4**, 784 (1936).
[18] C. O. Beckman and K. Cohen, *J. Chem. Phys.* **6**, 163 (1938).
[19] H. G. Rule and A. R. Chambers, *J. Chem. Soc.* 145 (1937).
[20] J. A. Schellman, *Compt. Rend. Trav. Lab. Carlsberg.* **30**, 363 (1958).

the dual effect of increasing the effective axial symmetry of groups about the bonds that attach them to the asymmetric carbon atom and of decreasing the interactions with the solvent. Where $[M]_D^\circ$ increases with temperature, the increase is slight. In most instances the value of $[M]_D^\circ$ reached at the highest temperatures is under 10°. The principal exception is isopropyl n-decyl carbinol, for which $[M]_D^\circ$ changes from 25·6° at 0°C to 25·3° at 200°C; in this molecule the steric repulsions between the groups attached to the asymmetric carbon atom are greater than in the other compounds shown in Fig. 3.

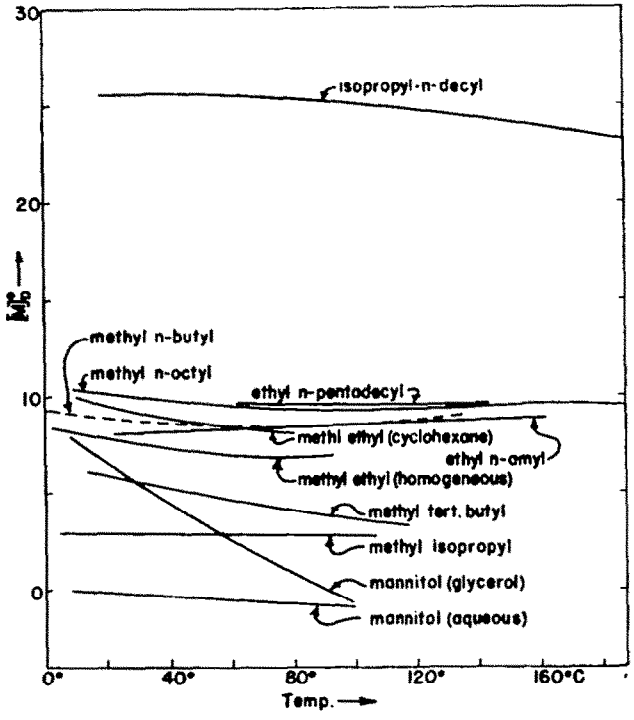


FIG. 3. Temperature dependence of the optical rotations of secondary carbinols (R_1R_2CHOH) and mannitol ($H(CHOH)_4H$). Except where otherwise stated, all rotations were measured on substances in the homogeneous state (no solvent). Data from Pickard and Kenyon (methyl carbinols,[21] isopropyl n-decyl carbinol,[22] ethyl carbinols[23]), Patterson and Todd[24] (mannitol) and Bernstein and Pedersen[25] (methyl ethyl carbinol in cyclohexane).

Several interpretations of these results are possible:

(1) It is possible that in all of these molecules the steric repulsions are so great that even in the temperature range from 0° to 150°C the groups attached to the asymmetric carbon atom are very far from axially symmetric. In this case the observed rotations would be caused principally by pairwise interactions, and the higher order contributions to $[M]_D^\circ$ would be well under 10°. This interpretation seems unlikely because, as we have seen earlier (Section A1), pairwise interactions between groups that are, in an optical sense, not very dissimilar from the alkyl and hydroxyl groups present in these

[21] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* **99**, 45 (1911).
[22] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* **101**, 620 (1912).
[23] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* **103**, 1923 (1913).
[24] T. S. Patterson and A. R. Todd, *J. Chem. Soc.* 2887 (1929).
[25] H. J. Bernstein and E. Pedersen, *J. Chem. Phys.* **17**, 885 (1949).

compounds often result in optical rotations that are considerably greater than 10°. Therefore, if the alkyl carbinols were highly restricted in their internal rotations we should expect to find much larger rotations than we do. We have also seen that in the sugar alcohols, where one would expect the steric repulsions to be at least as great, almost complete axial symmetry probably exists about all of the bonds.

(2) On the other hand it is possible that the steric repulsions in these compounds are sufficiently small that (especially in molecules such as methyl ethyl carbinol, where the groups are small) the groups behave almost as if they were axially symmetric between 20° and 150°C. In this case the higher order contributions to $[M]_D^\circ$ must once again be judged to have an upper limit of about 10°. Temperature-independent values of $[M]_D^\circ$ of 10° or more are observed for methyl butyl carbinol, methyl octyl carbinol, the ethyl alkyl carbinols and isopropyl n-decyl carbinol. All of these compounds have one or more relatively large groups attached to the asymmetric carbon atom. If these groups were to cause a small residual deviation from complete axial symmetry that cannot be removed in this temperature range, then we could conclude that the higher order contributions in compounds of this type must be well under 10°. Unfortunately the $[M]_D^\circ$ values for the smaller carbinols (methyl ethyl carbinol and methyl tertiary butyl carbinol) are available over narrower temperature ranges, because of their lower boiling points, so it is not possible to estimate the limiting value of $[M]_D^\circ$ at high temperatures for them.

Methyl tertiary butyl carbinol is especially interesting because only one of the four groups attached to the asymmetric carbon atom—the hydroxyl group—is not axially symmetric. For this substance $[M]_D^\circ$ shows a greater change with temperature than do most other carbinols. This change may be caused by changes in solvent effects (especially the rupture of intermolecular hydrogen bonds) as well as by changes in molecular conformation (i.e., changes in the orientation of the hydroxyl group about the carbon-oxygen bond). Measurements of the temperature variation of $[M]_D^\circ$ at infinite dilution in an inert solvent would make it possible to separate these two effects. Measurements of this kind have been made by Bernstein and Pedersen[25] on methyl ethyl carbinol dissolved in cyclohexane, and their results are included in Fig. 3. They indicate that the changes in $[M]_D^\circ$ of the homogeneous carbinol observed by Pickard and Kenyon probably arise largely from changes in conformation with temperature, rather than from changes in hydrogen bonding.*

The temperature dependence of the optical rotation of mannitol in water and glycerol has been studied by Patterson and Todd[24] between 15°C and 90°C, and their observations (corrected for the variation in the Lorenz factor) are included in Fig. 3. (Patterson and Todd's observations were made at wavelengths of 579, 546·1 and 435·9 $m\mu$; the rotations for the sodium D line have been estimated by extrapolation of their results, assuming simple Drude-type dispersion). The rotations of mannitol in the two solvents at room temperature are opposite in sign, but on warming the rotations in both solvents move in the levo direction. These results indicate that at high temperatures, where pairwise interactions should vanish, $[M]_D^\circ$ would be more levo than 1°, so we may take this as a lower limit for the contributions of the higher order interactions in

* Bernstein and Pederson have analysed their results assuming that [M]° for methyl ethyl carbinol dissolved in cyclohexane arises entirely from pairwise interactions, and that the contributions of higher order interactions to the optical rotation are so small that they can be neglected. This assumption is highly dubious, so it is not possible to accept their conclusion that the energy of the trans conformations of methyl ethyl carbinol is lower by 800 cals than the energy of the gauche conformation.

this substance. It would be interesting to have similar measurements of the temperature variation of the optical rotations of other sugar alcohols.

The temperature variation of the optical rotations of other types of compounds are shown in Figs. 4–10. The following conclusions may be drawn from these figures.

(1) Conversion of the carbinols to methyl ethers does not appear to affect greatly the magnitude of $[M]_D^\circ$ or its temperature variation (Fig. 4). Ethyl and n-nonyl ethers of methyl n-butyl carbinol have larger values of $[M]_D^\circ$ and the temperature variation

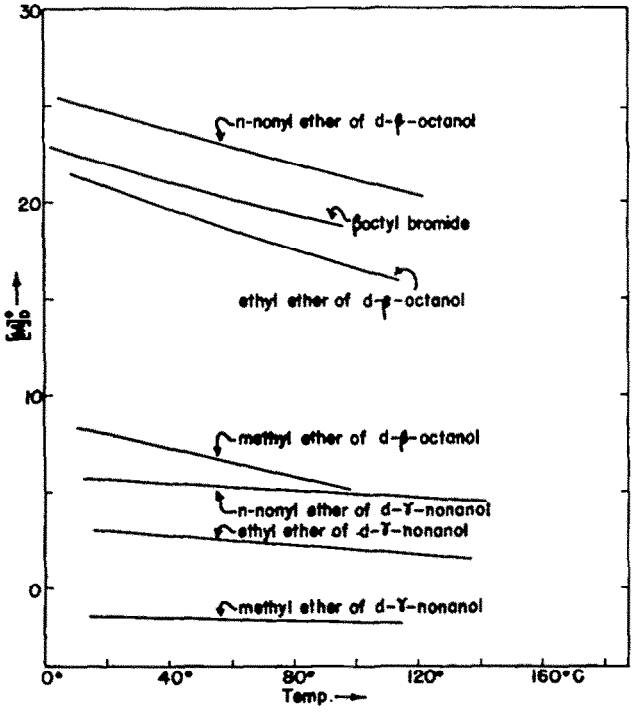


FIG. 4. Temperature dependence of the optical rotations of ethers of secondary carbinols and of β-octyl bromide. Data from Kenyon and McNicol[36] (ethers of d-β-octanol), Kenyon and Barnes[37] (ethers of d-γ-nonanol) and Pickard and Kenyon[21] (β-octyl bromide). Where rotations in the original reference have not been given for the sodium D line, the value has been interpolated from measurements at adjacent wave lengths by means of the Drude formula.

is greater. It appears that in the methyl ethers the effective axial symmetry of the groups attached to the asymmetric carbon atom is about as highly developed as it is in the corresponding alcohols. β-Octyl bromide has a considerably larger $[M]_D^\circ$ than most carbinols, and the temperature variation of $[M]_D^\circ$ is greater. This would indicate that the bulky bromine atom decreases the axial symmetry at room temperature to a greater extent than does the hydroxyl group. Unfortunately it is not possible to estimate the upper limit of $[M]_D^\circ$ at high temperatures for the bromide.

(2) Esters of the type $CH_3—CH(O—CO—R_1)—R_2$, where R_1 and R_2 are normal aliphatic groups (Figs. 5 and 6), have $[M]_D^\circ$ values at high temperatures that are of the order of 10° or less. For the formic acid esters (where $R_1 = H$ with R_2 larger than C_5H_{11}

[36] J. Kenyon and R. A. McNicol, *J. Chem. Soc.* **123**, 14 (1923).
[37] J. Kenyon and T. W. Barnes, *J. Chem. Soc.* **125**, 1395 (1924).

the high temperature values of $[M]_D^\circ$ tend to be somewhat greater, and $[M]_D^\circ$ increases very slightly as the temperature increases. The high temperature values of $[M]_D^\circ$ also tend to be greater when R_1 is a long chain and R_2 is a short chain. Pickard and Kenyon found that the esters show unusually large solvent effects, and that anamolous dispersion is sometimes observed at wavelengths in the visible region of the spectrum.

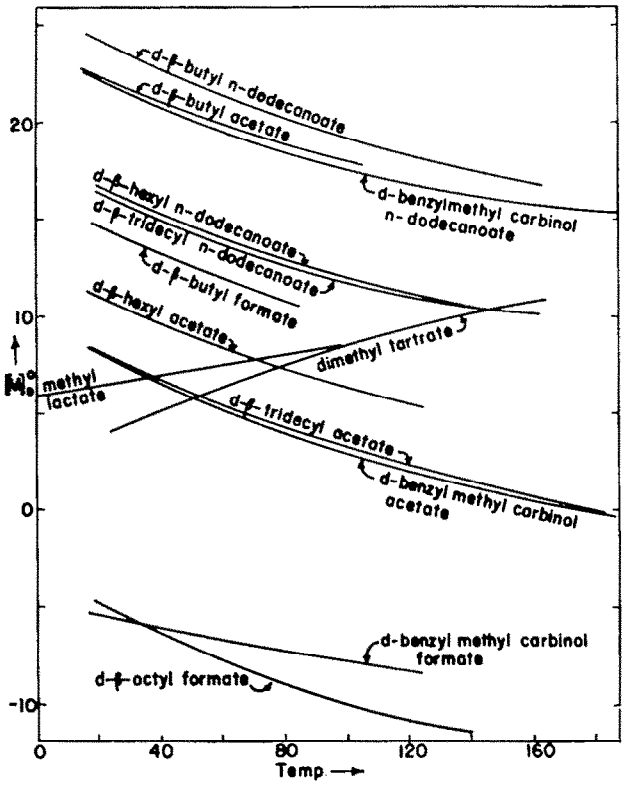


FIG. 5. Temperature dependence of the optical rotations of aliphatic esters of secondary carbinols, CH^3–CHOH–R. Data from Pickard and Kenyon[28] (acetates and n-dodecanoates where R is aliphatic), Kenyon and Pickard[29] (benzyl methyl carbinol acetate and n-dodecanoate), Pickard *et al.*[30] (formates), Wood and Nicholas[31] (methyl tartrate), and Patterson and Lawson[32] (methyl lactate). The rotations of methyl lactate were measured at 5790 A. rather than at the sodium D line.

The temperature dependence of the rotation of esters of the type C_2H_5—$CH(C_6H_{13})$—O—CO—R is small (Fig. 6) and $[M]_D^\circ$ values are well under 10° except for $R=CH_3$ and C_2H_5, where $[M]_D^\circ$ is just under 10°, and for R = H, where $[M]_D^\circ$ is about 20°.

Tartrates and lactates have $[M]_D^\circ$ values which are somewhat greater than 10° at high temperatures. These substances show large solvent effects, and they have two polar groups attached to each asymmetric center, so higher order interactions would

[28] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* **105**, 830 (1914).
[29] J. Kenyon and R. H. Pickard, *J. Chem. Soc.* **105**, 2262 (1914).
[30] R. H. Pickard, J. Kenyon and H. Hunter, *J. Chem. Soc.* **123**, 1 (1923).
[31] C. E. Wood and S. D. Nicholas, *J. Chem. Soc.* 1671 (1928).
[32] T. S. Patterson and A. Lawson, *J. Chem. Soc.* 2047 (1929).

be expected to give larger contributions than in the other compounds being discussed here.

(3) Introduction of aryl groups into the carbinols and their derivatives increases the magnitude of $[M]_D°$, especially if the aryl group is close to an asymmetric center (Figs. 7–10). If the aryl group is attached directly to the asymmetric center (see especially methyl α-naphthyl carbinol, methyl phenyl carbinol and ethyl phenyl carbinol in Fig. 8, and α-naphthyl n-hexyl carbinol and its esters in Fig. 10) the values of $[M]_D°$ at

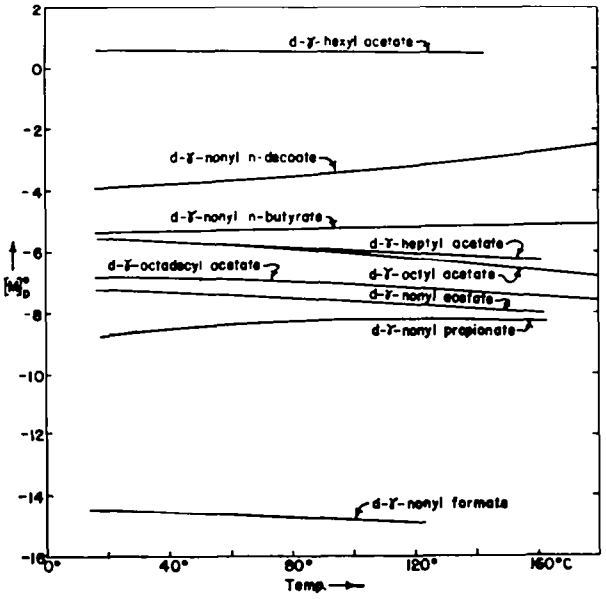


FIG. 6. Temperature dependence of the optical rotations of aliphatic esters of secondary carbinols, C_2H_5-CHOH-R. Data from Pickard, Kenyon and Hunter[30] (formate) and Kenyon[33] (all others).

high temperatures tend to be quite large and the effect of temperature on $[M]_D°$ is also large in most instances. If one or two methylene groups intervene between the aryl group and the asymmetric carbon atom, the magnitude of $[M]_D°$ at high temperatures and the variation of $[M]_D°$ with temperature tend to be smaller. These observations are understandable since the aryl groups are large and rigid and should produce large steric effects that both increase the apparent magnitude of the higher order contributions to the optical rotation (which makes $[M]_D°$ large at high temperatures) and increase the energy difference between the different conformers (which increases the temperature dependence of $[M]_D°$). Furthermore, it is quite likely that the higher order optical interactions that involve aryl groups, alkyl groups and hydroxyl groups or carboxylate groups are larger than those involving a pair of alkyl groups and a hydroxyl or carboxyl.

In summary, we may conclude that in the simple aliphatic carbinols and many of their derivatives at room temperature we have nearly complete three-fold axial symmetry about all of the single bonds. Unfortunately it is not possible to say whether the relatively small optical rotations that are observed for these compounds (of the order of

[33] J. Kenyon, *J. Chem. Soc.* **105**, 2226 (1914).

10°) arise almost entirely from higher order interactions, or whether they are caused by slight deviations from three-fold axial symmetry which could be eliminated by heating to still higher temperatures. In any case, the higher order interactions in these compounds can contribute no more than 10° to the optical rotation (if the molecules are immersed in a medium with refractive index unity), and they may be appreciably smaller. It is highly unlikely that they are completely negligible, however. If more bulky groups are close to the asymmetric carbon atom, and especially if aromatic groups are attached, rotations as large as 50° to 100° may result at high temperatures.

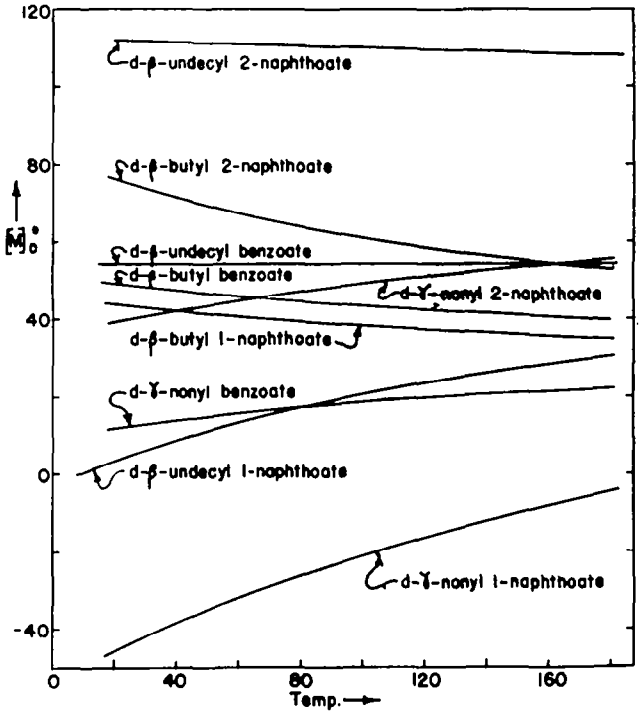


FIG. 7. Temperature dependence of the optical rotations of aromatic esters of secondary aliphatic carbinols. Data from Kenyon and Pickard.[84]

These large rotations may represent true higher order interactions, but they may also include some effects of non-axial symmetry.

(3) *Pairwise interactions and Hudson's rules rules of isorotation.* Hudson showed that if, in a series of sugars, the configuration about one of the carbon atoms is reversed, then the optical rotation is changed in a remarkably regular manner. This is illustrated in Tables 3 and 4. Table 3 shows the changes in rotation that occur when the configuration of the glycosidic carbon atom (C_1) is changed from D- to L- in a number of free sugars and their derivatives. The sugars in this table have been divided into two classes, depending upon the configuration at carbon atom C_2, which is next to the glycosidic carbon atom. In one of the classes (referred to a the "glucose class" because D-glucose is its best known member) C_2 is in the D configuration, and in the

[84] J. Kenyon and R. H. Pickard, *J. Chem. Soc.* **107**, 115 (1915).

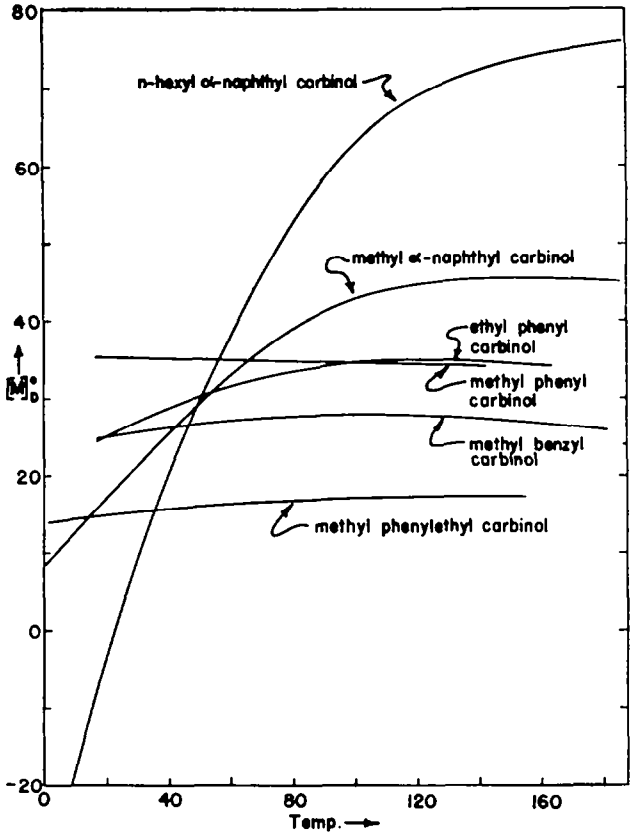
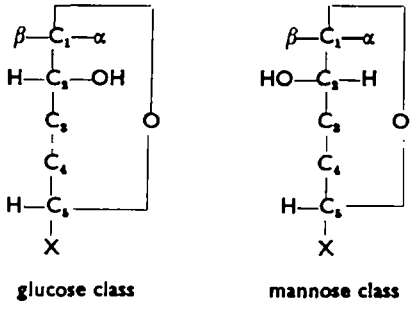


FIG. 8. Temperature dependence of the optical rotations of secondary d-carbinols, R_1-CHOH $-R_2$, where R_1 is aliphatic and R_2 contains an aromatic group. Data from Kenyon and Pickard[35] (n-hexyl α-naphthyl carbinol) and Pickard and Kenyon[36] (all others).

other class (the "mannose class") the configuration at C_2 is L. In a D-hexopyranose the two classes have the following structures:



where X stands for the group CH_2OH and α and β show the positions of the glycosidic hydroxyl in the α and β forms of the sugar. In the pentoses (xylose, arabinose, lyxose,

[35] J. Kenyon and R. H. Pickard, *J. Chem. Soc.* **105**, 2644 (1914).
[36] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* **105**, 1115 (1914).

ribose), X = H and the α derivative is generally taken as the one in which the configurations at C_1 and C_4 are identical (Bates,[38]). In the heptopyranoses, X = CH_2OH·CHOH. In Table 3 these two classes have been further subdivided on the basis of the configurations about the other atoms in the pyranose ring.

Table 3 shows that for free sugars belonging to the glucose class, a change in configuration at C_1 from D to L causes a change in optical rotation of about 175° in most

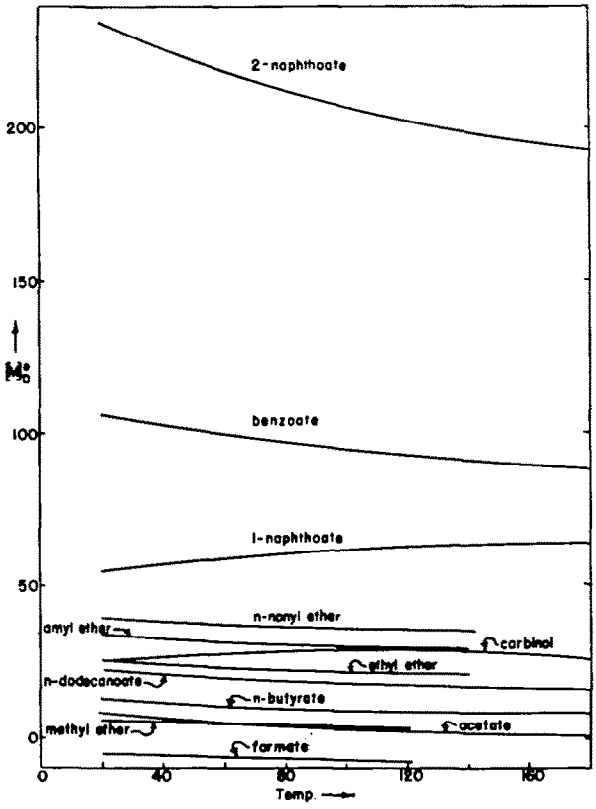


FIG. 9. Temperature dependence of the optical rotations of D-methyl benzyl carbinol and some of its derivatives. Data from Pickard and Kenyon[26] (carbinol), Kenyon and Pickard[29] aliphatic esters other than formate), Kenyon and Pickard[24] (aromatic esters), Pickard *et al.*[30] (formate) and Phillips[27] (ethers).

instances. In the free sugars of the mannose class the same change in configuration results in a rotation difference which is usually considerably smaller, ranging from 75° to 100° in most instances. The rotation changes in free sugars of the mannose class are also somewhat more variable in magnitude than are those of the glucose class. Similar regularities are observed for the rotation differences of each of the other types of derivatives listed in Table 3, although there is somewhat more variation here than for the free sugars.

In general it is found that for a given type of derivative the change in rotation resulting from the inversion of the configuration at C_1 is fairly constant in each class of

[27] H. Phillips, *J. Chem. Soc.* **123**, 29 (1923).

sugar. It is larger and more nearly constant for the glucose class than for the mannose class. The exceptions to this generalization frequently involve the pentose sugars, but exceptions are also found when different solvents were used to measure the rotation of the anomers in an α-β pair, and when one of the members of the pair could not be crystallized (indicating that it might not have been pure).

Table 4 shows that similar regularities are also found when the configurations about

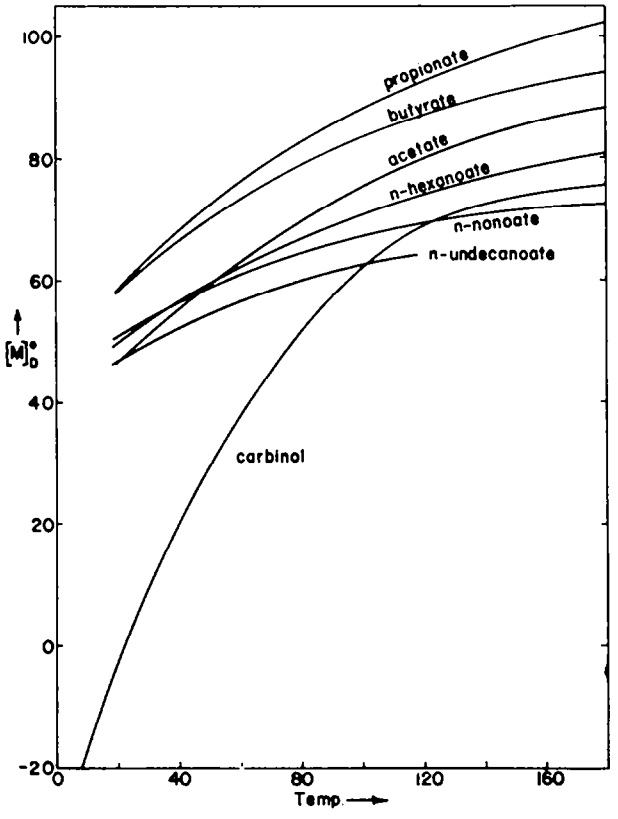


FIG. 10. Temperature dependence of the optical rotation of D-n-hexyl α-naphthyl carbinol and some of its esters. Data from Kenyon and Pickard.[35]

other carbon atoms in the sugar molecule are inverted. The differences in rotation between two substances which differ only in the configuration about one atom are again found to fall into distinct groups, depending (1) on which atom in the molecule is inverted, and (2) on the configurations of the two atoms adjacent to the atom on which the inversion occurs. Table 4A (which is based on a table in Bates[38]) shows this most clearly; here we see the changes in rotation that accompany inversions from L to D at atoms C_2, C_3 and C_4 of the free sugars. If a triad LLD at $C_{n+1}C_nC_{n-1}$ is changed to LDD, the rotation change is about $+150°$ if the atom in the middle of the triad is C_2 and -157 if the middle atom is C_3. If the triad is changed from DLL to DDL, the approximate change in rotation is $-60°$ if the middle atom is C_2, $+80°$ if it is C_3, and $-60°$ if it

[38] F. J. Bates, *Polarimetry, Saccharimetry and the Sugars*. National Bureau of Standards Circular C440, Washington (1942).

TABLE 3. DIFFERENCES IN MOLECULAR ROTATIONS OF α AND β PYRANOSE SUGARS AND THEIR DERIVATIVES
(Hudson's Rule of Isorotation)

Sugar	Free sugar	Methyl glycoside	Phenyl glycoside	Fully acetylated	Acetylated methyl glycoside	Acetylated phenyl glycoside	Fully methylated
A. *Glucose Class* (C_2 in D configuration)							
1. *Ring hydroxyls* DLDD → DLDL*							
D-xylose	—	+360	+538	+363	+524	+655	—
D-glucose	+168	+368	+647	+383	+539	+810	+318†
L-β-galaheptose	—	—	—	+398	+323	—	—
6-methyl D-glucose	—	+322‡	—	+329§	—	—	—
Cellobiose (= 4β-glucosido D-glucose)	—	+413	+768	+394‖ / +378	+529	+846	—
Maltose (= 4-α-D-glucosido D-glucose)	—	—	+686	+408	—	+910¶	—
Lactose (= 4-β-D-glucosido D-glucose)	+187	—	—	+396	—	—	—
Gentiobiose (= 6-β-D-glucosido D-glucose)	—	+361	—	+392	+543	—	—
6-deoxy-D-glucose	—	+362**	—	—	+546	—	—
D-glucosamine	—	—	—	+359	—	—	—
2. *Ring hydroxyls* LLDD → LLDL							
L-arabinose	+171	+372	+539	+328	—	—	+421
D-galactose	+176	+380	+669	+319	+533	+856‡	+425‡††
D-α-mannoheptose	+177	—	—	+401	—	—	—
D-fucose (= 6-deoxy-D-galactose)	—	+380	—	—	+481	—	—
3. *Ring hydroxyls* LDDD → LDDL							
L-lyxose	+117	+308	—	—	+405	—	—
D-gulose	—	+394	—	—	+469	—	—
D-α-glucoheptose	—	+418	—	+380	—	—	—
4. *Ring hydroxyls* DDDD → DDDL							
D-ribose	—	+341† ‖	—	+347† ‖	—	—	—

B. *Mannose Class* (C_2 in L configuration)							
1. *Ring hydroxyls* DLLD → DLLL							
D-lyxose	+117	+308	—	—	+405	—	—
D-mannose	+83	+279	+476	{+320‖ / +313}	+360	+581¶	+308
D-α-galaheptose	—	—	—	—	+426	—	—
4-β-D-glucosido-D-mannose	+75	+341	—	+334	+342	—	—
D-rhamnose (= 6-deoxy-D-mannose)	+79	+281	—	—	+303	—	—
2. *Ring hydroxyls* DDLD → DDLL							
D-arabinose	+171	+372	+539	+328	—	—	+421
D-altrose	—	+299	—	—	—	—	—
Celtrobiose (= 4-β-D-glucosido-D-altrose)	—	—	—	+414	—	—	—
Neolactose (= 4-β-D-galactosido-D-altrose)	—	—	—	+411	—	—	—
3. *Ring hydroxyls* LLLD → LLLL							
L-ribose	—	+341†	—	+347†	—	—	—
D-talose	+99	—	—	—	—	—	—
4. *Ring hydroxyls* LDLD → LDLL							
D-idose	—	—	+295‡,‡‡	—	—	—	—

The tabulated figures are the changes in $[M]_D$ resulting from a change in configuration at C_1 from D to L. In the D sugars and their derivatives this means that the rotation of the β form is subtracted from that of the α form; in the L sugars the rotation of the α form is subtracted from that of the β form. Where data for the rotations of a given D or L isomer are not available, the rotation of the enantiomorph has been taken with its sign reversed. Where not otherwise indicated the rotations are taken from Bates[38] for the free sugars, the methyl glycosides, the fully acetylated sugars, and the acetylated methyl glycosides; and from Conchie, *et al.*[39] for the phenyl glycosides and their acetates. Unless otherwise stated, the solvents used are water for the free sugars, the glycosides and the fully methylated sugars; and chloroform for the acetates.

* These letters refer to the configurations of the hydroxyls about atoms C_4, C_3, C_2 and C_1, respectively, with the ring drawn so that the hydroxyl at C_5 would be D. Thus α-D-glucose would be represented by DLDD, β-D-mannose would be DLLL, α-D-arabinose would be DDLD, and α-L-ribose would be LLLL.

† One of the two anomers not obtained in crystalline state; different solvents employed for measurement of rotations of α and β forms.

‡ One of the two anomers not obtained in crystalline state.

§ From Bourne and Peat.[40]

‖ From Conchie, Levvy and Marsh.[39]

¶ Solvent not known for one anomer.

** From Klyne.[6]

†† From Maher.[41]

‡‡ From Bentley.[42]

[39] J. Conchie, G. A. Levvy and C. A. Marsh, *Ad. Carbohyd. Chem.* **12**, 157 (1957).
[40] E. J. Bourne and S. Peat, *Ad. Carbohyd. Chem.* **5**, 145 (1950).
[41] G. G. Maher *Ad. Carbohyd. Chem.* **10**, 257 (1955).
[42] R. Bentley, *J. Amer. Chem. Soc.* **82**, 2811 (1960).

TABLE 4. ROTATION DIFFERENCES RESULTING FROM CHANGES IN CONFIGURATION ABOUT NON-GLYCOSIDIC CARBON ATOMS IN PYRANOSE SUGARS AND THEIR DERIVATIVES

Sugar with OH at C_n in D config.	Sugar with OH at C_n in L config.	Diff. in rotation (D − L)*	Config. of OH at adjacent atoms	
			at C_{n-1}	at C_{n+1}
A. *Free Sugars*				
1. Pairs of sugars differing in configuration only at C_2				
α-D-xylose	α-D-lyxose	+132	D	L
α-D-glucose	α-D-mannose	+149	D	L
α-D-galactose	α-D-talose	+149	D	L
α-L-β-guloheptose	α-L-α-gulheptose	+157	D	L
α-D-α-mannoheptose	α-D-β-mannoheptose	+170	D	L
α-D-glucomethylose	α-D-rhamnose	+104	D	L
β-D-allose	β-D-altrose	−59	L	D
β-D-α-glucoheptose	β-D-β-glucoheptose	−60	L	D
β-D-glucose	β-D-mannose	+64	L	L
β-D-galactose	β-D-talose	+71	L	L
α-L-arabinose	α-L-ribose	+85	L	L
β-cellobiose	β-4-β-glucosidomannose	+71	L	L
2. Pairs of sugars differing in configuration only at C_3				
β-D-allose	β-D-glucose	−34	D	D
α-D-gulose	α-D-galactose	−157	D	L
β-D-α-glucoheptose	β-D-α-mannoheptose	−157	D	L
β-D-altrose	β-D-mannose	+90	L	D
β-celtrobiose	β-4-β-glucosidomannose	+71	L	D
3. Pairs of sugars differing in configuration only at C_4				
α-D-xylose	β-L-arabinose	−146	L	†
β-D-lyxose	β-L-ribose	−140	L	†
α-D-glucose	α-D-galactose	−69	L	D
β-D-glucose	β-D-galactose	−61	L	D
α-D-mannose	α-D-talose	−70	L	D
β-D-mannose	β-D-talose	−54	L	D
α-L-α-galaheptose	α-L-α-guloheptose	−39	L	D
B. *Sugar Derivatives*				
1. Pairs differing in configuration at C_2				
a. Methyl glycosides (in water)				
Methyl α-D-guloside	Methyl α-D-idoside	+31	D	D
Methyl β-L-arabinoside	Methyl β-L-riboside	+228	D	L
Methyl α-D-xyloside	Methyl α-D-lyxoside	+154	D	L
Methyl α-D-glucoside	Methyl α-D-mannoside	+148	D	L
Methyl α-cellobiose	Methyl α-4-β-glucosido-mannose	+181	D	L
Methyl α-D-gluco-methyloside	Methyl α-D-rhamnoside	+153	D	L
Methyl β-D-guloside	Methyl β-D-idoside	−68	L	D
Methyl β-D-xyloside	Methyl β-D-lyxoside	+102	L	L
Methyl β-D-glucoside	Methyl β-D-mannoside	−68	L	L
Methyl β-D-gluco-methyloside	Methyl β-D-rhamnoside	+72	L	L
b. Phenyl glycosides (in water)				
Phenyl α-D-glucoside	Phenyl α-D-mannoside	+171	D	L
Phenyl β-D-glucoside	Phenyl β-D-mannoside	0	L	L

TABLE 4 (*cont'd*)

Sugar with OH at C_n in D config.	Sugar with OH at C_n in L config.	Diff. in rotation (D − L)	Config. of OH at adjacent atoms	
			at C_{n-1}	at C_{n+1}
c. *Polyacetates* (in chloroform)				
β-L-arabinose tetracetate	β-L-ribose tetracetate	+283	D	L
α-D-xylose tetracetate	α-D-lyxose tetracetate	+203	D	L
α-D-glucose pentacetate	α-D-mannose pentacetate	+176	D	L
α-D-galactose pentacetate	α-D-talose pentacetate	+144	D	L
α-cellobiose octacetate	α-4-β-glucosidomannose octacetate	+46	D	L
α-L-arabinose tetracetate	α-L-ribose tetracetate	+308	L	L
β-D-glucose pentacetate	β-D-mannose pentacetate	+113	L	L
β-cellobiose octacetate	β-4-β-glucosidomannose octacetate	−14	L	L
d. *Haloacetates* (in chloroform)				
1-fluo tetracetyl α-D-glucose	1-fluo tetracetyl α-D-mannose	+241	D	L
1-fluo heptacetyl α-cellobiose	1-fluo heptacetyl α-4-β-glucosidomannose	+108	D	L
1-chloro triacetyl β-L-arabinose	1-chloro triacetyl β-L-ribose	+221	D	L
1-chloro tetracetyl α-D-glucose	1-chloro tetracetyl α-D-mannose	+279	D	L
1-chloro heptacetyl α-cellobiose	1-chloro heptacetyl α-4-β-glucosidomannose	+135	D	L
1-bromo triacetyl β-L-arabinose	1-bromo triacetyl β-L-ribose	+250	D	L
1-bromo tetracetyl α-D-glucose	1-bromo tetracetyl α-D-mannose	+272	D	L
1-bromo tetracetyl α-D-galactose	1-bromo tetracetyl α-D-talose	+291	D	L
1-bromo heptacetyl β-cellobiose	1-bromo heptacetyl α-4-β-glucosidomannose	+125	D	L
1-iodo tetracetyl α-D-glucose	1-iodo tetracetyl α-D-mannose	+215	D	L
1-iodo heptacetyl α-cellobiose	1-iodo heptacetyl α-4-β-glucosidomannose	+106	D	L
e. *Methylated sugars* (in water)				
3,4,6 trimethyl α-D-glucose	3,4,6 trimethyl α-D-mannose	+157	D	L
2,3,4,6 tetramethyl α-D-glucose	2,3,4,6 tetramethyl α-D-mannose	+190	D	L
Methyl 2,3,4,6 tetramethyl β-D-glucose	Methyl 2,3,4,6 terramethyl β-D-mannose	+157	L	L
2. *Pairs differing in configuration at* C_3				
a. *Methyl glycosides* (in water)				
Methyl α-D-guloside	Methyl α-D-galactoside	−148	D	L
Methyl β-D-guloside	Methyl β-D-galactoside	−162	D	L
Methyl tetramethyl α-D-altroside	Methyl tetramethyl α-D-mannoside	+137	L	D

TABLE 4 (*cont'd*)

Sugar with OH at C_n in D config.	Sugar with OH at C_n in L config.	Diff. in rotation (D − L)	Config. of OH at adjacent atoms	
			at C_{n-1}	at C_{n+1}
b. *Acetylated methyl glycosides* (in chloroform)				
Methyl tetracetyl α-D-guloside	Methyl tetracetyl α-D-galactoside	−130	D	L
Methyl tetracetyl β-D-guloside	Methyl tetracetyl β-D-galactoside	−66	D	L
3. *Pairs differing in configuration at* C_4				
a. *Methyl glycosides and methylated sugars* (in water)				
Methyl α-D-altroxide	Methyl α-D-idoside	+48	D	D
Methyl α-D-glucoside	Methyl α-D-galactoside	−74	L	D
Methyl β-D-glucoside	Methyl β-D-galactoside	−62	L	D
Methyl 2-methyl β-D-glucoside	Methyl 2M-methyl β-D-galactoside	−75	L	D
2,3,4,6 tetramethyl β-D-glucose	2,3,4,6 tetramethyl β-D-galactose	−118	L	D
Methyl 2,3,4,6 tetramethyl β-D-glucoside	Methyl 2,3,4,6 tetramethyl β-D-galactoside	−94	L	D
3-methyl α-D-glucose	3-methyl α-D-galactose	−89	L	D
b. *Polyacetates* (in chloroform)				
α-D-glucose pentacetate	α-D-galactose pentacetate	−20	L	D
β-D-glucose pentacetate	β-D-galactose pentacetate	−73	L	D
α-D-mannose pentacetate	α-D-talose pentacetate	−52	L	D
α-D-xylose tetracetate	β-L-arabinose tetracetate	−185	L	†
c. *Haloacetates* (in chloroform)				
1-chloro tetracetyl α-D-glucose	1-chloro tetracetyl α-D-galactose	−169	L	D
1-chloro tetracetyl β-D-glucose	1-chloro tetracetyl β-D-galactose	−69	L	D
1-bromo tetracetyl α-D-glucose	1-bromo tetracetyl α-D-galactose	−159	L	D

* Data from Bates[38], Bourne and Peat[40], Bell[43], Bentley[43], Aspinall[44], Hayes and Newth[45], Maher[41,46], Conchie *et al.*[39] and Reeves[47].

† C_4 not asymmetric because sugar is a pentose.

is C_4. If the triad $C_3C_2C_1$ is changed from LLL to LDL then the rotation change is about +70°. Table 4B shows that analogous regularities exist among various types of sugar derivatives, although once again considerably more variation is observed with the derivatives than with the free sugars.

The regularities which Hudson discovered were at first regarded as examples of the van't Hoff superposition principle. It was thought that each asymmetric center in the molecule could be assigned a "partial rotation", and that when the configuration of a

[43] D. J. Bell, *Advanc. Carbohyd. Chem.* **6**, 11 (1951).
[44] G. O. Aspinall, *Advanc. Carbohyd. Chem.* **8**, 217 (1953).
[45] L. J. Hayes and F. H. Newth, *Advanc. Carbohyd. Chem.* **10**, 207 (1955).
[46] G. G. Maher, *Advanc. Carbohyd. Chem.* **10**, 273 (1955).
[47] R. E. Reeves, *J. Amer. Chem. Soc.* **72**, 1499 (1950).

center was inverted the sign of the partial rotation belonging to that center merely had to be reversed. The partial rotation of a center was assumed to be independent of the configurations about the other asymmetric centers in the molecule. It is now known that this cannot be the case, and indeed, the data reported in Tables 3 and 4 are totally inconsistent with such an assumption. Nevertheless, Tables 3 and 4 do demonstrate that numbers can be assigned to each center. These numbers depend on the configurations about adjacent carbon atoms, but they do not depend very much on the configurations about the remaining centers in the molecule. Therefore we may conclude from Hudson's rules that some form of the principle of pairwise interactions must operate in the carbohydrates and their derivatives. The contributions to the optical rotation arising from the interactions between groups located on a pair of adjacent carbon atoms often do not seem to be strongly influenced by the configurations of the groups elsewhere in the molecule.

(4) *Pairwise interactions and current empirical rules of optical rotation.* Whiffen[4], and more recently Brewster[5], have proposed interesting empirical rules by means of which they have been able to account for the signs, and in many instances even the magnitudes of the optical rotations of a large number of optically active compounds. Both workers have made extensive use of assumptions which are equivalent to the principle of pairwise interactions. Whiffen's approach is based upon the idea that bonds located on adjacent atoms, but arranged relative to one another in a skewed sense, will make a contribution to the optical rotation which depends on the nature of the bonds and the angle between the bonds. The optical rotation of a molecule is merely the sum of these contributions. When a given arrangement of a pair of bonds is replaced by its mirror image, the contribution of this pair is reversed in sign but not altered in magnitude. Brewster distinguishes between "atomic asymmetry", "conformational asymmetry", and "permolecular asymmetry"; the contributions of "conformational asymmetry" to the optical rotation of a molecule are dealt with in a manner very similar to that used by Whiffen, except that more explicit rules are given for computing the magnitudes of the contributions by given pairs of groups.

Both Whiffen and Brewster have included in their treatments only interactions between groups located on adjacent carbon atoms, arguing that the interactions giving rise to optical rotation decrease rapidly with distance between the interacting groups. It is, however, well known that in certain molecular conformations groups attached to non-adjacent carbon atoms may come very close to each other. For instance, two axial groups at positions 1 and 3 of a chair form of a cyclohexane ring are somewhat closer to one another than are the hydroxyls at positions 1 and 2 in any chair conformation. Chair conformations which result in more than one axial group on the same side of the ring are said to be unstable, but there may be instances in which they must occur. On the other hand, as we shall find by means of elementary symmetry arguments, pairwise interactions between symmetrical axial groups (such as chloride, methyl or freely rotating hydroxyl groups) on a chair form of a cyclohexane ring cannot contribute to the optical rotation, so in this particular instance the interactions between groups on non-adjacent atoms may be small. Yet it is always possible that, for instance, a pair of axial hydroxyls at C_1 and C_3 of a cyclohexane ring will not be able to take on an effective three-fold symmetry about the C—O bond, and that their interaction might therefore make a considerable contribution to the optical rotation. Furthermore, it is quite unlikely that the interactions between, say, an equatorial

group at C_1 and an axial group at C_3 of a cyclohexane ring will give a completely negligible contribution to the optical rotation. Therefore the neglect of interactions between non-adjacent atoms must be made with some caution, and a theory will be more accurate if these interactions are included. We shall see that it is frequently not difficult to do this and thus arrive at a somewhat more reliable set of predictions for the optical rotations of certain types of compounds than would be possible using the theories of Brewster and Whiffen.

Other empirical rules have been proposed which are equivalent to the assumption that optical rotation arises exclusively from four-way interactions between the groups attached to an asymmetric atom. This is true of the rules proposed by Crum-Brown and Guye (see Partington[48]) and by Marker.[3] It is also the case for the "atomic asymmetry" contribution discussed by Brewster.[5] Such rules would be most likely to be valid under conditions in which pairwise interactions vanish—that is, at high temperatures in compounds containing asymmetric carbon atoms which are not located in rings, and in compounds in which the groups attached to the asymmetric atoms are not bulky and do not interact strongly with one another by means of hydrogen bonds or other secondary forces. The theoretical approaches of Oseen,[49] Born,[50] de Malleman[51] and Boys[52] would also seem to be most appropriate under these conditions. Brewster has, indeed, shown that in a group of simple compounds which may fulfill the above conditions the sign of the rotation may be predicted successfully from the contribution of the atomic asymmetry alone. It should be pointed out, however, that four-way interactions would be expected to give smaller contributions to the optical rotation than three-way interactions. It would therefore seem more reasonable to start with the concept of three-way interactions in setting up an empirical theory of optical rotation that is to be applied to this type of compound.

III. SOME SIMPLE QUANTITATIVE RELATIONSHIPS BASED ON THE PRINCIPLE OF PAIRWISE INTERACTIONS

In this section we shall show that if the principle of pairwise interactions is valid, interesting relationships should exist between the optical rotations in certain groups of compounds. Many of the compounds that will be discussed have not been synthesized and may not be synthesized in the near future. They are considered as convenient examples to illustrate how the principle may be employed to correlate the optical rotations of configurationally related compounds. It will be evident that the principle may be useful in determining the absolute configurations and conformations of molecules, once we understand the limitations on its validity. The examples should make the application of the principle clear enough to enable the organic chemist to find other, and perhaps more interesting applications. Indeed, as has been mentioned, Whiffen and Brewster have already made extensive use of the principle in a restricted form. Our aim is to show that these restrictions are not necessary in many instances.

It should be emphasized, too, that the establishment of the limits of the validity of the principle of pairwise interactions is of paramount importance to the theoretical

[48] J. R. Partington, *An Advanced Treatise on Physical Chemistry* Vol. 4, p. 341. Longmans, Green, London (1953).
[49] C. W. Oseen, *Ann. Physik.* **48**, 1 (1915).
[50] M. Born, *Physik. Z.* **16**, 251 (1915).
[51] R. de Mallemann, *C.R. Acad. Sci., Paris.* **181**, 298 (1925).
[52] S. F. Boys, *Proc. Roy. Soc.* A **144**, 655, 675 (1934).

understanding of optical rotatory power. We need to know more about the effects of solvents on pairwise interactions, the extent to which solvent molecules participate in pairwise interactions, the influence of steric effects on pairwise interactions, and the relative magnitudes of pairwise and higher order interactions. At the moment this problem is at least as significant as the possibility that the principle may provide a useful tool for the study of molecular configurations and conformations in optically active substances. If progress is to be made with this aspect of the problem we cannot afford to be satisfied with the more limited assumptions of Whiffen and Brewster.

The application of the principle is illustrated in a particularly simple fashion by the three possible optically active methyl cyclopropane derivatives, *trans*-1,2-dimethyl

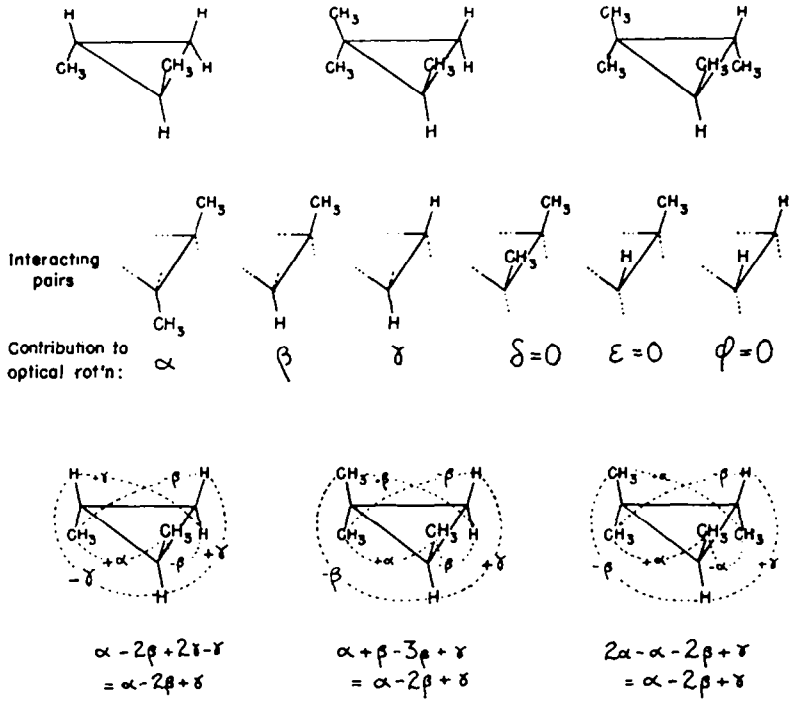


FIG. 11. Application of the principle of pairwise interactions to the three optically active methyl derivatives of cyclopropane.

cyclopropane, 1,1,2-trimethyl cyclopropane and *trans*-1,1,2,3-tetramethyl cyclopropane (see Fig. 11). It will be assumed that the bonds from the cyclopropane ring to the hydrogen atoms and methyl groups are symmetrically disposed on either side of the plane of the ring.*

Six types of pairwise interactions will occur between the groups attached to the ring (the interactions between the three carbon atoms in the ring could not, of course, give

* Since eclipsed configurations about carbon-carbon single bonds are unfavourable energetically, it is possible that this assumption is incorrect. The methylene groups in the cyclopropane ring would then spend much of the time rotated slightly to either side of the plane of the carbon atoms in the ring, and the bonds from the ring would not, at any given moment, be symmetrically disposed on either side of the plane of the ring. Nevertheless, each methylene group would be able to assume at least two equilibrium positions, and on averaging over these multiple positions the six bonds of attachment to the ring would become equivalent. Provided that the equilibrium positions were equally populated, the assumptions made here would then still be completely valid.

rise to any optical rotation because this triplet of atoms is superimposable on its mirror image). These are the interactions that occur between a pair of *trans* methyl groups (making a contribution α to the optical rotation), a *trans* methyl-hydrogen (contribution β), a *trans* hydrogen-hydrogen (contribution γ), a *cis* methyl-methyl (δ), a *cis* methyl-hydrogen (ε) and a *cis* hydrogen-hydrogen (φ). Since the axes of the groups in the three *cis* arrangements are coplanar, however, all of the *cis* pairs of groups are superimposable on their mirror images, so their interactions can give no contribution to the optical rotation, and $\delta = \varepsilon = \varphi = 0$. When the non-vanishing interactions in the three molecules are added together, assuming the absolute configuration shown in Fig. 11, the remarkable result is obtained that all three molecules should have the same rotation, $\alpha - 2\beta + \gamma$. The same result will be true if instead of methyl groups any other axially symmetric groups are present on the ring. Unfortunately such compounds appear to be difficult to prepare in optically pure form, so this result is at the moment of little more than academic interest as a test of the principle of pairwise interactions.

A somewhat similar situation is found for the nine non-enantiomorphic optically active polymethylcyclobutanes (Fig. 12). In this case there is evidence that the ring is not planar (Lemaire and Livingston[53], Dunitz and Schomaker[54], Owen and Hoard[55]) but it is probably safe to assume that the ring undergoes oscillations which make the bonds from the ring in effect symmetrically disposed on either side of the average plane of the ring. (It is difficult to agree with Brewster's contention that in the puckered cyclobutane rings the interferences across the ring would be sufficiently great to eliminate some of the conformations.) Pairwise interactions between methyl groups or hydrogen atoms attached to carbon atoms that lie across the ring from each other will vanish because these atoms and groups are coplanar. Consequently, interactions between groups attached to adjacent atoms on the ring are the only ones which can give rise to optical rotation. As was the case for the methyl cyclopropanes, only interactions between groups in the *trans* relationship to each other need to be considered. Three types of interactions are therefore present in these molecules: The *trans* methyl-methyl, the *trans* methyl-hydrogen, and the *trans* hydrogen-hydrogen. The contributions of these interactions to the rotation are again denoted by α, β and γ, respectively. (The values of these constants will presumably be slightly different in the cyclobutanes and in the cyclopropanes because the spatial relationships are not quite the same.) It is seen from Fig. 12 that seven of these optically active compounds should have the same optical rotation, the eighth should have double the rotation of the rest, and the ninth should have zero optical rotation (despite the fact that it is not superimposable on its mirror image). Of course, the same relationships should hold among any set of derivatives of cyclobutane involving axially symmetric groups.

The thirty-five non-enantiomorphic optically active polymethyl derivatives of cyclopentane provide us with a slightly more complicated example which may also be dealt with by means of the principle of pairwise interactions. The cyclopentane ring is known to be non-planar, but it is also known that the distortions away from planarity are highly mobile and that in cyclopentane itself there exists a plane such that, if a time exposure is made of a given molecule, any one atom in the molecule will spend an equal

[53] H. P. Lemaire and R. L. Livingston, *J. Chem. Phys.* **18**, 569 (1950).
[54] J. D. Dunitz and V. Schomaker, *J. Chem. Phys.* **20**, 1703 (1954).
[55] T. B. Owen and J. L. Hoard, *Acta Cryst.* **4**, 172 (1951).

amount of time in equivalent positions on either side of this plane (Kilpatrick *et al.*[56]). The average positions of the bonds joining groups to the ring will therefore be symmetrical with respect to this plane. Thus in cyclopentane the molecule possesses an effective plane of symmetry in the plane of the ring. We may assume that this state of affairs will remain true in cyclopentane derivatives provided that the groups attached

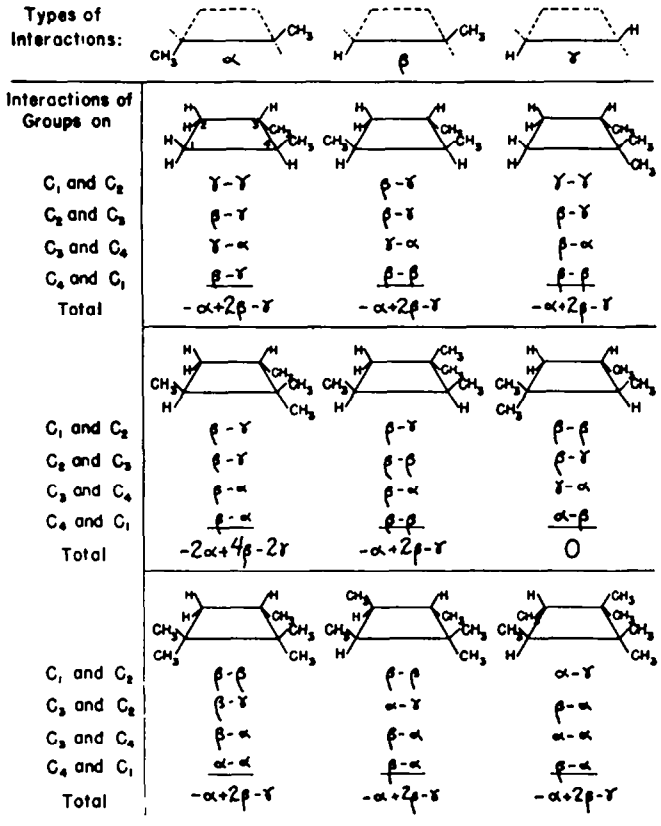


FIG. 12. Application of the principle of pairwise interactions to the nine optically active methyl derivatives of cyclobutane.

to the ring are not too bulky and that they do not approach too closely to one another as the ring undergoes its twisting motions from one conformation to another. This assumption will be far from true if the cyclopentane ring is fused to other rings, especially in a trans conformation.

Starting with this assumption it is readily shown that the optical rotations of the 35 non-enantiomorphic optically active methylated derivatives of cyclopentane ought to be related to one another as shown in Table 5. We see that all of these rotations should be expressible in terms of but two empirical constants (viz., the rotations of *trans*-1,2-dimethyl cyclopentane and *trans*-1,3-dimethyl cyclopentane).

The optical rotations of derivatives of cyclohexane are more complicated to discuss

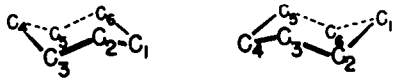
[56] J. E. Kilpatrick, K. S. Pitzer and R. Spitzer, *J. Amer. Chem. Soc.* **69**, 2483 (1947).

TABLE 5. OPTICAL ROTATIONS OF THE METHYL CYCLOPENTANES

Compound*	$[M]_D$	Compound*	$[M]_D$
1/2 dimethyl	A	1,2/2,3,4 pentamethyl	2A + B
1/3 dimethyl	B	1,2,3,4/2 pentamethyl	−B
1,2/2 trimethyl	A	1,1,2,3,4 pentamethyl	A
1,3/3 trimethyl	B	1,4/1,2,3 pentamethyl	B
1,2/3 trimethyl	A + B	1,2,4/1,2,5 hexamethyl	−B
1,4/2 trimethyl	A − B	1,2,5/1,2,3 hexamethyl	2A + B
1,3/1,2 tetramethyl	−B	1,2,3/1,4,5 hexamethyl	−A − B
1,2/2,3 tetramethyl	2A + B	1,4/1,2,3,5 hexamethyl	B
1,2/3,4 tetramethyl	A + B	1,5/1,2,3,4 hexamethyl	A
1,2,4/3 tetramethyl	B	1,3,4/1,4,5 hexamethyl	A
1,2,3/4 tetramethyl	A	1,3,4,5/1,4 hexamethyl	A − B
1,4/1,2 tetramethyl	A	1,2,3/1,2,3,4 heptamethyl	A
1/1,2,4 tetramethyl	A − B	1,3,4/1,3,4,5 heptamethyl	B
1,2,3/1,2 pentamethyl	−A − B	1,2,5/1,2,3,4 heptamethyl	A + B
1,3,4/1,2 pentamethyl	−B	1,3,4/1,2,4,5 heptamethyl	A − B
1,3/1,2,4 pentamethyl	A − 2B	1,2,3,5/1,2,3,4 octamethyl	A
1,3,5/1,2 pentamethyl	A	1,2,3,4/1,3,4,5 octamethyl	B
1,3/1,2,5 pentamethyl	−A		

* The configurations of the methyl groups are indicated in the same fashion as are those of the hydroxyl groups in Table 1B.

because the ring can exist in two stable chair conformations. Using the notation of Reeves[47,57] these will be denoted by the symbols 1C and C1:



C1 1C

It will be seen that in conformation C1 the axial groups at C_1, C_3 and C_5 point downward and the axial groups at C_2, C_4 and C_6 point upward, whereas in conformation 1C the axial groups at C_1, C_3 and C_5 point upward and those at C_2, C_4 and C_6 point downward. The axial groups in conformation 1C become equatorial groups in C1 and *vice versa*. Since the axial bonds are all parallel, the contributions to the optical rotation by pairwise interactions between any pair of symmetrical axial groups, such as a halide or a methyl or a freely orienting hydroxyl, must vanish. Furthermore, equatorial groups at ring atoms 1 and 3, or 2 and 4, or 3 and 5, or 4 and 6, or 5 and 1, are coplanar, so that the contributions by any pair of equatorial groups at these positions must also vanish. It is found that, as a consequence of these geometrical simplifications, the optical rotations of all polymethyl cyclohexanes should be expressible in terms of two empirical constants—namely the rotation of the conformer of *trans*-1,2-dimethyl cyclohexane in which both methyl groups are equatorial, and the rotation of either of the two chair conformers of *trans*-1,3-dimethyl cyclohexane (both conformers of the latter turn out to have the same rotation, according to the principles set forth here).

It is interesting to consider these conclusions in the light of the known rotations of

[57] R. E. Reeves, *Advanc. Carbohyd. Chem.* **6**, 107 (1951).

the polyhydroxy cyclohexanes, as summarized in Table 6. If the hydroxyl groups in these compounds exist with equal probability in the three equilibrium positions about each carbon-oxygen bond, they can be treated as geometrically equivalent to methyl groups. The rotations calculated using this assumption for each of the chair forms of the known optically active hydroxy cyclohexanes are shown in Table 6. The observed rotations for these compounds are shown in the Table, and it is seen that these rotations are impossible to reconcile with those expected if the two chair forms were in all instances present in equal amounts. (For instance, if 1,2,4/3,5,6 hexitol existed as a mixture of equal amounts of the two chair forms, it should have no optical rotation due to pairwise interactions, yet this compound has the largest rotation of the entire series.) On the other hand, quite good agreement is obtained if we accept Whiffen's assumptions that (1) only that chair form will be present which has the fewest axial hydroxyl groups, and (2) the optical rotation of *trans*-1,3-cyclohexanediol can be neglected in comparison with that of *trans*-1,2-cyclohexanediol. The appreciable rotation of the 1,3,4/2,5 pentitol indicates, however, that the rotation of the 1/3 diol may be of the order of 20 per cent of the rotation of the 1/2 diol.

It would be most interesting to have measurements of the rotations of these compounds at elevated temperatures in inert solvents. We should expect that the rotations of 1/3-cyclohexanediol and 1,3,4/2,5 cyclohexane-pentitol would be small and independent of temperature, whereas all of the other rotations should decrease in magnitude with temperature as the two chair forms tended to occur in equal amounts. The rotation of 1,3,4/2,5 pentitol should change sign at high temperatures. Unfortunately the data at present available do not provide a very sensitive test for the principle of pairwise interactions, since it is not known to what extent the observed deviations from the predicted values are caused by non-axial symmetry of the hydroxyl groups, by violations of Whiffen's assumptions, or by interactions with the solvent. These data do, however, suggest that the hydroxyl groups in these compounds must be nearly symmetrical, and that one or the other of the two chair forms is rather strongly preferred at room temperature.

The substitution of a carbon in a cyclohexane ring by an oxygen atom should not greatly alter the geometry of the ring. The six-membered pyranose rings of the sugars should therefore exist in two chair forms that resemble those of cyclohexane, and the vicinal actions between hydroxyl groups attached to the pyranose ring should not be very different from the vicinal actions between hydroxyl groups located at equivalent positions on the cyclitols. It is interesting to compare the shifts in rotation that are tabulated in Tables 3 and 4 with the shifts that would be expected in the light of the discussion of the cyclitols.

Let us say that it is carbon atom C_6 in the ring that is replaced by oxygen. A complication arises because this substitution makes it possible for contributions to the optical rotation to arise from interactions between the ring and groups attached to the ring at positions C_1, C_2, C_4 and C_5. The complication can be avoided for the moment if we consider at first only those groups that are attached to the ring at position C_3, since the interactions between the pyranose ring and a freely rotating hydroxyl group at C_3 cannot make any contribution to the optical rotation. Therefore the change in optical rotation that results from a shift in the hydroxyl group from the D to the L configuration at C_3 should involve the same interactions as those that occur in the cyclitols. The discussion is greatly simplified if we assume that the groups on C_3

TABLE 6. OPTICAL ROTATIONS OF SOME CYCLITOLS

Compound	Conformation	No. axial OH groups		Calculated rotation	Calculated rotation based on:*		Calculated by Whiffen[4]	Observed rotation†
		Above ring	Below ring		Assumption I	Assumption II		
1/2 diol	C1	0	0	A	A/2	A	−45	−48
	1C	1	1	O				
1/3 diol	C1	0	1	B	B	B	0	—
	1C	1	0	B				
1,2/3 triol	C1	1	1	−A + B	$\frac{A}{2}$ + B	2A + B	−90	−92
	1C	1	0	2A + B				
1,2,3/4 tetrol	C1	1	0	A + B	$\frac{A}{2}$ + B	A + B	−45	−49
	1C	2	1	B				
1,2,4/3 tetrol	C1	2	1	−A + B	B	A + B	−45	−57
	1C	1	0	A + B				
1,3/2,4 tetrol	C1	0	0	A	A/2	A	−45	−43
	1C	2	2	O				
1,2/3,4 tetrol	C1	1	1	−2A + 2B	$\frac{A}{2}$ + 2B	‡	‡	−110
	1C	1	1	3A + 2B				
1,2,4/3,5 pentitol	C1	2	2	−A	A/2	2A	−90	−91
	1C	1	0	2A				
1,2,3,5/4 pentitol	C1	1	0	B	B	B	0	−9
	1C	3	1	B				
1,3,4/2,5 pentitol	C1	1	1	−A − B	$\frac{A}{2}$ − B	− A− B	+45	+41
	1C	2	1	2A − B				
1,2,4/3,5,6 hexitol	C1	2	2	−3A	O	3A	−135	−117
	1C	1	1	3A				

* Assumption I: Conformations 1C and C1 present in equal amounts.
Assumption II: Only that conformation is present which has the fewest axial groups. Whiffen's calculation was based on this assumption; Whiffen also assumed A = −45°, B = 0.

† Data from Angyal and Anderson[12], Wilson and Read[58], Posternak, Friedli and Reymond[59,60] and Posternak and Reymond[61].

‡ Since both chair forms have the same number of axial groups, one would expect a rotation of A/2 = −23° using Whiffen's results. If C1 alone were present one would expect a rotation of −2A = +90°, and if 1C alone were present the rotation would be 3A = −135. The observed rotation of −110° would indicate that the substance is predominantly in the 1C conformation but it is not readily evident why this should be so.

[58] N. A. B. Wilson and J. Read, *J. Chem. Soc.* 1269 (1935).
[59] T. Posternak, H. Friedli and D. Reymond, *Helv. Chim. Acta* **36**, 251 (1953).
[60] T. Posternak, H. Friedli and D. Reymond, *Helv. Chim. Acta* **38**, 205 (1955).
[61] T. Posternak and D. Reymond, *Helv. Chim. Acta* **38**, 195 (1955).

interact predominantly with groups that are located on the adjacent carbon atoms, C_2 and C_4; this means that we shall follow Whiffen in assuming that the interactions involved in the constant B of Table 6 will be neglected. We have seen that this assumption leads to good results with the cyclitols, even though it cannot be exactly correct. Under these conditions it is readily seen that, provided the ring conformation remains fixed as either Cl or 1C, a change in configuration at $C_2C_3C_4$ from DDD to DLD or from LDL to LLL should result in no change in optical rotation. Unfortunately there is only one example with which to test this production, namely the change in rotation in going from β-D-glucose to β-D-allose, which amounts to $-34°$.

The failure of this rotation change to vanish might be explained in several ways. Perhaps the interactions between the groups at C_3 with the groups at C_1 and C_5 are not negligible. It seems, however, unlikely that these interactions would be as large as 34°, in view of the considerably smaller upper limit to the value of B in the cyclitols. An alternative possibility is that β-D-glucose and β-D-allose do not have the same chair conformation. This disagrees with the considerations of Reeves[47], which indicate that both sugars are probably in the Cl conformation. (The correctness of Reeves' views also gains support in what follows.) The only other explanation that seems plausible (aside, perhaps, from an error in the rotation of β-D-allose) is that in one of these two compounds—probably β-D-allose—there is for some reason a restricion in the ability of the hydroxyl groups to assume axial symmetry about the bonds that hold them to the ring.

It is also readily seen that, again assuming that the constant B in Table 6 can be neglected, a change in configuration at $C_2C_3C_4$ from LDD to LLD will produce a change in rotation of $-3A$ if the ring conformations for both configurations is Cl, and $+3A$ if the ring conformations are both 1C, A being the same constant as that appearing in Table 6. Furthermore, a change from DDL to DLL at these positions will produce a rotation change of $+3A$ if the rings are in the Cl conformation, and $-3A$ if they are in the 1C conformation.

Reeves[47] has given reasons for believing that the Cl conformation is almost exclusively present in the α and β forms of D-glucose, D-galactose, D-mannose, D-gulose, D-talose, D-ribose, D-xylose and L-arabinose. The pyranose ring of α-D allose is also believed to exist in the Cl conformation. On the other hand, α- and β-D-altrose, D-idose and D-lyxose, and β-D-allose probably do not exist exclusively in the Cl conformation.

The following rotation changes are found in Table 4 for pairs of sugars and sugar derivatives which are believed to exist in the Cl conformation, and which have the configurations DDL and DLL at $C_2C_3C_4$:

α-D-gulose, α-D-galactose	$-157°$
β-D-α-glucoheptose, β-D-α-mannoheptose	$-157°$
Methyl α-D-guloside, methyl α-D-galactoside	$-148°$
Methyl β-D-guloside, methyl β-D-galactoside	$-162°$
Methyl tetracetyl α-D-guloside, methyl tetracetyl α-D-galactoside	$-130°$
Methyl tetracetyl β-D-guloside, methyl tetracetyl β-D-galactoside	$-66°$

(D-α-glucoheptose and D-α-mannoheptose have pyranose rings in which the hydroxyl

configurations are identical with those in D-gulose and D-galactose, respectively.) If we take Whiffen's value of $-45°$ for A, then a rotation change of $+3A = -135°$ would be expected in these compounds. This is not very different from the observed values, even in the methyl glycosides, and surprisingly enough the correct sign and the correct order of magnitude are obtained even for the acetylated methyl glycosides, whose rotations were measured in chloroform.

The conformation change LDD to LLD at $C_2C_3C_4$ brings about the following rotation changes:

β-D-altrose, β-D-mannose	$+90°$
β-celtrobiose, β-(4-β-glucosido)-D-mannose	$+71°$
Methyl tetramethyl α-D-altroside, methyl tetramethyl α-D-mannoside	$+137°$

(Celtrobiose is 4-(β-glucosido)-D-altrose.) The predicted rotation change for sugars in the Cl conformation is $-3A = +135°$. In spite of the fact that D-altrose is not believed to exist exclusively in the Cl conformation, the observed shifts in rotation are correct in sign and not far off in order of magnitude.

Similar considerations can be applied to the changes in rotation that result when configurations are changed at positions C_1 and C_2 in the pyranose sugars. Let us assume that when the ring is in the conformation Cl a change in the configuration at C_2 from D to L produces a change R_2 in the contribution to the optical rotation arising from the interaction between the groups at C_2 and the ring. Then it is easily seen that a change in configuration at $C_1C_2C_3$ fromDDD to DLD or from LDL to LLL should produce a change in rotation equal to R_2, provided, as before, that we neglect interactions of the type that lead to the quantity B in Table 6. The observed rotation changes are as follows (changes which involve sugars not believed to be exclusively in the Cl conformation are given in brackets):

DDD → DLD:	
[Methyl α-D-guloside, methyl α-D-iodoside	$+31°$]
LDL → LLL:	
β-D-glucose, β-D-mannose	$+64°$
β-D-galactose, β-D-talose	$+71°$
[α-L-arabinose, α-L-ribose	$+85°$]
β-cellobiose, β-(4-β-glucosido)-D-mannose	$+71°$
Methyl β-D-glucoside methyl β-D-mannoside	$+68°$
Methyl β-D-glucomethyloside, methyl β-D-rhamnoside	$+72°$
[Methyl β-D-xyloside, methyl β-D-lyxoside	$+102°$]
Phenyl β-D-glucoside, phenyl β-D-mannoside	$0°$
[α-L-arabinose tetracetate, α-L-ribose tetracetate	$+308°$]
β-D-glucose pentacetate, β-D-mannose pentacetate	$\div 113°$
β-cellobiose octacetate, β-(4-β-D-glucosido)-mannose octacetate	$-14°$
Methyl 2,3,4,6 tetramethyl β-D-glucose, methyl 2,3,4,6 tetramethyl α-D-mannose	$+157°$

The results show that R_2 has a value of about $+70°$; all of the observations that differ appreciably from this value involve compounds that are not exclusively in the Cl conformation or are heavily acetylated or methylated.

A change at $C_1C_2C_3$ from DDL to DLL results in the following changes in rotation (as above, changes involving sugars not believed to be exclusively in the Cl conformation are given in brackets):

[α-D-xylose, α-D-lyxose	+132°
α-D-glucose, α-D-mannose	+149°
α-D-galactose, α-D-talose	+149°
α-L-β-guloheptose, α-L-α-guloheptose	+157°
α-D-α-mannoheptose, α-D-β-mannoheptose	+170°
α-D-glucomethylose, α-D-rhamnose	+104°
[Methyl β-L-arabinoside, methyl β-L-riboside	+228°]
[Methyl α-D-xyloside, methyl α-D-lyxoside	+154°]
Methyl α-D-glucoside, methyl α-D-mannoside	+148°
Methyl α-cellobiose, methyl α-(4-β-glucosido)-D-mannose	+181°
Methyl α-D-glucomethyloside, methyl α-D-rhamnoside	+153°
Phenyl α-D-glucoside, phenyl α-D-mannoside	+171°
Various acetates	+46° to +283°
Various haloacetates	+106° to +291°

A consideration of the molecular geometry in the Cl conformation shows that one would predict a rotation change of $R_2 - 3A$ for this group of compounds. Setting $R_2 = +70°$ and $A = -45°$, this gives a predicted change of +205°—somewhat greater than is observed, but of the correct sign and order of magnitude, even for the methyl and phenyl glycosides and for the methylated and acetylated derivatives.

For a sugar in the Cl conformation a configuration change from LDD to LLD at $C_1C_2C_3$ would be expected to produce a change in rotation of $R_2 + 3A = -70° - 135° = -65°$. The examples listed in Table 4 all involve sugars that are not entirely in the Cl conformation, but in spite of this the values are quite close to the expected one:

[β-D-allose, β-D-altrose	−59°]
[β-D-α-glucoheptose, β-D-β-glucoheptose	−60°]
[Methyl β-D-guloside, methyl β-D-idoside	−68°]

It is also possible to interpret the changes in optical rotation accompanying a configuration change at position C_1, the glycosidic carbon atom. A hydroxyl group at C_1 will, according to the assumptions made in these paragraphs, contribute to the rotation (a) through its interaction with the ring, and (b) through its interaction with the groups at position C_2. Let R_1 denote the contribution of the ring interaction (a) to the change in rotation when a hydroxyl at C_1 is converted from the D configuration to the L configuration, the ring conformation being Cl. Consideration of the ring geometry in the usual manner shows that if the ring conformation is Cl and the hydroxyl at C_2 is in the D configuration, then interaction (b) will change by $-2A$ when the hydroxyl at C_1 is changed in configuration from D to L (i.e. from α to β in the more usual nomenclature of groups at the glycosidic carbon atom). On the other hand, if the hydroxyl at C_2 is L and the ring conformation is Cl,

then interaction (b) will change by $+A$ when the configuration at C_1 is changed from D to L. Thus we see that if the configuration at atoms C_1C_2 is changed from DD to LD in a sugar whose ring is in the Cl conformation, the optical rotation should change by $R_1 - 2A$, whereas a configuration change at the same positions from DL to LL will change the rotation by $R_1 + A$. As seen in Table 3, free sugars in the "glucose class" undergo a configuration change of the former type (DD to DL) in transforming from the α to the β form, and the accompanying change in optical rotation is about $+175°$ for the free sugars. Sugars in the "mannose class" undergo a configuration change of the DL to LL type in going from the α form to the β form, and the optical rotation change (where both forms are in the Cl ring conformation) is about $+80°$. Thus we expect that

$$R_1 - 2A = +175°$$

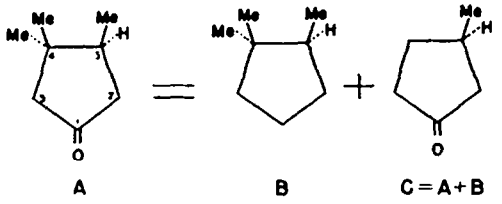
$$R_1 + A = +80°$$

which leads to the results, $R_1 = +112°$, $A = -32°$. This value of A is in only fair agreement with that obtained from the study of the cyclitols (viz., $A = -45°$). It is interesting to note that, in contrast with the findings of many other sugar derivatives in Table 4, groups other than free hydroxyls (e.g. methoxy, phenoxy and acetyl) give considerably different values of A from that just found with the unsubstituted sugars.

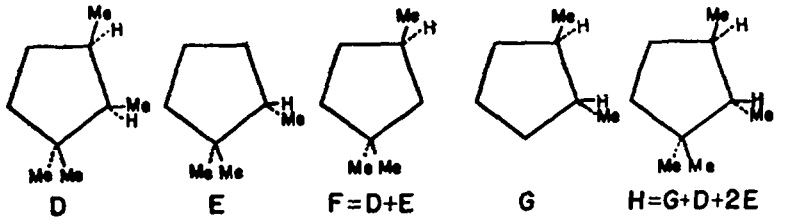
In summary, it appears that the rotation changes in the sugars are at least roughly consistent with the observed rotations of the cyclitols, indicating that the interactions between hydroxyl groups are similar in magnitude, though not exactly the same. It is evident that the principle of pairwise interactions cannot lead to very accurate predictions of the rotations of the sugars, possibly because of restricted rotation of the hydroxyl groups and solvation effects that vary irregularly with configuration.

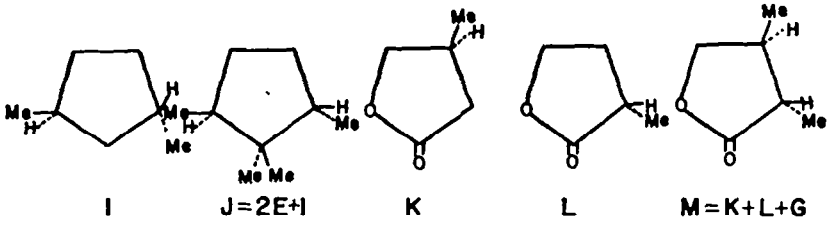
Fig. 13 shows a number of further relationships between the optical rotations of compounds containing five-membered rings. These relationships are all derived assuming that the ring has an effective plane of symmetry in the plane of the ring, as previously discussed. Figs. 14 and 15 show relationships involving some compounds with fused five- and six-membered rings.

Many bicyclo compounds have the advantage that the ring systems are relatively rigid, so that uncertainties arising from the possibility of several ring conformations, or even from distortions of otherwise stable symmetrical ring conformations, do not arise. Numerous relationships may be deduced for the optical rotations of such compounds, and it is probably here that the best tests of the principle of pairwise interactions should be sought. For instance, in the dilactones A and B shown in Fig. 16 the optical rotations should be independent of the nature of the groups R_1, R_2, R_3 and R_4 so long as these groups are axially symmetric (H, CH_3, halide or CN) or so long as they can acquire axial symmetry by rotation about the bonds joining them to the bridgehead carbon atoms (ethyl, hydroxyl). This results from the fact that none of the pairwise interactions between either R_1 or R_2 and the rest of the molecule, or between R_1 and R_2 themselves, can result in any contribution to the optical rotation, since each pair of groups involving R_1 or R_2 as one member of the pair either may be superimposed on its own mirror image or it is counteracted by another pair which bears a mirror image

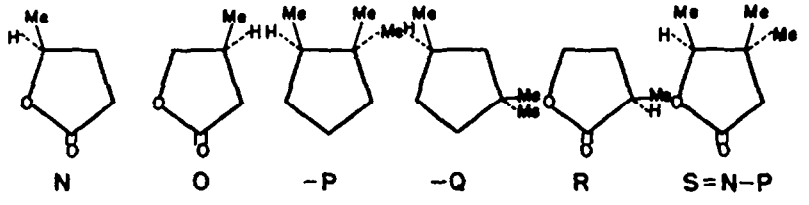


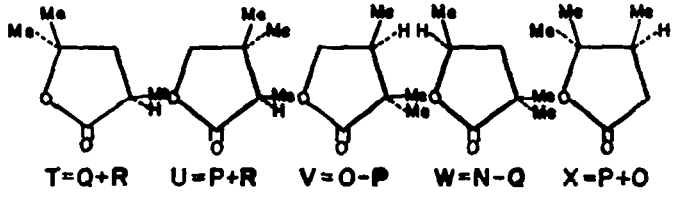
13 (a)





13 (b)





13 (c)

FIG. 13a,b,c. Relationships between the optical rotations of compounds containing five-membered rings.

relationship to it. In the compounds C, D, E and F in Fig. 16 it is easily seen that the rotations should be related by

$$C = D = \tfrac{1}{2}(E + F)$$

where the R_i are any axially symmetric groups.*

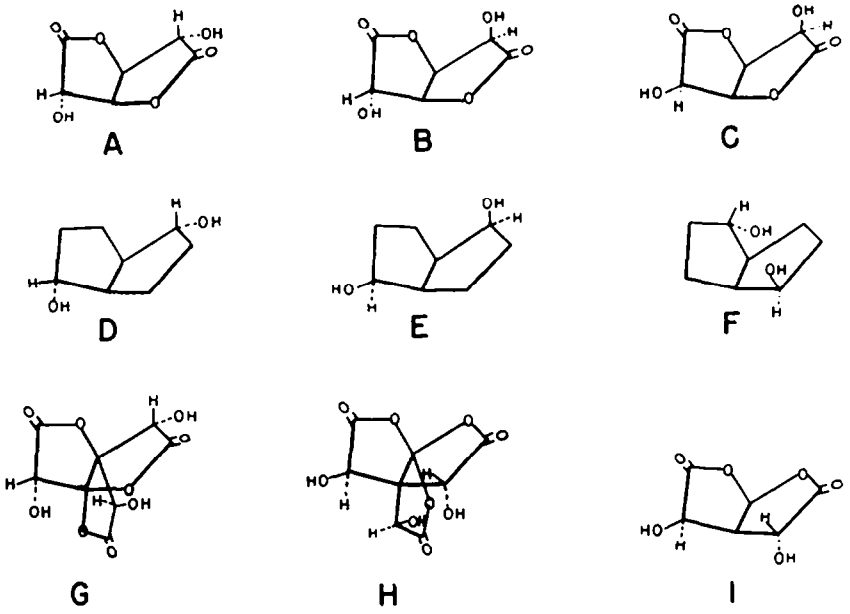


FIG. 14. Compounds containing fused five-membered rings. If the principle of pairwise interactions is valid, one should expect the following relationships:

$$A + C = 2B + D - E + F$$
$$A + I = B + G + H$$

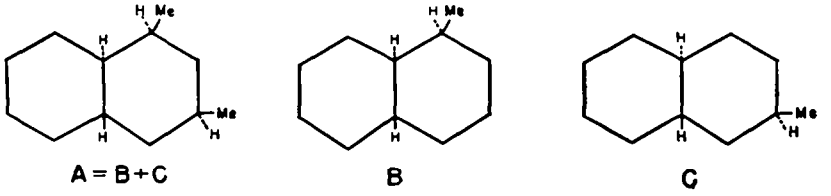


FIG. 15. Expected relationship between the optical rotations of compounds containing fused six-membered rings.

The bicyclo compounds related to camphor offer a particularly fruitful area for the application of the principle of pairwise interactions because their rigidly cross-braced frame-work produces a well defined and fairly symmetrical structure which should not change appreciably when groups are substituted on it at different positions. Furthermore, the optical rotations of many of these compounds are known, so that some of the expected relationships may be tested.

* Turner, Meador and Winkler[62] have pointed out that these bicyclo compounds are not entirely rigid, but that the upper half of the molecule may twist through an appreciable angle relative to the lower half without distortion of the bond angles. Mr. F. Fong[63] has shown, however, that when account is taken of the barrier to internal rotation about the carbon-carbon bonds in this molecule, the symmetrical, untwisted form is probably the most stable. J. J. MacFarlane and I. G. Ross (*J. Chem. Soc.* 4169 (1960) have also shown from infra-red and Raman spectra that the molecule is probably not twisted.

[62] R. B. Turner, W. R. Meador and R. E. Winkler, *J. Amer. Chem. Soc.* 79, 4121 (1957).
[63] F. Fong, personal communication.

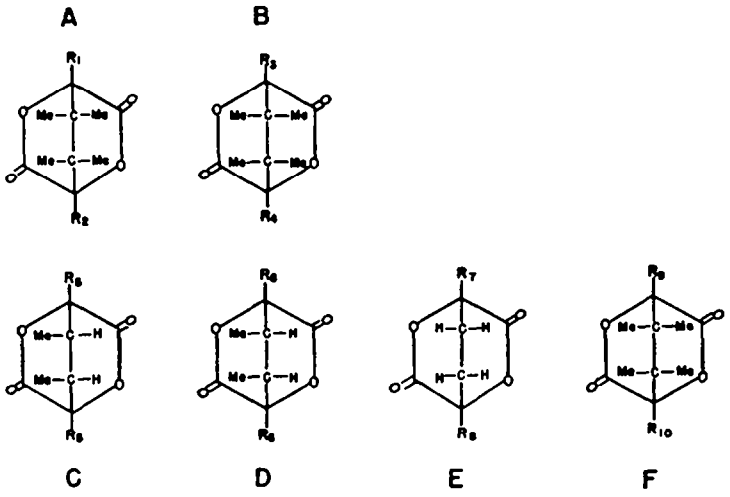


FIG. 16. Compounds containing fused ring systems. See text for relationships between the optical rotations.

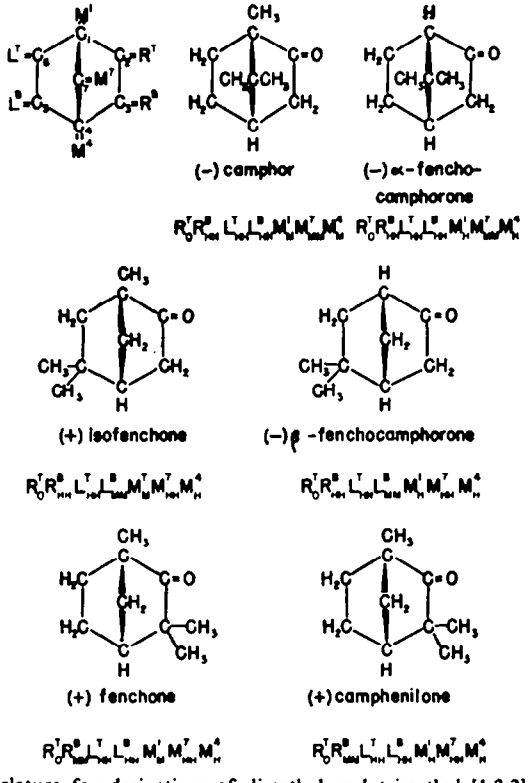


FIG. 17. Nomenclature for derivatives of dimethyl and trimethyl [1.2.2] bicycloheptanes.

The derivation of relationships between the rotations of compounds of this type is facilitated by adopting a simple notation. The positions of the seven ring carbon atoms in the bicyclo [1.2.2] heptanes are given the symbols shown in Fig. 17, R^t referring to the atom on the right that lies toward the top of the paper (generally designated as C_2),

R_b referring to the atom on the right that lies toward the bottom (generally designated as C_3), M^1, M^4 and M^7 referring to the atoms C_1, C_4 and C_7 that lie in the mid-plane of the molecule and L^t and L^b referring to the atoms C_5 and C_6 that lie on the left and, respectively, toward the top and bottom of the page. It will be assumed that the framework has a configuration such that, if carbon atoms C_2, C_3, C_5 and C_6 are in the plane of the page, then C_1, C_4 and C_7 lie above the page, toward the reader. These symbols are in addition given subscripts which describe the atoms or groups that are attached to the corresponding positions in the ring: O for an oxygen atom, as in a ketone, M for a methyl group, MM for two methyl groups, HH for two hydrogen atoms, etc. Note that only one monovalent group can be attached to the bridgehead positions, M^1 and M^4, whereas two monovalent groups or one bivalent group may be attached elsewhere. The various derivatives of bicyclo [1.2.2] heptane can then be indicated by symbols as follows. Levorotatory camphor is $R^t_O R^b_{HH} L^t_{HH} L^b_{HH} M^1_M M^7_{MM} M^4_H$, and dextrorotatory fenchone is $R^t_O R^b_{HH} L^t_{HH} L^b_{MM} M^1_M M^7_{HH} M^4_H$ (see Fig. 17 for structural formulae).

According to the principle of pairwise interactions the optical rotation is the sum of the effects of the different parts of the molecule on each other. For instance, in camphor the group of atoms symbolized by M^1_M (the upper bridgehead with its methyl group) interacts with the group of atoms symbolized by R^t_O (the carbonyl group at position 2) to produce a contribution to the optical rotation that will be denoted by $[M^1_M, R^t_O]$. The optical rotation of (−) camphor* will be the sum of all interactions between the seven symbols that represent camphor:

$$\begin{aligned}[M] = {} & [R^t_O, R^b_{HH}] + [R^t_O, L^t_{HH}] + [R^t_O, L^b_{HH}] + [R^t_O, M^1_M] + [R^t_O, M^7_{MM}] + [R^t_O, M^4_H] \\ & + [R^b_{HH}, L^t_{HH}] + [R^b_{HH}, L^b_{HH}] + [R^b_{HH}, M^1_M] + [R^b_{HH}, M^7_{MM}] + [R^b_{HH}, M^4_H] \\ & + [L^t_{HH}, L^b_{HH}] + [L^t_{HH}, M^1_M] + [L^t_{HH}, M^7_{MM}] + [L^t_{HH}, M^4_H] + [L^b_{HH}, M^1_M] \\ & + [L^b_{HH}, M^7_{MM}] + [L^b_{HH}, M^4_H] - [M^1_M, M^7_{MM}] + [M^1_M, M^4_H] + [M^7_{MM}, M^4_H]\end{aligned}$$

It should be pointed out that although the symbol [A,B] does not correspond to ordinary multiplication of the quantities A and B, it does possess some of the characteristics of ordinary multiplication. For instance it is true that

$$[A,B] = [B,A]$$

for any pair of symbols A and B. It is also possible to define the operation

$$[A,(B + C)] = [A,B] + [A,C]$$

This permits us to write the pairwise contributions to the optical rotation of camphor in the somewhat more compact form

$$\begin{aligned}[M] = {} & [R^t_O, (R^b_{HH} + L^t_{HH} + L^b_{HH} + M^1_M + M^7_{MM} + M^4_H)] \\ & + [R^b_{HH}, (L^t_{HH} + L^b_{HH} + M^1_M + M^7_{MM} + M^4_H)] \\ & + [L^t_{HH}, (L^b_{HH} + M^1_M - M^7_{MM} + M^4_H)] + [L^b_{HH}, (M^1_M + M^7_{MM} + M^4_H)] \\ & + [M^1_M, (M^7_{MM} + M^4_H)] + [M^7_{MM}, M^4_H]\end{aligned}$$

* The absolute configurations of camphor and other bicyclo derivatives considered here have been assigned by a study of the reactions through which these substances may be interconverted (Hückel[64]; Clough[65]; Jacob *et al.*[66]).

[64] W. Hückel, *J. Prakt. Chem.* **157**, 225 (1941).
[65] F. B. Clough, Ph.D. Dissertation, Princeton University (1950).
[66] G. Jacob, G. Ourisson and A. Rassat, *Bull. Soc. Chim. Fr.* 1374 (1959).

Further simplifications are possible because certain of the pairwise contributions vanish as a result of the symmetry of the molecule. This is true of all of the interactions of M^1_M, M^7_{MM} and M^4_H with each other (that is, all of the interactions among the atoms in the portion CH_3—C—$C(CH_3)_2$—CH of the camphor molecule), since all of the pairs of atoms and groups concerned are superimposable on their mirror images. The interactions $[L^t_{HH},L^b_{HH}]$, $[R^t_{HH},L^t_{HH}]$, $[R^b_{HH},L^b_{HH}]$, $[R^t_{HH},R^b_{HH}]$, and $[R^t_O,R^b_{HH}]$, also make no contribution to the optical rotation. Furthermore, certain interacting pairs are mirror images of other interacting pairs, so their contributions to the optical rotation differ only in sign. Thus

$$[M^1_M,R^b_{HH}] = -[M^1_M,L^b_{HH}]$$

$$[R^b_{HH},L^t_O] = -[L^b_{HH},R^t_O]$$

$$[R^t_{HH},L^b_{HH}] = -[R^b_{HH},L^t_{HH}]$$

$$[R^t_O,L^t_{HH}] = -[L^t_O,R^t_{HH}]$$

$$[R^b_{HH},L^b_{MM}] = -[L^b_{HH},R^b_{MM}]$$

When these simplifications are taken into account we find that the pairwise contributions to the rotation of (—) camphor are given by

$$[M] = [R^t_O,L^b_{HH}] + [R^b_{HH},L^t_{HH}] + [R^t_O,L^t_{HH}] + [(L^t_{HH} + R^t_O)(M^1_M + M^7_{MM} + M^4_H)]$$

Similar reasoning can be applied to the remaining compounds illustrated in Fig. 17, and the resulting expressions for the optical rotations are given in Table 7. Inspection of this table shows that the following relationships between the optical rotations should exist. (The optical rotations are represented by [I] for (—) camphor, [II] for (—)α fencho-camphorone, etc., the Roman numerals being those in the left hand column of Table 7).

$$[I] - [II] = [(L^t_{HH} + R^t_O),(M^t_M - M^1_H)]$$

$$[III] - [IV] = [(L^t_{HH} + R^t_O + L^b_{MM} + R^b_{HH}),(M^1_M - M^1_H)]$$

$$[V] - [VI] = [(L^t_{HH} + R^t_O + L^b_{HH} + R^b_{MM}),(M^1_M - M^1_H)]$$

The symmetry of bicyclo [1.2.2] heptane is such that the pair $R^b_{MM}M^1_M$ and the pair $L^b_{MM}M^1_M$ are mirror images of each other, and the same is true of $R^b_{MM}M^1_H$ and $L^b_{MM}M^1_H$. Therefore $[R^b_{MM},M^1_M] = -L^b_{MM},M^1_M]$ and $[R^b_{MM},M^1_H] = -[L^b_{MM},M^1_H]$. Consequently we arrive at the relation

$$[I] - [II] = \tfrac{1}{2}\{([III] - [IV]) + ([V] - [VI])\}$$

The observed rotations of these compounds in various solvents are shown in Table 7. Unfortunately all of the rotations have not been measured in an inert solvent, nor have they even been measured in a common solvent, and it is evident that rather large solvent effects exist. Taking the extreme values of the observed rotations of each compound in all of the solvents in which measurements have been made we find that

$$[I] - [II] \text{ lies between } -40° \text{ and } -68°$$

$$\tfrac{1}{2}\{([III] - [IV]) + ([V] - [VI])\} \text{ lies between } -10{\cdot}5° \text{ and } +42{\cdot}5°$$

TABLE 7. OPTICAL ROTATIONS OF SOME CONFIGURATIONALLY RELATED BICYCLO-KETONES

Compound	Expression for optical rotation	$[M]_D$	Solvent
I. (−)camphor	$R^b_{HH}L^t_{HH} + R^t_OL^b_{HH} + R^t_OL^t_{HH} + (R^t_O + L^t_{HH})(M^1_M + M^7_{MM} + M^4_H)$	−88	hexane
		−87	ether
		−75, −77	acetone
		−68	CS_2
		−63, −65	ethanol
		−62	methanol
		−58, −61	benzene
II. (−)α-fencho-camphorone	$R^b_{HH}L^t_{HH} + R^t_OL^b_{HH} + R^t_OR^t_{HH} + (R^t_O + L^t_{HH})(M^1_H + M^7_{MM} + M^4_H)$	−20	ether
III. (+)isofenchone	$R^b_{HH}L^t_{HH} + R^t_OL^b_{MM} + R^t_OL^t_{HH} + R^b_{HH}L^b_{MM} + (R^t_O + R^b_{HH} + L^t_{HH} + L^b_{MM})(M^1_M + M^7_{HH} + M^4_H)$	+13, 15	undiluted
		+10	ethanol
IV. (−)β-fencho-camphorone	$R^b_{HH}L^t_{HH} + R^t_OL^b_{MM} + R^t_OL^t_{HH} + R^b_{HH}L^b_{MM} + (R^t_O + R^b_{HH} + L^t_{HH} + L^b_{MM})(M^1_H + M^7_{HH} + M^4_H)$	−23	ether
		+10	ethanol
V. (+) fenchone	$R^b_{MM}L^t_{HH} + R^t_OL^b_{HH} + R^t_OL^t_{HH} + R^b_{MM}L^b_{HH} + (R^t_O + R^b_{MM} + L^t_{HH} + L_{HH})(M^1_M + M^7_{HH} + M^4_H)$	+115	benzene
		+104, 110	ethanol
		+95, 102	undiluted
		+91	methanol
		+86, 89	cyclohexane
		+76	ether
VI. (+)camphenilone	$R^b_{MM}L^t_{HH} + R^t_OL^b_{HH} + R^t_OL^t_{HH} + R^b_{MM}L^b_{HH} + (R^t_O + R^b_{MM} + L^t_{HH} + L_{HH})(M^1_H + M^7_{HH} + M^4_H)$	+97	ethanol
		+85, 89	benzene
		−75	ether
		−70	cyclohexane

If we restrict ourselves to the solvent diethyl ether (except for isofenchone, where the averaged values in the undiluted state and in alcohol will be used) we find

$$[I] - [II] = -67°$$

$$\tfrac{1}{2}\{([III] - [IV]) + ([IV] - [VI])\} = +18{\cdot}6°$$

If only the measurements in ethanol are used (except for α-fenchcamphorone, where the only available measurement is in ether),

$$[I] - [II] = -44°$$

$$\tfrac{1}{2}\{([III] - [IV]) + ([V] - [VI])\} = +5°$$

In none of these methods of treating the data is the agreement with the expected values at all satisfactory.* Whether this is caused by the use of different solvents for the different substances, or whether one or more of the measurements is in error, or whether the principle of pairwise interactions is for some reason not applicable in these

* Jacob *et al.*[66] have indicated that the optical rotations and the rotatory dispersions of all of the compounds listed in Table 7 have been measured in their laboratory and promise that the results will appear in a future publication.

compounds it is not possible to say. It should be emphasized, however, that this set of compounds would be expected to be particularly suitable for testing the principle since the molecular skeletons are rigid. Furthermore, all of the groups involved other than carbonyl are non-polar and the changes that are made in going from one compound to another occur at relatively well separated points, so that the effects of higher order interactions ought to be especially small.

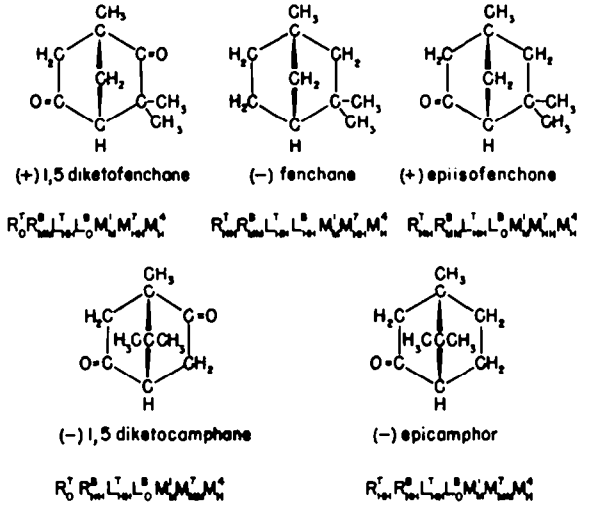


FIG. 18. Methyl ketones of [1.2.2] bicycloheptanes whose rotations should be interrelated as described in the text.

Another group of compounds whose rotations can be shown to be related is shown in Fig. 18 and Table 8. Using the same reasoning as that employed above, and denoting the optical rotations by the bracketed capital letters given in the left hand column of Table 8, one finds that

$$[A] + [B] - [C] - [D] = [R^t_O L^b_O] + [R^t_{HH} L^b_{HH}] - [R^t_O L^b_{HH}] - [R^t_{HH} L^b_O]$$

$$[E] - [F] - [G] = [R^t_O L^b_O] - [R^b_{HH} L^t_{HH}] - [R^t_O L^b_{HH}] - [R^t_{HH} L^b_O]$$

Since $[R^t_{HH} L^b_{HH}] = -[R^b_{HH} L^t_{HH}]$ we should expect that

$$[A] + [B] - [C] - [D] = [E] - [F] - [G]$$

Although the rotations of all of these compounds are available, several solvents have been used and we have no set of rotations in a common solvent. Taking the extreme rotations of each of the compounds in all of the solvents in which they have been measured we find that

$$[A] + [B] - [C] - [D] \text{ takes values between } +3° \text{ and } -27°$$

and

$$[E] - [F] - [G] \text{ takes values between } +7° \text{ and } -93°$$

This result is consistent with the prediction, but the solvent effects are evidently too variable to make a real test possible.

TABLE 8. OPTICAL ROTATIONS OF CONFIGURATIONALLY RELATED BICYCLO-KETONES, DIKETONES AND HYDROCARBONS

Compound	Expression for optical rotation	$[M]_D$	Solvent
A. (+), 1,5-diketo-fenchane	$R^t_O L^b_O + R^b_{MM} L^t_{HH} + R^t_O L^t_{HH} + R^b_{MM} L^b_O + (R^t_O + R^b_{MM} + L^t_{HH} + L^b_O)(M^1_M + M^7_{HH} + M^4_H)$	+126 +125	benzene methanol
B. (−) fenchane	$R^t_{HH} L^b_{HH} + R^b_{MM} L^t_{HH} + R^b_{MM} L^b_{HH} + (R^b_{MM} + L^b_{HH})(M^1_M + M^7_{HH} + M^4_H)$	−25 −23, −25	undiluted ethanol
C. (+) fenchone	$R^b_{MM} L^t_{HH} + R^t_O L^b_{HH} + R^t_O L^t_{HH} + R^b_{MM} L^b_{HH} + (R^t_O + R^b_{MM} + L^t_{HH} - L^b_{HH})(M^1_M + M^7_{HH} + M_H)$	See Table 7	
D. (+) epiisofenchone	$R^t_{HH} L^b_O + R^b_{MM} L^t_{HH} + R^b_{MM} L^b_O + (R^b_{MM} + L^b_O)(M^1_M + M^7_{HH} + M^4_H)$	+21	undiluted
E. (−), 1,5-diketo camphane	$R^t_O L^b_O + R^b_{HH} L^t_{HH} + R^t_O L^t_{HH} + R^b_{HH} L^b_O + (R^t_O + R^b_{HH} + L^t_{HH} + L^b_O)(M^1_M + M^7_{MM} + M^4_H)$	−220 −172, −194 −177 −162	ligroin ethanol ether water
F. (−) camphor	$R^b_{HH} L^t_{HH} + R^t_O L^b_{HH} + R^t_O L^t_{HH} + (L^t_{HH} + R^t_O)(M^1_M + M^7_{MM} + M^4_H)$	See Table 7	
G. (−) epicamphor	$R^b_{HH} L^t_{HH} + R^t_{HH} L^b_O + R^b_{HH} L^b_O + (R^b_{HH} + L^b_O)(M^1_M + M^7_{MM} + M^4_H)$	−96 −89 −69	CS_2 benzene methanol

TABLE 9. RELATIONSHIPS BETWEEN THE OPTICAL ROTATIONS OF THE 3-HALO CAMPHORS (LOWRY[67])

Compound	$[M]_{5461}$ (benzene)
camphor	79·7
3α-chlorocamphor	153·7
3β-chlorocamphor	69·9
α + β − camphor	143·9
3,3-dichlorocamphor	147·3
3α-bromocamphor	324·2
3β-bromocamphor	−101·1
α + β − camphor	143·4
3,3-dibromocamphor	147·6

Lowry[67] prepared the 3α- and 3β-monochlorides and monobromides and the 3,3-dichloride and dibromide of camphor and measured the optical rotations in benzene (Table 9). He demonstrated that the rotations very closely obey the relationship

3α-monohalocamphor + 3β-monohalocamphor − camphor
= 3,3-dihalocamphor

It is easily shown that the observation is a consequence of the principle of pairwise interactions if one makes the same assumptions regarding the geometry of the bicyclo

[67] T. M. Lowry, *Optical Rotatory Power* p. 310. Longmans, Green, London (1935).

[1.2.2] heptane skeleton that have been employed in the previous discussion. Let us introduce the symbols $R^b_{X\alpha}, R^b_{X\beta}, R^b_{H\alpha}, R^b_{H\beta}$ to represent, respectively, X(the halogen atom) in the α configuration, X in the β configuration, H(the hydrogen atom) in the α configuration, and H in the β configuration, at position R^b. The carbon atom in the ring at R^b will be represented by R^b_C. Then writing the symbol [A] for the sum of those pairwise interactions which are common to all of the compounds studied by Lowry,

$$[A] = [R^b_C, L^t_{HH}] + [R^t_O, L^b_{H\Pi}] + [R^t_O, L^t_{H\Pi}] + [R^b_C, L^b_{HH}] + [(R^b_C + R^t_O + L^t_{HH} + L^b_{HH}), (M^1_M + M^7_{MM} + M^4_H)]$$

we find that camphor has the rotation

$$[M] = [A] + [(R^b_{H\alpha} + R^b_{H\beta}), (R^t_O - L^t_{HH} + L^b_{HH} + M^1_M + M^7_{MM} + M^4_H)]$$

The α halogen derivative of camphor as the rotation

$$[M] = [A] + [(R^b_{X\alpha} + R^b_{H\beta}), (R^t_O - L^t_{HH} + L^b_{HH} + M^1_M + M^7_{MM} + M^4_H)]$$

The β halogen derivative has the rotation

$$[M] = [A] + [(R^b_{H\alpha} + R^b_{X\beta}), (R^t_O + L^t_{HH} + L^b_{HH} + M^1_M + M^7_{MM} + M^4_H)]$$

The 3,3-dihalogen derivative has the rotation

$$[M] = [A] + [(R^b_{X\alpha} + R^b_{X\beta}), (R^t_O + L^t_{HH} - L^b_{HH} + M^1_M + M^7_{MM} + M^4_H)]$$

Lowry's relationship follows directly from these expressions.

The success of this relationship here is surprising because these compounds would not be expected to be as favorable for the application of the principle of pairwise interactions as were the bicyclo [1.2.2] heptane derivatives that were previously discussed. The substitution of one or two rather strongly polar halogen atoms for hydrogen atoms on the carbon atom adjacent to the carbonyl group in camphor might be expected to have an appreciable effect on the pairwise interactions of the carbonyl group with the remaining groups in the molecule (i.e., on the terms that go to make up the quantity [A]). Furthermore, one would think that the interaction terms $[R^b_{X\alpha}, R^b_O]$ and $[R^b_{X\beta}, R^b_O]$ between the halogens at C_3 and the carbonyl might depend considerably on whether the second atom at C_3 is hydrogen or halogen. The success of the principle here makes it all the more likely that the much poorer agreement observed in the previous examples of bicyclo [1.2.2] heptane derivatives must be ascribed either to solvent effects or to erroneous experimental data.

Several other relationships among the optical rotations of derivatives of bicyclo [1.2.2] heptane derivatives are indicated in Fig. 19. These relationships may be derived by the methods illustrated above. Data are not available to test these relationships.

One other group of compounds has been found in which the pairwise interaction principle may be tested. This group is made up of steroids in which ring fusion freezes the rings into conformations which presumably resemble one or the other of the chair forms of cyclohexane. It has been shown above that any pair of axially symmetrical groups whose axes lie in the same plane cannot contribute to the optical rotation by pairwise interactions. Such a relationship exists for any pair of groups attached to a cyclohexane ring at axial (i.e., "polar") positions, and it also exists for any pair of 1,3

TABLE 10. RELATIONSHIPS BETWEEN THE OPTICAL ROTATIONS OF STEROIDS DATA FROM MATHIEU AND PETIT[68]

	$[M]_D$ (in $CHCl_3$)
1. 1α-hydroxy-5α-cholestane	+96
2. 3α-hydroxy-5α-cholestane	+126
3. 5α-cholestane	+91
(1) + (2) − (3)	+131
1α,3α-dihydroxy-5α-cholestane	+101
1. 3α-hydroxy-5α-cholestane	+126
2. 5α-hydroxy-5α-cholestane	+39
3. 5α-cholestane	+91
(1) + (2) − (3)	+74
3α,5α-dihydroxy-5α-cholestane	+69
1. 3α-hydroxy-5α-cholestane	+126
2. 4β hydroxy-5α-cholestane	+113
3. 5α-cholestane	+91
(1) + (2) − (3)	+148
3α,4β-dihydroxy-5α-cholestane	+157
1. 2β-hydroxy-5α,22a-spirostane	−210
2. 3α-hydroxy-5α,22a-spirostane	−242
3. 5α,22a-spirostane	−273
(1) + (2) − (3)	−179
2β,3α-dihydroxy-5α,22a-spirostane	−225
1. 2ξ-bromo-3,17-dioxoandrosta-4-ene	+620
2. 6α-bromo-3,17-dioxoandrosta-4-ene	+394
3. 3,17-dioxoandrosta-4-ene	+566
(1) + (2) − (3)	+448
2ξ.6α-dibromo-3.17-dioxoandrosta-4-ene	+475

substituents on the ring if both are in equatorial positions. Insofar as the six-membered rings in the steroids resemble cyclohexane chairs it is readily seen that the optical rotation of any steroid substituted with axially symmetrical groups X and Y in the cyclohexane rings at positions m and n in the configurations χ or φ (where χ and φ stand for either endo- or exo-, i.e. for either α or β in the usual terminology employed by steroid chemists) should be related in the following way to the rotations of the monosubstituted and unsubstituted steroids,

$$m\chi\text{X-}n\varphi\text{Y-steroid} = m\chi\text{X-steroid} + n\varphi\text{Y-steroid} - \text{steroid}$$

provided that the groups X and Y are *both* in either axial positions or in coplanar equatorial positions. This relationship is tested in Table 10, where the groups X- and Y- are in four instances hydroxyl groups, which are assumed to have axial symmetry due to rotation about the C—O bond attaching them to the ring. In one instance X- and Y- are bromine atoms. The predicted relationship, while not obeyed perfectly, is

[68] J. P. Mathieu and A. Petit, *Tables de Constantes et Données Numériques. Constantes Sélectionnées. Pouvoir Rotatoire Naturel I. Stéroides.* Masson et Cie, Paris (1956).

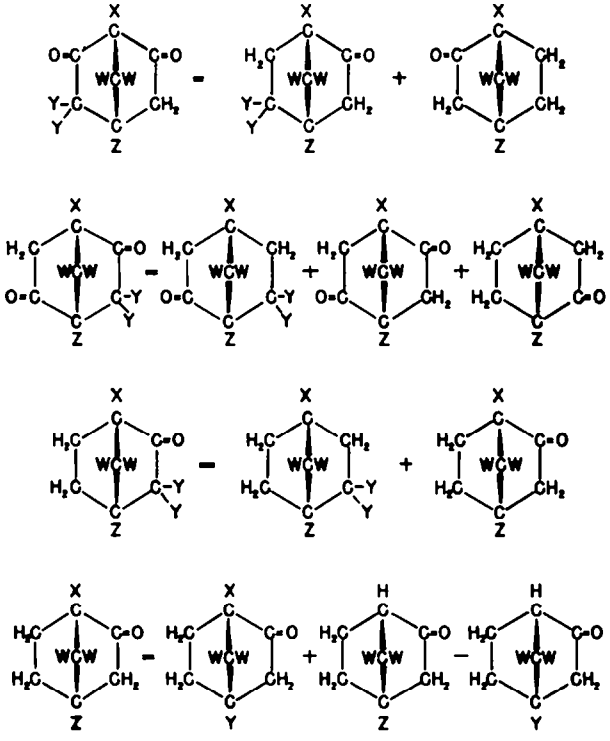


FIG. 19. Further relationships between the optical rotations of derivatives of [1.2.2] bicycloheptane. The symbols W, X, Y and Z denote any axially symmetric groups (H, CH_3, halide, CN, freely orienting OH, etc.).

nevertheless in reasonably good accord with the observations. What discrepancies there are might be accounted for by the failure of the hydroxyl groups to behave as truly axially symmetric groups because of partially restricted rotation in one or more compounds in each set. The presence of the five-membered ring "D" in these steroids might also cause slight distortions of the six-membered rings from the assumed symmetrical cyclohexane chair conformations.