The Effect of the Rotation of Groups about Bonds on Optical Rotatory Power

Walter Kauzmann and Henry Eyring

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tion of the effect of lack of symmetry would be complicated. A detailed consideration of non-electrolytes of finite size will be given in a later paper. One danger which this treatment accentuates should be noted here—the danger of considering the nonelectrostatic part of the chemical potential as a function only of the concentration, independent of the concentration gradient even though the change is enormous over the dimensions of a single molecule, and independent of any order in the orientation even though the orientation must be nearly fixed.

We may conclude that the extension of the Debye method which takes into account the sorting of nonelectrolytes near an ion but neglects their discrete structure represents the solubilities of sodium and potassium chlorides in ethanol-water mixtures less well than the simple Born expression, and fails to represent the flattening of the solubility curves in dioxane-water mixtures or the similar flattening of the reaction rate curves in many mixtures. If the size of the nonelectrolyte molecules is to explain the flattening, the effect of size must be much larger for solutions rich in dioxane than for those containing a small amount; if it is also to explain the solubilities in ethanol, asymmetry must play an important role.

The Effect of the Rotation of Groups about Bonds on Optical Rotatory Power*

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It is shown that the numerical value of the optical activity of an optically active compound is markedly reduced if the groups surrounding the asymmetric atoms in the compound possess a threefold axial symmetry about the bonds connecting them with the asymmetric atoms. This threefold symmetry may be either inherent in the groups themselves, or it may be acquired by them through the free rotation of the groups about these bonds or by their orienting themselves to equal extents in each of the three possible equilibrium positions about each bond. The order of magnitude of the numerical value of the optical activity is thus a measure of the freedom of orientation about single bonds of the groups in an asymmetric molecule. That this effect is actually a dominant factor in determining the order of magnitude of the optical activity is proved by the contrast in the optical activities of cyclic and open chain compounds. It is shown to have an important effect on the temperature coefficient of optical activity and to lie at the root of the observed differences in the orders of magnitude of the rotatory powers of liquids and crystalline solids. The structures of certain sulphur compounds, polypeptides, and proteins are discussed in the light of the magnitudes of their optical activities.

A STUDY of the dependence of the optical rotations of many substances upon the wave-length of the light used in their measurement has shown that rotatory power is closely associated with the absorption bands characteristic of the groups in the molecule. This has given rise to the concept of a *chromophoric group* whose electronic transitions have been rendered optically active by the *vicinal actions* of surrounding groups.[1] It is the purpose of this paper to show that, without going into the detailed physical nature of these vicinal actions, a consideration of only certain of their very general and fundamental characteristics makes it possible to use the optical rotatory power as a tool in investigating molecular structure and conformation.

When one proceeds to a calculation of the optical activity of a molecule, the vicinal actions which are to be considered can be classified

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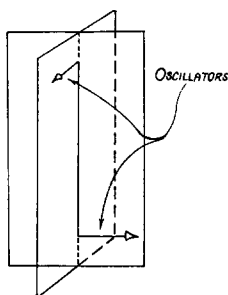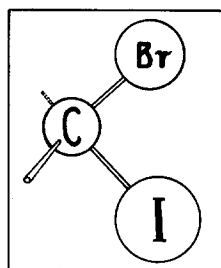[1] Kuhn, Trans. Faraday Soc. **26**, 293 (1930).
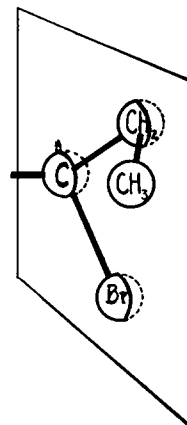
FIG. 1.

FIG. 2.

FIG. 3.

naturally according to a general order as follows. A chromophoric group such as OH or Br, when it is separated from the influences of neighboring groups, is not optically active since it possesses a plane of symmetry. Under certain circumstances, a *single* neighboring group may, however, distort the chromophore in such a way as to destroy its symmetry and render it optically active. Such a vicinal action we call a *first-order vicinal action*. The sum of all of the separate vicinal actions of individual groups on otherwise symmetrical chromophores we may speak of as giving rise to the *first-order contribution* to the optical rotation. The next type of vicinal action arises from the interaction of one vicinal group with a chromophore which has already been considered as distorted by another group. This gives rise to a *second-order vicinal effect* and a *second-order contribution* to the optical rotation. Similarly, we may have vicinal effects and contributions of third and higher order.

To illustrate a first-order vicinal action we may take Kuhn's simple case of two coupled oscillators:[1] A single linear oscillator is optically inactive, but if another linear oscillator with a suitable interaction and orientation in space be introduced, the system may become optically active (see Fig. 1). A second-order vicinal effect might arise as follows: Two three-dimensional isotropic oscillators when brought close to one another are no longer isotropic. The slight anisotropy thus produced may now interact with a suitably oriented linear oscillator to give rise to optical activity in a manner similar to the case of two linear oscillators.

The simplest way to determine the order of a given vicinal action is to ascertain how many groups are interacting simultaneously in the perturbation of the chromophoric group. Thus, any interaction involving two groups at a time (one vicinal group and one chromophore) will be a first-order vicinal action, while one involving the interaction of three groups (two vicinal groups and one chromophore) will be a second-order vicinal action. The sum total of all groups taken two at a time will give the first-order contribution to the rotation, while the sum total of all interactions of three groups taken at a time will give the second-order contribution to the rotation.

First-order contributions to the rotation should in general be larger than second- and higher-order contributions. This is evident from the examples given above, where the ratio of the first-order contribution to the second-order contribution would be of the order of magnitude of the ratio of the anisotropy of a group such as C : O, in which the atoms are separated by one or one and a half angstroms, to the mutually induced anisotropies of two atoms about two or three angstroms apart. Since the induced anisotropy of two otherwise isotropic spheres varies inversely as the cube of the distance between them, this would signify that in general the first-order contribution should be at least five or ten times as large as the second-order contribution. This estimated ratio agrees with that found by other and more general lines of reasoning.[2] The third- and higher-order contributions

[2] Kauzmann, Walter and Eyring, Chem. Rev. **26**, 339 (1940).

to the rotation will, of course, be by the same reasoning of even less importance than the second and first.

We now consider the results of vicinal actions according to the above classification for some simple types of substances. First, let us consider the interactions of two axially symmetrical groups such as those shown in Fig. 2. It is at once evident that two such groups can alone give rise to no first-order contribution to the optical activity, since there is a plane of symmetry for the three atoms there shown. Next, consider the interaction of an ethyl group and a C—Br bond (Fig. 3). As long as no plane can be drawn through the ethyl group and the C—Br bond, there can be a first-order contribution to the optical activity. But if, in a given compound, the ethyl group is freely rotating about the bond connecting it with the asymmetric carbon atom so that it becomes axially symmetric around this bond, or even if it can take up with equal probability several positions which are, however, symmetrically disposed about the plane shown in Fig. 3, then no first-order contribution to the optical activity is possible for these groups.

These arguments may easily be extended to prove the general statement that *if the groups about an asymmetric atom possess cylindrical symmetry about the bond connecting them to the asymmetric atom, or if the groups can effectively acquire this symmetry by freely rotating or by taking up a number of equilibrium positions, then the first-order contribution to the optical activity will vanish and any observed rotation must be due to higher order effects.* Coupling this statement with what we know about the relative orders of magnitude and of first- and second-order effects, we may state further that *those influences which tend to restrict freedom of rotation and of orientation about bonds will tend to increase the order of magnitude of the optical activity.*

The consequences of this statement will now be considered.

1. Comparison of the rotatory powers of substances in which the asymmetric centers are in closed rings and open chains

Since ring formation severely restricts the freedom of rotation of groups about bonds, it should have a big effect in increasing the optical

activity when an asymmetric center is one of the ring atoms. Such an effect has long been noticed[3] and is particularly striking in those substances (e.g., polyhydroxy alcohols and sugars) for which there is the most reason to believe that the open chain form can exhibit the greatest freedom of rotation because the groups attached to the asymmetric carbon are the smallest, as will be seen in Table I, where the rotations of various types of open chain and closed ring compounds are compared.
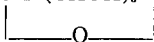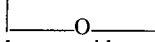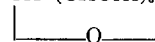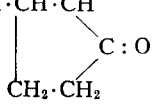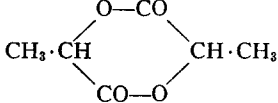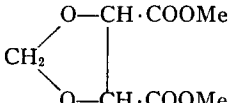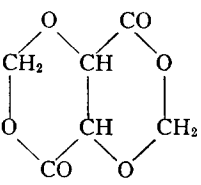
This very low optical activity of many open chain compounds has a bearing on the question of the conformations assumed by long chains in general. It has been suggested by some workers that such chains are usually stretched out, while others believe that chains tend to roll up into balls; from the evidence presented here, however, it would seem that in the absence of large side groups, chains are predominantly neither stretched out nor rolled up into balls, but that they tend to take up all conformations with very nearly the same probability. Recent theories of the elasticity of rubber have assumed this randomness to occur even in the absence of a solvent, and some evidence as to the validity of this assumption could be found in the rotations of glasses of polyhydroxy alcohols. A persistence of the low rotations of these substances as glasses would indicate that their chains are randomly twisted even when no small solvent molecules are present to fill up the holes in the structure of the glass which result from the poor packing of the molecules as a consequence of this randomness.

2. Effect of temperature on optical activity

Changing the temperature will affect the optical activity of a substance chiefly in two ways: by changing the extent of the interaction the active molecules and the solvent, and by changing the conformations of the active molecules. It will be shown later that an increase in the temperature generally causes the interaction between solvent and solute to decrease, so that at higher temperatures the optical activity of a substance tends to become independent of the solvent in which it is dissolved

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[3] Van't Hoff, *Arrangement of Atoms in Space* (Longmans, New York, 1898), p. 146.

TABLE I. *Comparison of the rotations of cyclic and open chain compounds.*

OPEN CHAIN COMPOUNDS		CYCLIC COMPOUNDS	

Type $CH_2OH \cdot (CHOH)_n \cdot CH_2OH$ Type $H \cdot (CHOH)_n \cdot CH \cdot (CHOH)_3 \cdot CHOH$ with O bridge

	$[M]_D$		$[M]_D$
Arabite	8	Ribose	32
Talite	6	Alpha-arabinose	263
Mannite	1	Beta- "	75
Idite	6	Alpha-xylose	138
Sorbite	4	Alpha-mannose	54
		Beta- "	25
		Alpha-galactose	260
		Beta- "	25
		Alpha-glucose	302
		Beta- "	34

Type $CH_2OH \cdot (CHOH)_4 \cdot CH(OMe)_2$ Type $CH_2OH \cdot CH \cdot (CHOH)_3 \cdot CHOMe$ with O bridge

Mannose dimethyl acetal	1	Alpha-methyl mannoside	159
Galactose " "	34	Alpha-methyl galactoside	345
Glucose " "	34	Beta- " "	1
		Alpha- " glucoside	307
		Beta- " "	62

Type $CH_2OAc \cdot (CHOAc)_4 \cdot CH(OMe)_2$ Type $CH_2OAc \cdot CH \cdot (CHOAc)_3 \cdot CHOMe$ with O bridge

Mannose dimethyl acetal pentacetate	69	Alpha-methyl mannose tetracetate	162
Glucose " " "	52	Beta- " " "	170
		Alpha- " galactose "	474
		Beta- " " "	65
		Alpha- " glucose "	478
		Beta- " " "	50

$CH_3 \cdot CH_2 \cdot CHCH_3 \cdot CH_2 \cdot CHO$ 9

$$\begin{array}{c} CH \cdot CH \cdot CH \\ | \quad\quad\quad\; C:O \\ CH_2 \cdot CH_2 \end{array} \quad 130$$

$CH_3 \cdot CHOH \cdot COOH$ $2[M]_D = 9$

$CH_3CHOH \cdot COOEt$ $2[M]_D = 29$

$COOEt \cdot CHOH \cdot CHOH \cdot COOEt$ $[M]_{5461}^{190°C} = 35$

$$\begin{array}{c} O-CO \\ CH_3 \cdot CH \quad\quad CH \cdot CH_3 \\ CO-O \end{array} \quad [M]_D = 400$$

$$\begin{array}{c} O-CH \cdot COOMe \\ CH_2 \quad\quad | \\ O-CH \cdot COOMe \end{array} \quad [M]_{5461}^{100°C} = 204$$

$$\begin{array}{c} O \quad CO \\ CH_2 \quad CH \quad O \\ O \quad CH \quad CH_2 \\ CO \quad O \end{array} \quad [M]_{5461}^{20°C} = 129$$

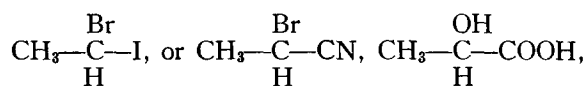| ACID	$[\alpha]_D$ OF FREE ACID	$[\alpha]_D$ OF GAMMA-LACTONE	$[\alpha]_D$ OF DELTA-LACTONE
Arabonic	18	74	—
2,3,4 trimethyl arabonic	16	—	178
2,3,5 " "	2	44	—
2,3,4 " lyxonic	13	—	35
2,3,5 " "	21	82	—
3,4 dimethyl rhamnonic	16	—	153
Rhamnonic	8	40	98
Gluconic	7	68	62
Mannonic	10	52	112
Galactonic	13	77	—
2,3,4,6 tetramethyl gluconic	22	—	72
2,3,5,6 " "	34	101	—

(aside from a factor of $(n^2+2)/3$, where n is the refractive index). An increase in the temperature generally affects the conformation of the molecule by increasing the freedom of rotation about bonds—and if there is not complete freedom of rotation, due to the presence of a potential barrier of the type supposed to exist in ethane, then an increase in the temperature will tend to equalize the times spent by a group in the various positions of minimum potential energy on either side of the barriers. In either case, when an symmetric center is not a member of a closed ring, a temperature increase brings about more and more axial symmetry of the groups attached to the asymmetric atom, and so reduces the first-order contribution to the optical activity. From what we have said before, it is evident that this means that at high temperatures all open chain compounds should have rather small rotations, while the orders of magnitude of the optical activities of compounds in which the asymmetric centers are the members of rings should be unaffected.

Before proceeding to an investigation of the actual data, however, it will be convenient to study some further structural effects which will influence the magnitudes of higher order contributions to the rotatory power. Consider the secondary butyl alcohol molecule ($CH_3 \cdot CH_2 \cdot CHMe \cdot OH$). Suppose that all the groups attached to the asymmetric atom are axially symmetric due to free rotation or its equivalent, so that the first-order vicinal actions are all zero. The largest of the second-order vicinal actions will clearly be those involving groups and portions of groups closest to the asymmetric carbon atom. Therefore, in secondary butyl alcohol, the most important of the higher order vicinal actions should be those involving the atoms

$$\begin{array}{ccc} C & & C \\ \diagdown & & \diagup \\ & C & \\ \diagup & & \diagdown \\ H & & O \end{array}$$
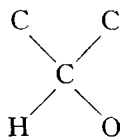
But this group of atoms possesses a plane of symmetry, so cannot by itself contribute to the optical activity. Nonvanishing higher order vicinal actions in secondary butyl alcohol at high temperatures only become important when the terminal methyl of the ethyl group is con-

sidered along with the rest of the molecule. Now this methyl group is some distance away from the asymmetric center, so that its interactions with the other groups will be rather weak, and the higher order contributions to the optical activity in secondary butyl alcohol should be much smaller than those in, say,

$$\begin{array}{ccc} Br & Br & OH \\ CH_3\!-\!\overset{|}{\underset{|}{C}}\!-\!I, \ \text{or} \ CH_3\!-\!\overset{|}{\underset{|}{C}}\!-\!CN, & CH_3\!-\!\overset{|}{\underset{|}{C}}\!-\!COOH, \\ H & H & H \end{array}$$

where all of the atoms directly attached to the asymmetric center are considerably different from one another. (It is to be expected that a carbon atom in a COOH group or a $-CN$ will behave optically in a very different way from one in a CH_3 group, since it has been very differently modified by its neighbors.)

In what follows, therefore, we shall divide the compounds which we consider into various classes. In one class (referred to hereafter as *class A*) we shall have those substances in which axial symmetry of groups attached to asymmetric centers is rendered impossible due to the presence of a ring in the molecule. Another class of substances (*class B*) will have groups which rotate freely about the bonds attaching them to the asymmetric centers and will have two or more similar atoms attached to each of these centers. Secondary butyl alcohol would thus fall in class *B*. A third class (*class C*) will include those substances in which axial symmetry of groups is possible, but in which the atoms directly attached to the asymmetric center are considerably different in their optical behavior. Lactic acid therefore belongs in class *C*.

Class *A* compounds should show large optical rotations at both high and low temperatures, and if a class *A* compound has a large optical activity, an increase in the temperature should be just as apt to cause an increase in the optical activity as it is to cause a decrease. Class *B* and *C* compounds should generally tend to show low optical rotations, but if any should happen to have large rotations, then an increase in the temperature should cause a decrease in the magnitudes of these rotations. Class *C* compounds should generally have larger rotations at high temperatures than do class *B* compounds.

In Figs. 4 and 5 are represented the temperature coefficients of the rotations of most of the
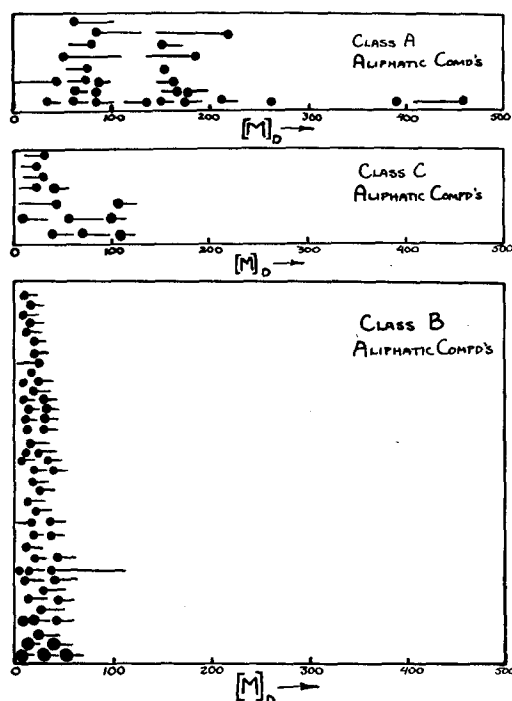
FIG. 4.

FIG. 5.

substances in the literature for which data are available over an appreciable temperature range. In the figures, a black dot represents the rotation of one substance at the highest temperature at which measurements have been made. From each dot is drawn a line in the direction toward which the rotation tends as the temperature is lowered. The length of each line has been made numerically equal to one hundred times the rate of change of the rotation of each substance per degree centigrade at 20°C. Figure 4 includes only aliphatic compounds, and Fig. 5 includes only aromatic compounds; this distinction has been made in order to keep more constant all of those factors not immediately concerned in the determination of the amount of rotation of groups about bonds.[4]

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[4] Most of the data used here are from (1) a long series of papers by Pickard, Kenyon et al. in J. Chem. Soc. London, 1911 ff.; (2) Guye and Amaral, Comptes rendus 120, 1345 (1895); (3) Guye and Aston, Comptes rendus 124, 194 (1897); and (4) some unpublished data from this laboratory. Where there are data in the literature for a large number of compounds belonging to the same homologous series, only two or three examples have been included in the figures. Thus, Pickard and Kenyon (J. Chem. Soc. 99, 45 (1911); 101, 620 (1912); 105, 830 (1914)) have determined the effects of temperature on eleven alkyl carbinols and 73 of their fatty acid esters. The results among
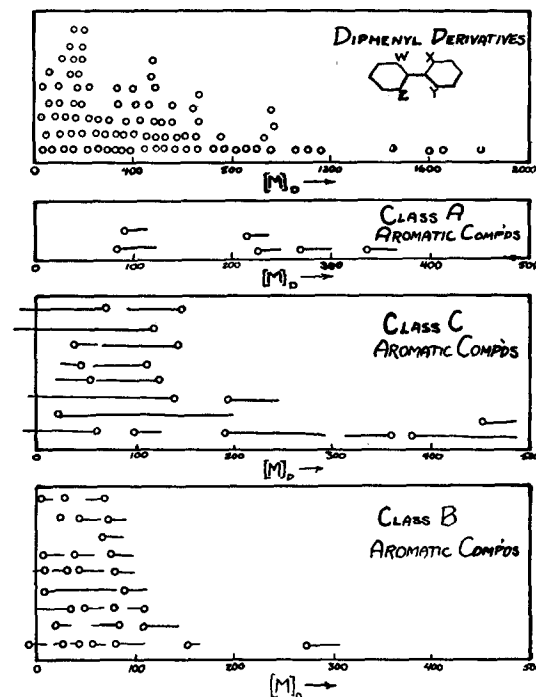
A study of the figures will show the following:

(a) Among the aliphatic compounds the open chain molecules (classes B and C) with large rotations all tend to have smaller rotations as the temperature increases, while the ring molecules (class A) have temperature coefficients whose sign is independent of whether or not their rotations are large or small. This is as we have predicted.

(b) Aliphatic compounds of class B tend to have smaller rotations at high temperatures than do those of class C. This is evident from the fact that the rotations of a larger proportion of the latter tend to increase with increasing temperatures, even when fairly large rotations are involved.

(c) Aromatic compounds as a whole possess larger rotations than do aliphatic compounds, so that the relationship between class B and class C compounds, although similar to that

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the carbinols are very similar; in all, there is a slight initial decrease in rotation to a small, constant value. At high temperatures there is a very slight tendency for the rotation to increase, probably associated with changing solvent effects as the boiling point is approached. For all of the 73 esters, too, the temperature vs. rotation curves are very similar, all being, in fact, very nearly superimposable.

found among aliphatic substances, occurs against a background of an entirely different scale of orders of magnitude. The relationship between aromatic substances of class A and those of classes B and C is obscured by a scarcity of data for the class A compounds. To circumvent this partially we have added to Fig. 5 a "map" of the distributions of the orders of magnitude of the rotations of some optically active diphenyl derivatives. These substances should behave in the same way as class A compounds, since no planes of symmetry can be drawn through pairs of groups attached to the "asymmetric centers" in the molecules. That they do indeed behave like class A compounds is shown by their tendency to have very large rotations; so great is this tendency that the scale of rotations for these compounds in Fig. 5 is reduced by four-fold as compared with the scales for the other aromatic compounds in order to make it possible to include the data for all of the known compounds. The dependence on the temperature for these compounds has not been studied, but we would predict that in the absence of racemization, just as many will be found to have rotations whose numerical value increases with the temperature as those whose numerical value decreases with the temperature. Furthermore, this will tend to be just as true among those substances having large rotations as among those having small rotations.

The fact that aromatic compounds seem to show larger rotations than aliphatic compounds may be due to either of two effects. There may be incomplete axial symmetry in even the high temperature forms of the aromatic compounds due to greater steric repulsions by aryl groups, or the effect may be due to a greater polarizability or susceptibility to distortion possessed by aryl groups which tends to increase both the first- and second-order vicinal actions in molecules in which they occur.

(d) There would appear to be some relationship between the sizes of groups attached to the asymmetric center and the magnitude of the temperature effect. This shows itself best in the contrast between the magnitudes of the temperature coefficients (lengths of the lines in Fig. 5) for aromatic compounds of classes B and C, where the direct attachment of the bulky phenyl or naphthyl group to the asymmetric center greatly increases the temperature coefficient of the optical rotation. All of this effect cannot be directly due to the sizes of the groups concerned, however, for in benzoin and in benzoin methyl ether,[5] where there are very large temperature coefficients, not only the magnitude of the temperature effect, but its sign as well depends upon the nature of the solvent. Therefore, the solvent must play a considerable, if not a dominant role in determining many of the temperature coefficients which have been measured. (Of course, when a complex aromatic compound is in the pure, so-called "homogeneous" state, solvent effects, i.e. effects due to surrounding molecules, are every bit as large as when it is dissolved in, say, benzene.) Therefore, only when data are available for substances in dilute solutions of inert, nonpolar solvents such as hexane (or even better, for substances in the vapor state) will it be possible to make a clear distinction between the effects of changing conformation and changing solvent effects on the optical activity. When such data become available, however, it should be possible to learn a great deal about the little-known field of molecular conformations in general.

3. The optical activity of crystals

Molecules can probably usually pack best into a crystal when they all have the same conformations or at most only a very few different conformations; therefore, in the crystalline state there is usually a high degree of restriction of the amount of freedom of rotation and of orientation of groups about bonds. Aside from this, however, two other effects occur which tend to make the rotations of optically active molecules in crystals different from those of the same molecules in solution. First, there is the occurrence of a "structural" contribution to the optical activity due to the vicinal actions between groups in different molecules. This structural effect is what is responsible for the rotations of crystals made up of the molecules which are themselves not optically active. Second, there is the fact that experimentally the rotation can usually only be measured along the optic axes of the crystal. This prevents the averaging

[5] Rule, J. Chem. Soc. p. 138 (1937).

TABLE II. *Rotations of substances in the solid and liquid states. (Data from I. C. T.).*

SUBSTANCE	ROTATION BY CRYSTAL (IN DEGREES PER DM., Na D LIGHT)	ROTATION IN LIQUID STATE ($[\alpha]_D$)
Open Chain Compounds		
$NaNH_4$ tartrate·$4H_2O$	155	33 in water
NaK " "	76#	33 " "
Rb_2 "	1040	24 " "
Cs_2 "	1700	5 " "
Tartaric acid	609#	15 " "
Zinc malate·$2H_2O$	310#	55 amorphous
$(NH_4)_2$ tartrate	880	29 in water
Asparagine	590	5 " "
Ring Compounds		
$(MoO_4)_2$·$(NH_4)_2$ malate·$2H_2O$	3080	220 for $Na_2(MoO_3)_2C_4H_4O_4$ in H_2O
" Ba " "	3168	
$K_3Ir(C_2O_4)_3$·H_2O	1200	86 in water
$K_3Rh(C_2O_4)_3$·H_2O	640	16 " "
Methyl glucoside (alpha)	440	139 " "
Common camphor	66#	65 molten
Matico "	198	28 "
Patchouli "	133	120 in EtOH
Benzylidene "	818	451 in chloroform
Anisal "	3620	467 in toluene
Corydine	1320	204 in chloroform
Hydrocinchonine sulphate	1280	164 in EtOH
Strychnine	1000	34 in water
Cinchonine antimonyl tartrate	980#	414 molten
Apocinchonine succinate	350	212 in HCl
Quercitol ("strong" axis)	460	26 in water
("weak" axis)	370	
Sucrose ($\lambda = 5790A$)		
("strong" axis)	336#	69 in water ($\lambda = 5790A$)
("weak" axis)	101#	
Substances Active only as Crystals		
Diacetyl phenolphthalein	1980	
Guanidine carbonate	1460	
Ethylene diamine sulphate	1550	
Ammonium oxalate	1200 ($\lambda = 5790A$)	
$LiKSO_4$	350	
HIO_3	5050 ($\lambda = 5790A$)	
SiO_2	2173	
$Pb(CHOO)_2$	1560 ($\lambda = 5790A$)	
$ZnSO_4$·$7H_2O$	241 ($\lambda = 5790A$)	
$NaClO_3$ (Isotropic crystal)	316	
$NaBrO_3$ (" ")	213	
$NaUO_2(C_2H_3O_2)_3$ (" ")	148	
$K_2S_2O_8$	820	

=corrected for density.

of the quantity $\beta \cdot \bar{H}$ over all orientations of the molecule in space in the derivation of the Rosenfeld equation[6] for the optical rotation in terms of the electronic states of a molecule. The usual form of the Rosenfeld equation is then no longer applicable.

In Table II are given the optical rotations of a number of optically active substances in the solid and liquid (or dissolved) states. The optical rotations of some crystals made up of inactive molecules are also given in order that

[6] E. U. Condon, Rev. Mod. Phys. 9, 432 (1932).

some idea might be had of the magnitude of the "structural" contribution to the optical activity. The remarkably large rotations shown by most crystals, regardless of the natures of the molecules of which they are made up, is indicative of the operation of many large first-order vicinal actions arising from the severity of the restrictions imposed by crystallization on the freedom of internal and external molecular orientation.

The structural contribution to the optical rotations of crystals is discussed further in connection with solvent effects. below.

4. Quadrivalent sulphur

The compound

CH₃—⟨benzene ring⟩—S—⟨benzene ring⟩—NH₂
with S→O below
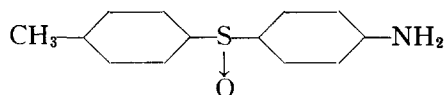
has a very large optical rotation ($[M]_D = 224°$).[7] From the considerations given above and from the probable effective axial symmetries of NH_2

and CH_3, such a large rotation is not possible if only the direct interaction of NH_2, CH_3 and S→O is responsible for the rotation. It seems likely that some force is operating which causes the interactions involving the two benzene rings to be considerably different.

5. Other compounds containing sulphur

The following are the rotations of some sulphur-containing organic acids:[8]

cystein:	$HS \cdot CH_2 \cdot CHNH_2 \cdot COOH$	$[M]_{5461}^{26°C} = 12\frac{1}{2}°$;	$d\lvert[M]\rvert/dT = -0.12°$ per deg. C
	$HS \cdot CHCH_3 \cdot COOH$	$[M]_D^{15°C} = 48°$	
cystine:	$(\cdot S \cdot CH_2 \cdot CHNH_2 \cdot COOH)_2$	$\frac{1}{2}[M]_{5461}^{26°C} = 386°$;	$\frac{1}{2}d\lvert[M]\rvert/dT = -1.8°$ per deg. C
	$(\cdot S \cdot CH_2 \cdot CHCH_3 \cdot COOH)_2$	$\frac{1}{2}[M]_D = 510°$;	
	$S(CH_2 \cdot CHCH_3 \cdot COOH)_2$	$\frac{1}{2}[M]_D = 196°$	
	$(\cdot S \cdot CH_2 \cdot CHOH \cdot COOH)_2$	$\frac{1}{2}[M]_D = 13°$.	

The very large rotations shown by most of those substances in which the sulphur atom is not directly bonded to a hydrogen atom suggest that in these compounds there operate forces which very severely restrict the freedom or orientation of groups. On the other hand, the very large temperature coefficient of the rotation of cystine as compared with that of cystein indicates that these forces are rapidly becoming less important in cystine as the temperature increases. It would be most interesting to know what is the nature of these restricting forces in cystine and the other compounds with large rotations. It would also be interesting to know why they apparently do not operate in $(S \cdot CH_2 \cdot CHOH \cdot COOH)_2$.

6. Polypeptides

The following are the rotations of a series of polypeptides of alanine:[9]

	$[M]_D$ IN 2N HCl	$[M]_D \div$ No. OF ALANINE RESIDUE
1-alanine, $C_3H_7O_2N$	+ 13	+ 13
1-alanyl 1-alanine, $C_6H_{12}O_3N_2$	− 58	− 29
di-alanyl 1-alanine, $C_9H_{17}O_4N_3 \cdot \frac{1}{2}H_2O$	−186	− 63
tri-alanyl 1-alanine, $C_{12}H_{22}O_5N_4 \cdot \frac{1}{2}H_2O$	−358	− 90
tetra-alanyl 1-alanine, $C_{15}H_{27}O_6N_5 \cdot H_2O$	−518	−104

It is apparent that as the number of alanine residues in the polypeptide increases, not only does the rotation of the molecule as a whole increase, but there is a marked increase in the rotation per alanine residue. This means that there must be an increasing amount of restriction of the orientation of the groups within the molecule as the polypeptide chain becomes longer. This restriction may arise from the formation of rings involving hydrogen bonds or some other type of bond between amide links, such as[10]:

\C : O+H₂N→ \C with OH and NH—

[7] Harrison, Kenyon and Phillips, J. Chem. Soc. p. 2079 (1926).
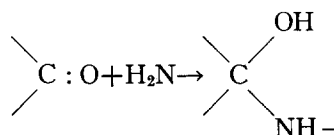
[8] Toennies and Bennett, J. Biol. Chem. **112**, 497 (1935). Toennies, Lavine, and Bennett, J. Biol. Chem. **112**, 493 (1935). Louven, J. prakt. Chem. **78**, 63 (1908). Neuberg and Ascher, Biochem. Zeits. **5**, 451 (1907).

[9] Abderhalden and Gohdes, Ber. **64**, 2667 (1931). Levene and Yang, J. Biol. Chem. **99**, 405 (1933).

[10] Wrinch, Phil. Mag. (7) **24** (suppl.), 940 (1937). Mirsky and Pauling, Proc. Nat. Acad. Sci. U.S.A. **22**, 439 (1936).

In the light of the very low rotations shown by the polyhydroxy alcohols, in which purely steric effects would certainly be no less important than they are here, it is difficult to understand how anything not involving bond formation of this type could have such a great effect on the optical rotation. An investigation of the effect of temperature on these rotations would be of interest here.

7. Proteins

Associated with the behavior of the rotatory powers of the polypeptides is that of the proteins. It is known that in the denaturation of egg albumin, serum albumin, casein and edestin,[11] the change in rotation which occurs is not at all marked—the change in the optical rotation during denaturation being of the same order of magnitude as the variation caused by changing the pH. This would indicate that the changes in conformation which occur on denaturation are rather small in the immediate neighborhood of any given asymmetric center. There may thus be an analogy between the melting of a solid and the denaturation of a protein: in melting, it is well known that although the long range order typical of the crystal vanishes, the short range order typical of the crystal persists (the number and arrangement of the nearest and next nearest neighbors to a given atom being about the same before and after melting). Denaturation may similarly involve merely a change in the spatial relationships of two widely separated parts of the protein molecule without affecting very markedly the arrangement of atoms in a more restricted region of the molecule. Such a change might result from the breaking of a very few strategically located primary valencies and would not drastically alter the optical activity.

Crystalline proteins in aqueous solutions appear to possess rotations of about the same order of magnitude as other proteins. Thus, pepsinogen has an $[\alpha]_D^{25}$ of $-61°$,[12] pepsin, one of $-70°$,[12] and trypsin, one of about $-50°$.[13] Since the molecular weights of most amino acids average around 100 to 150, these rotations may be taken as a rough measure of the molecular rotations per amino acid residue for these proteins. These rotations are about the same as those found for the noncrystalline proteins mentioned above in connection with denaturation. This similarity between the two is an indication that there is no appreciable difference in the amount of rigidity and of freedom of orientation about asymmetric centers for crystallizable and noncrystallizable proteins; the difference probably arises again from the presence of a higher degree of long range order in the crystallizable proteins.

We may point out the apparently general absence of such large rotations among the proteins as are found in the crystalline solids—a fact which seems to demand a certain looseness in the protein structure, at least when the proteins are in solution. The very large optical rotation of dry gelatin, however (see below), makes a further study of this point desirable.

It has been shown by Smith[14] that there is a definite relationship between the optical activity of a solution of gelatin and other of the properties of the solution, especially its ability to gel. In cooling a solution of gelatin from 35°C to 15°C, there is a reversible increase in the rotatory power from $[\alpha]_D^{35} = -120°$ to $[\alpha]_D^{15} = -270°$. This was proven to arise from a shifting equilibrium between two moles of a high temperature form and one mole of a low temperature form:

$$2A(\text{high temp.}) \rightarrow B(\text{low temp.}).$$
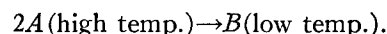
Gelatin solutions also metarotate in this temperature region, the kinetics of the reaction corresponding again to two molecules of a high temperature form going to one of a low temperature form. Addition of salts to a solution of gelatin below 15°C causes a change to the high

TABLE III. *Equilibrium in gelatin solutions.*

$t°C$	$1000/T$	$K =$ EQUI- LIBRIUM CONSTANT	$-R$ LN K
24	3.3670	0.57	1.12
25	3.3557	1.1	−0.19
26	3.3445	2.0	−1.39
27	3.3333	4.0	−2.77

[11] Pauli and Kölbe, Kolloid Chem. Beihefte **41**, 418 (1935). Pauli and Hoffman, *ibid.* **42**, 34 (1935). Barker, J. Biol. Chem. **103**, 1 (1933).

[12] Northrop, *Crystalline Enzymes* (Columbia University Press, New York, 1939).

[13] Northrop and Kunitz, J. Gen. Physiol. **16**, 267 (1932). The specific rotation of trypsin was calculated from the rotation per milligram of nitrogen per cc ($[\alpha]_D = -0.33°$ per mg N per ml in a one dm tube) and from the elementary analysis of the protein (15 percent N).

[14] Smith, J. Am. Chem. Soc. **41**, 135 (1919).

temperature form to take place. Below 15°C and above 35°C the rotations of gelatin solutions change only very slowly with the temperature. The amorphous solid obtained on evaporating a solution of gelatin at a temperature above 35°C has about the same rotation as the gelatin in the solution from which it was obtained ($[\alpha]_D \cong -100°$), while the rotation of the amorphous solid from a solution evaporated down at a temperature below 15°C has a rotation of $[\alpha]_D = -600$ (assuming a density of 1.27 for solid gelatin and taking Smith's value of $-75°$ per centimeter layer for the rotation).

Analysis (see Table III and Fig. 6) of the temperature dependence of the equilibrium constant found by Smith for these two forms of gelatin gives for the heat of the reaction $2A \rightarrow B$, $\Delta H = -110,000$ calories. In order that the equilibrium constant be about equal to unity at 25°C, the entropy in going from $2A$ to B must decrease by about 370 entropy units. That the imposition of such a severe amount of restriction as is implied by an entropy change of 370 entropy units should have no more effect on the rotatory power than to change it from $-120°$ to $-270°$ is perhaps surprising in the light of the fact that evaporation of a cold gelatin solution can bring about a further increase in the levorotation to $-600°$. This indicates that the removal of water from gelatin can probably impose more restrictions on the movements of the groups in the gelatin molecule than is observed to occur in the change from the high temperature form of the protein to the low temperature dimer. The behavior of gelatin solutions is understandable if, as was suggested for denaturation (where similar exceptionally large heat and entropy effects are known to be involved[15]) the changes which occur involve chiefly an alteration in the long range order of the molecules, accompanied by moderate changes in the arrangement of the atoms in the immediate neighborhood of any given atom. On evaporation of a cold gelatin solution, this tightening of the arrangement about the asymmetric centers appears to be rather more marked, even approaching the state of affairs in crystalline solids.

In the study of such a complex problem as that of the structure of the proteins, it is of more than

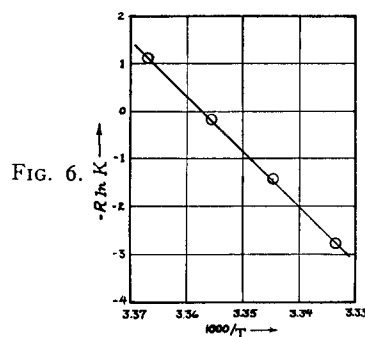[15] Eyring and Stearn, Chem. Rev. **24**, 253 (1939).

FIG. 6.

ordinary importance that all possible methods of attack on the problem be utilized. The optical activities of the proteins are capable of being applied as such a tool and are more sensitive than most properties to variations in experimental conditions. It is unfortunate that they are not being studied more intensively than they are, since they would appear to be capable of answering many structural questions.

8. Solvent effects on the optical rotatory power

A liquid or solid may be considered to be a large molecule made up of many smaller molecules between which there operate forces of attraction and repulsion of some sort. The very fact that one substance can dissolve in another can only be a result of the forces which act between the two different kinds of molecules. We may say, therefore, that when one substance is dissolved in another, a compound is formed between the molecules involved. The properties of this compound may bear a very complex relationship to those of the molecules of which it is composed, and in general it is the understanding of this relationship which is the object of the study of what are usually spoken of as solvent effects.

From this point of view, the effects of solvents on the rotatory power are merely the result of the formation of some kinds of compounds between the solvents and the optically active molecules concerned, and in calculating completely the optical rotation of a solution (or of any liquid or solid, for that matter), we must consider not only the optically active molecule itself, but its environment as well. This environment may affect the optical rotation by changing the vicinal actions within the active molecule (e.g., through a distortion of the molecular
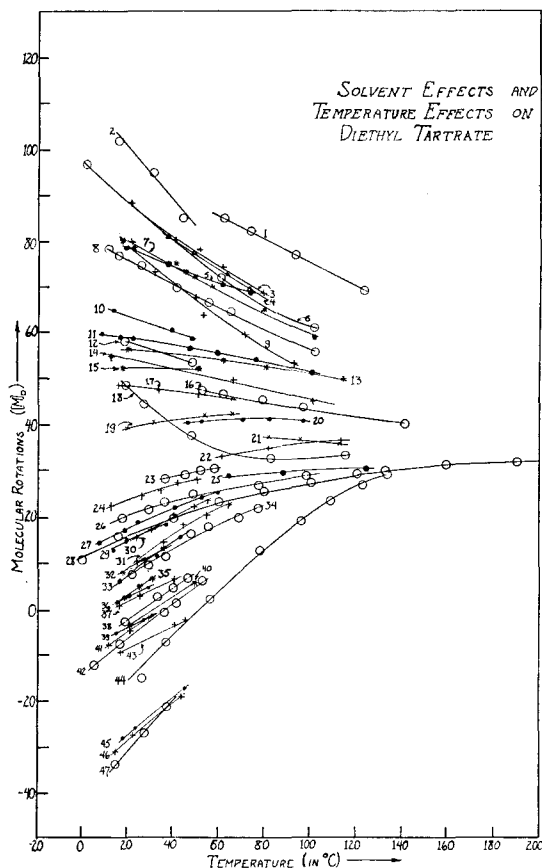
FIG. 7. Solvent effects and temperature effects
on diethyl tartrate.

KEY TO FIG. 7

1. alpha-nitro naphthalene	25. 2,4, dinitro toluene
2. meta toluidine	26. glycerol
3. benzaldehyde	27. ethanol
4. paratoluidine	28. no solvent
5. aniline	29. $C_6H_5 \cdot OC_2H_5$
6. pyridine	30. n-propanol
7. nitrobenzene	31. iso-butanol
8. orthonitro toluene	32. anisol
9. phenol	33. dimethyl aniline
10. orthotoluidine	34. secondary octanol
11. meta nitro toluene	35. carbon tetrachloride
12. benzyl alcohol	36. methyl iodide
13. salicyl aldehyde	37. bromoform
14. water	38. methylene iodide
15. ortho $CH_3 \cdot O \cdot C_6H_4 \cdot NO_2$	39. methylene chloride
16. 2,6, dinitro toluene	40. ethyl iodide
17. methyl aniline	41. ethylidene chloride
18. quinoline	42. chloroform
19. ortho $C_2H_5 \cdot O \cdot C_6H_4 \cdot NO_2$	43. ethylene chloride
20. paranitro toluene	44. anti-benzaldoxime
21. meta dinitro benzene	45. acetylene tetrabromide
22. orthonitro phenol	46. ethylene bromide
23. para $CH_3 \cdot O \cdot C_6H_4 \cdot NO_2$	47. acetylene tetrachloride
24. methanol	

framework), or it may affect the optical activity
by itself exerting vicinal actions on the chromo-
phores of the active molecules and by the vicinal

actions of the groups in the active molecule on
the chromophoric groups in the surrounding
solvent molecules.

The effect of freedom of orientation and rota-
tion of groups on the rotatory power has an
important bearing when we come to consider the
magnitude of the solvent effect. The distances
between molecules in solutions are considerably
greater than those between groups on an asym-
metric carbon atom; therefore, in order to be
appreciable, any vicinal actions which operate
between groups in two different molecules must
be first-order vicinal actions. But these will
obviously vanish unless the two molecules are
kept from taking on all possible orientations
with respect to one another; that is, in order that
there can.be large vicinal actions between two
molecules, the forces acting between them must
tend to cause a considerable amount of orienta-
tion of the molecules with respect to one another.
(Note, however, that even when neighboring
molecules can take up all possible orientations
with respect to one another, there may still
be a nonvanishing though small contribution
to the rotation due to higher order vicinal ac-
tions.) Thus, forces such as van der Waals
interactions, which depend predominantly on
intermolecular distance rather than on the
relative orientations of molecules, should result
in only negligible vicinal actions between solvent
and solute molecules. This probably accounts
for the small solvent effects which have been
found for the saturated hydrocarbon pinane,
whose rotation is nearly constant in most
solvents, once secondary effects of the refrac-
tive index have been taken into account.[16]

We may say, then, that those factors which
reduce the directional character of the inter-
action between solvent and solute will generally
reduce the solvent effect on the rotatory power.
Now, one of the most effective ways of reducing
a relatively large frequency of occurrence of
certain preferred orientations of solvent and
solute molecules is to increase the temperature.
That is, by increasing the temperature, solvent
effects should decrease, and when the tempera-
ture is raised, the rotations of a given substance
in different solvents should tend to approach one
another (correction having been made for the

[16] Rule and Chambers, J. Chem. Soc. p. 145 (1937).

different refractive indices of different solvents by dividing the rotation² by $(n^2+2)/3$. This has frequently been noticed,[17] but the effect is most strikingly shown by the very completely investigated case of diethyl tartrate. In Fig. 7 the temperature dependence of the rotations of diethyl tartrate in various solvents is shown. It will be seen that at high temperatures the rotations of diethyl tartrate in all solvents tend to have a value of about 35°–45°. If the rotations used in the figure had been corrected for the effect of the refractive index, the tendency of all of the curves to converge on a single rotation would presumably have been even more marked.[18]

The so-called "structural" contribution to the optical rotatory power of solids (that is, the difference between the rotatory power of a crystal averaged over all orientations of the crystal with respect to the light wave, and that of the same substance in the dilute vapor) is really only another aspect of a solvent effect, this time carried to an extreme. It is again merely due to interactions which occur between neighboring molecules which have taken up very definite orientations with respect to one another, so forming a clearly defined "solvent-solute" complex. In the case of those crystals, such as quartz, or better, diacetyl phenolphthalein, which are optically active in spite of the fact that the molecules of which the crystal is made are themselves inactive, we thus arrive at the interesting conclusion that all of the optical rotatory power arises from "solvent effects" of one kind or another.

An interesting exception to the tendency of the structural contributions to be large in solids is to be found in camphor, where the optical rotations of the solid and liquid forms are very nearly the same. This is doubtless due to the fact that camphor molecules are nearly freely rotating with respect to one another in the crystal as well as in the melt—a fact which is known from the study of the dielectric constant of solid camphor.[19]

[17] Lowry, *Optical Rotatory Power* (Longmans, Green and Co., New York, 1935), p. 353.

[18] The data used in preparing Fig. 7 were obtained from a series of papers by Patterson and co-workers in J. Chem. Soc. London, 1901 ff.

[19] White and Morgan, J. Am. Chem. Soc. 57, 2078 (1935).

9.

A number of optically active substances are known in which the axes of symmetry of the groups attached to the asymmetric carbon atom all intersect in one point. Where the groups are linear or the axes are threefold, the optical rotations which are observed must be due to vicinal actions of higher order than the first. The following are the rotations of some of these substances:

$$
\begin{array}{ll}
\begin{array}{c} H \\ CH_3 \cdot C \cdot CN \\ Br \end{array} & [M]_D = 21° \text{ [20]} \\[2em]
\begin{array}{c} H \\ CH_3 \cdot C \cdot CN \\ NH_3^+ \end{array} & [M]_D = 13° \text{ [21]} \\[2em]
\begin{array}{c} I \\ H \cdot C \cdot SO_3^- \\ Cl \end{array} & [M]_D = 36° \text{ [22]}
\end{array}
$$

The orders of magnitude of the rotations which are found here should be taken as typical of those to be expected for class C aliphatic compounds. It would be very interesting to have data on the effects of temperature and solvent on the rotations of these compounds in order to evaluate the importance of first-order interactions with neighboring solvent molecules in determining the value of the optical rotatory power.

10.

Whether or not the optical rotatory power of a given molecule arises from first-order vicinal actions is a question of great importance when one is trying to calculate the optical rotation. It is well to point out the probable unsoundness of any theory with attempts to explain optical activity without taking into account first-order vicinal actions. Until a more complete knowledge of these is available, it is hard to see how progress can be made in understanding higher order vicinal actions, since these are probably best regarded as a result of the compounding of first-order effects.

[20] Berry and Sturtevant, J. Am. Chem. Soc. **61**, 3583 (1939).

[21] Delepine, Bull. Soc. Chim. (3) **29**, 1195 (1903).

[22] Read and McMath, J. Chem. Soc. p. 273 (1932).