RECENT PROGRESS IN STEREOCHEMISTRY[1]

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One of the basic demands of organic structural chemistry is that there be a clear and precise relationship between the constitutional formula of a substance and its chemical and physical behavior. Butlerow, one of the most distinguished champions of this principle, expressed it as follows: "Two molecules of the same empirical composition must be identical when the chemical relationship of each single constituent atom toward other elements is the same." Countless cases of isomerism, especially that of the lactic acids, which was thoroughly investigated by Wislicenus, seemed to contradict this principle, and were the direct occasion for the conception of stereochemistry. It was the happy idea of van't Hoff and LeBel to assign tetrahedral symmetry to the valences of the carbon atom which, together with a few surprisingly simple auxiliary hypotheses, made the development of a complete system of structural chemistry possible.

From the very beginning stereochemistry developed beyond its original problem, namely, the explanation and prediction of isomerism. The conception of structural formulas in three-dimensional space immediately affected the entire system of organic reactions. The space structure of molecules furnished an explanation for the facility or difficulty of reactions observed in cases of condensation, splitting-off, ring-closure, and the phenomena of steric hindrance. The still unexplained phenomenon of the Walden inversion led directly to research on substitution problems. From the stereochemistry of carbon there gradually developed a stereochemistry of other elements. Passing beyond

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[1] Translated from the German by the Editor.

their original sphere in organic chemistry, the concepts of stereochemistry showed their validity in the entire chemical realm. Werner's system of inorganic complex compounds reached its climax in the splitting of complex salts into optical isomers.

The methods of stereochemistry provided a subtle means of penetrating into the structure of molecules. On the other hand, the splendid development of atomic physics in the present century has led to new and quite independent statements in regard to the structure of molecules. Thus today stereochemistry finds it necessary to take into account the results of research in physics, and thereby has again entered a new phase of its development. For the older stereochemistry it was sufficient to describe approximately the symmetry characteristics of the molecules and their chemical consequences. But modern atomic physics gives us, in principle at least, the means for determining the absolute dimensions of molecules, the atomic coördinates, and the gradation of valence forces. As a result, the demands which we must make of a molecular model today are incomparably more severe than in any former epoch.

Even this hasty sketch shows sufficiently the multiple anchoring of stereochemistry, not only in the science of chemistry, but in physics as well. Even if we confine ourselves to recent times, it is not possible to give a survey of the entire subject of stereochemistry in the narrow confines of a single essay. The discussion will therefore be restricted to the consideration of several interesting questions, the solution of which might be expected to result in important advances in stereochemistry as a whole.

I. OPTICALLY ACTIVE DERIVATIVES OF DIPHENYL

One of the most valuable advances in stereochemistry was the discovery by Christie and Kenner of the optically active derivatives of diphenyl. As is so often the case, erroneous observations gave the final impetus to this discovery. In 1907 Kaufler (1) had concluded from the presumption of a ring-closure reaction in benzidine that this substance had a structural formula containing two parallel benzene rings (formula I). If this configuration

were also attributed to diphenyl, then we should expect *cis* and *trans* forms to result from certain substitutions (formulas II and III).

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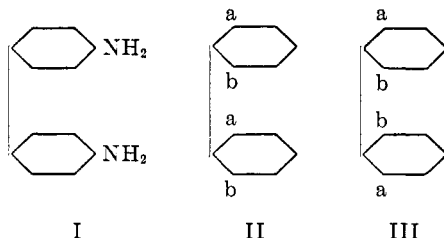
In certain cases these were, in fact, found (2). Inspection of the formulas shows furthermore that the *trans* form (III) has no plane of symmetry and therefore must be resolvable into optical isomers (3). In 1921 Kenner and Stubbings (4) prepared synthetically a 6,6'-dinitrodiphenic acid (γ-acid) which appeared to be a stereoisomer of the already known 6,6'-dinitrodiphenic acid (β-acid). Since the γ-acid, unlike the β-isomer, forms a dilactam (formula V) on reduction, formula IV was considered the correct representation of its constitution.
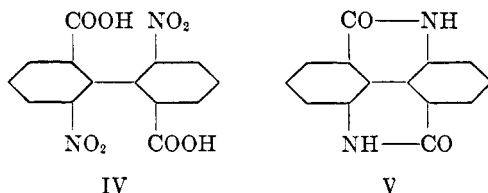
Assuming Kaufler's diphenyl formula, the γ-acid must be resolvable into optical isomers. In fact, this proved to be possible not only with the γ-dinitro acid but also with the 4, 6, 4,' 6'-tetranitrodiphenic acid (5). This seemed at first to form a strong support for Kaufler's assumption. Nevertheless a few years later the work of LeFèvre and Turner (6) showed that the diphenyl derivatives which were regarded as *cis-trans* isomers are in reality structural isomers, and that ring-closure cannot be accomplished between the amino groups of benzidine. Neither is there any such isomerism in the case of the dinitrodiphenic acids.

The β-acid proved on investigation by Christie, Holderness, and Kenner (7) to be 4, 6'-dinitrodiphenic acid and was also resolvable into optical isomers.   On the basis of these facts there is only *one* possibility of explaining the occurrence of optical activity. We must assume that the free rotation of the two phenyl groups about their connecting axis is prevented by substitution in the ortho position and that as a result the planes of the rings, while they possess a common axis, nevertheless form an angle with each other.

As is shown by formula VI in the case of 6, 6'-dinitrodiphenic acid,[2] such a molecule does not possess any plane or center of symmetry
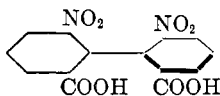
VI

and must therefore be resolvable into optical isomers.   In this manner these unique cases of isomerism were included in the concept of steric hindrance and were thus deprived of their exceptional character.   Proof that this explanation is correct is furnished by tables 1 and 2, in which are listed all the diphenyl derivatives and their analogs which have been studied with a view to resolution into optical isomers.   The minimum requirement for isomerism appears to be substitution in the 2, 6, and 2' positions.   Hence at least *three* of the four ortho positions must be occupied.

There has been active discussion concerning the immediate causes of steric hindrance in these diphenyl derivatives.   In opposition to the majority of workers (34) in this field, Turner (35) has defended the opinion that this is not a case of purely "mechanical" hindrance, determined only by the volume of the substituent groups, but that an "inherent property" of the parent hydrocarbon is involved and that a dominant rôle is played by the residual affinities in the sense of Thiele's theory.   Apart

[2] The left-hand ring lies in the plane of the paper; the right-hand one is perpendicular to it and is bisected by the plane of the paper.
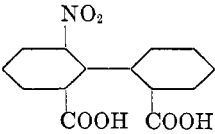
TABLE 1

Optically resolved diphenyl derivatives
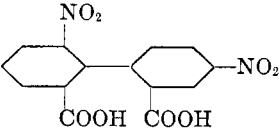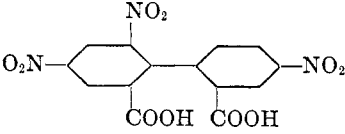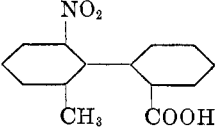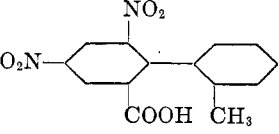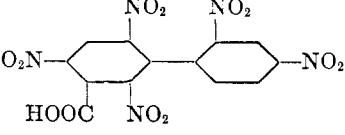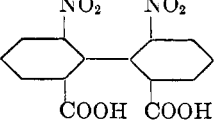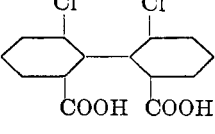
SUBSTANCE		REFER-ENCE
6-Nitrodiphenic acid		8
4,6'-Dinitrodiphenic acid		10
4,6,4'-Trinitrodiphenic acid		13
2-Methyl-6-nitrodiphenyl-2'-carboxylic acid		41
2,4-Dinitro-2'-methyldiphenyl-6-carboxylic acid		17
* 2, 4, 2', 4', 6'-Pentanitrodiphenyl-3'-carboxylic acid		40
* 6,6'-Dinitrodiphenic-acid		9
6, 6'-Dichlorodiphenic acid		11

TABLE 1—*Continued*
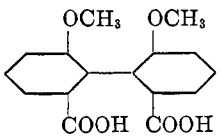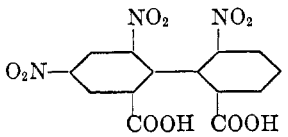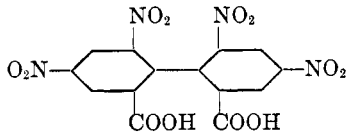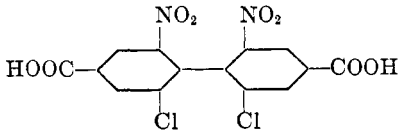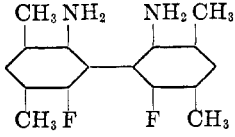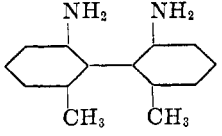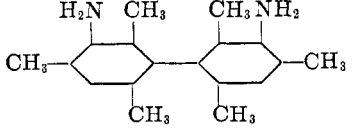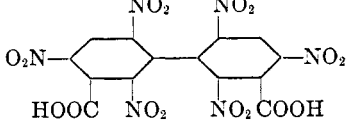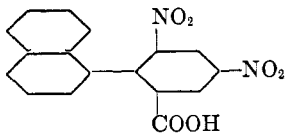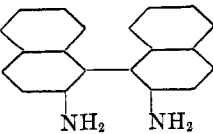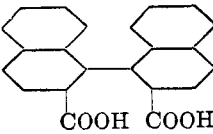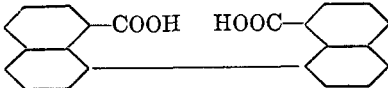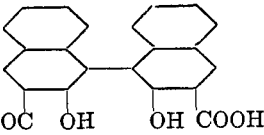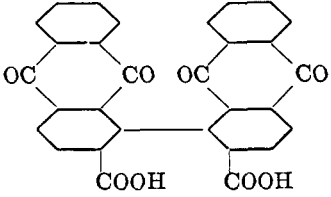
SUBSTANCE		REFER-ENCE
6,6'-Dimethoxydiphenic acid	OCH₃ OCH₃ (structure) COOH COOH	12
4,6,6'-Trinitrodiphenic acid	NO₂ NO₂ O₂N— (structure) COOH COOH	14
*4,6,4',6'-Tetranitrodiphenic acid	NO₂ NO₂ O₂N— (structure) —NO₂ COOH COOH	9
6,6'-Dichloro-2,2'-dinitrodiphenyl-4,4'-dicarboxylic acid	NO₂ NO₂ HOOC— (structure) —COOH Cl Cl	15
2,2'-Difluoro-6,6'-diamino-3,5,3',5'-tetramethyldiphenyl	CH₃ NH₂ NH₂ CH₃ (structure) CH₃ F F CH₃	42
* 6,6'-Diamino-2,2'-ditolyl	NH₂ NH₂ (structure) CH₃ CH₃	16
* 3,3'-Diamino-2,4,6,2',4',6'-hexamethyldiphenyl	H₂N CH₃ CH₃ NH₂ CH₃— (structure) —CH₃ CH₃ CH₃	18
* 2,4,6,2',4',6'-Hexanitrodiphenyl-3,3'-dicarboxylic acid	NO₂ NO₂ O₂N— (structure) —NO₂ HOOC NO₂ NO₂ COOH	39

The chemical structures in the table are:

TABLE 1—*Concluded*

SUBSTANCE		REFER-ENCE
* 3,5-Dinitro-2-α-naph-thylbenzoic acid		43
* 2,2'-Diamino-1,1'-di-naphthyl		19
* 1, 1'-Dinaphthyl-2, 2'-di-carboxylic acid		20
1, 1'-Dinaphthyl-8, 8'-di-carboxylic acid		44
* 2,2'-Dihydroxy-1,1'-di-naphthyl-3, 3'-dicarbox-ylic acid		21
* 1, 1'-Dianthraquinonyl-2, 2'-dicarboxylic acid		22

from the fact that we cannot realize the meaning of these in-definite ideas, we should expect, if Turner were right, depen-dence of the effect upon the "polarity," or the substitution type, of the substituents. As is shown by table 1, this is not the case. Resolution into isomers was revealed in every possible combination of meta directing and of ortho-para directing sub-stituents in the four ortho positions (15, 18). Although this

specific hypothesis of Turner may thus be questioned, the assumption of a purely mechanical effect is also inadequate. Actually we are dealing with an electrostatic influence between the approaching electron orbits of the substituents (36).

If the interpretation of these phenomena as steric hindrance is correct, it should not be limited to the derivatives of diphenyl, but

TABLE 2

Compounds which are not resolvable

COMPOUND	REFERENCE
o-Nitrobenzoic acid	16
5-Nitro- and 8-nitro-1-naphthoic acids	16
Diphenyl-2-carboxylic acid	25
Diphenic acid	8,23
4-Nitrodiphenic acid	8
4, 4'-Dinitrodiphenic acid	24
5, 5'-Dichlorodiphenyl-3, 3'-dicarboxylic acid	26
4, 6-Dinitrodiphenyl-2-carboxylic acid	27
4, 6-Dinitro-3'-methyldiphenyl-2-carboxylic acid	27
Diphenyl-2, 2'-disulfonic acid	28
Benzidine-2, 2'-disulfonic acid	23
1, 1'-Diamino-2, 2'-dinaphthyl	29
1, 1'-Dianthraquinonyl-4, 4'-dicarboxylic acid	30
ar-Stilbenecarboxylic acids	31
6-Nitro-2-carboxybenzoic acid isopropyl ester	32
6-Nitro-2'-hydroxy-4'-methylbenzophenone-2-carboxylic acid	32
3-Bromo-4'-amino-2, 4, 6-trimethylbenzophenone	32
3-Bromo-3', 5'-diamino-2, 4, 6-trimethylbenzophenone	32
6-Hydroxy-2-methylbenzoic acid	33
2, 5-Dinitro-α, 3, 4, 6-tetramethylcinnamic acid	32
4-Amino-2-isobutenylmesitylene	32
2, 4, 6-Tribromo-3-amino-α-methylcinnamic acid	32

should be encountered with other compounds of the appropriate structure. Actually, not only has a series of analogous derivatives of 1, 1'-dinaphthyl and of 1, 1'-dianthraquinonyl been resolved, as is shown in table 1, but Mills (37) has succeeded in demonstrating similar hindrance effects in the 1, 8-disubstituted derivatives of naphthalene and quinoline. The constitution of these compounds is represented in formulas VII and VIII.

VII VIII
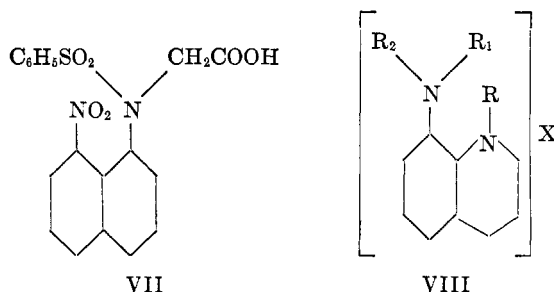
Several derivatives of N-phenylpyrrole and of N, N'-dipyrryl have been resolved by Adams and his coworkers (46, 47), but similar attempts with derivatives of 2-phenylpyridine and 3-phenylpyridine have to date failed (48). Adams (32) has also attempted unsuccessfully to resolve into optical components several compounds of the following types:
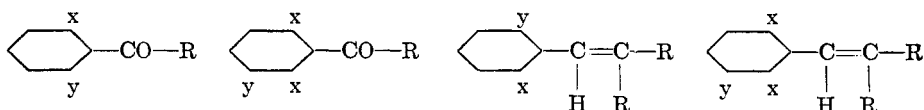
The difficulties of optical resolution, which may become impossible with high velocities of racemization, are avoided by turning to the derivatives of terphenyl. It is evident that a compound of the type

a b
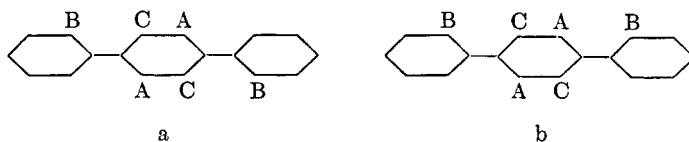
must exist in a meso form (a) and a racemic form (b) if free rotation is excluded. In fact, Browning and Adams (49) have found two stereoisomeric forms of 3,6-dibromo-2,5-di-m-xylylhydroquinone.
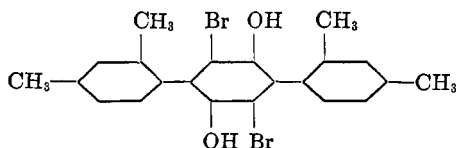
A number of analogous cases have been described by Adams and his coworkers (50).

The reason for the reported isomerism is therefore unquestionably determined and the data already available are ample. It would now be of great interest to ascertain the stability of the optical isomers that have been isolated. Presumably every degree of racemization velocity will be encountered, correspond-

TABLE 3

Overlapping of ortho substituents in diphenyl derivatives

GROUPS IN POSITION		SUM OF INTERNUCLEAR DISTANCES OF 2,2′ GROUPS IN Å.	INTERFERENCE OVER 2.90Å. VERTICAL DISTANCE BETWEEN 2,2′ CARBON ATOMS
2,2′	6,6′		
A {CH₃	CH₃	3.46	0.56
CH₃	NH₂	3.29	0.39
COOH	Cl	3.45	0.55
COOH	CH	3.46	0.56
COOH	CO	4.01	1.11
OH	CH	3.44	0.54
COOH	NO₂	3.48	0.58
NO₂	NO₂	3.84	0.94
F	NH₂	2.95	0.05
B {COOH	F	2.95	0.05
F	Cl	3.28	0.38
F	F	2.78	−0.12
F	OH	2.93	0.03
F	CO	3.91	1.01
OH	OH	3.08	0.18
OH	NH₂	3.1	0.20
COOH	COOH	3.12	0.22
COOH	H	2.5	−0.4

ing to the steric hindrance effects which the substituents exert upon each other.

Stanley and Adams (38) have attempted to estimate the volume occupied by the substituents in several diphenyl derivatives by utilizing the apparent atomic diameters measured by means of x-rays. They assume a value of 2.90 Å. for the distance between the 2 and the 2′ positions in unsubstituted diphenyl. Table 3 gives the results of their calculations. The members of the

diphenic acid series which have been optically resolved are listed in section A of the table. Obviously the overlapping is in every case considerable. Section B of the table shows further that with these combinations every grade of stability is to be expected. Clearly the numerical relationships can be regarded merely as rough qualitative approximations. The available x-ray data are neither plentiful nor consistent; also, the application of these figures to the liquid state is not directly self-evident.

The quantitative data now available on the racemization velocity of such diphenyl compounds are not very abundant, but in view of the very uncertain methods of calculation involved the agreement between theory and experiment is not unsatisfactory. Evidence on this point has been furnished by R. Kuhn (45) and by Adams. The majority of the compounds that have been studied racemize with great difficulty or not at all. These compounds are marked with an asterisk in table 1. They are, in general, compounds in which all four ortho positions are occupied. On the other hand, as was to be expected, 4,6'-dinitrodiphenic acid is racemized with relative ease; its solution in $2 N$ sodium carbonate is stable at room temperature, but it loses its activity on boiling, falling to half-value in 18 minutes. A heat of activation of 26 kg-cal. per mole is calculated from the unusually high temperature coefficient of 5.2 (between 70° and 100°). Also easily racemized is 4, 6, 4'-trinitrodiphenic acid, the heat of activation being 22 kg-cal. per mole. 2,2'-Difluoro-6, 6'-diamino-3, 5, 3', 5'-tetramethyldiphenyl is racemized by merely boiling in alcohol. The naphthalene derivative described by Mills is racemized in a short time at room temperature; its heat of activation is 18.5 kg-cal. per mole. And 1,1'-dinaphthyl-8,8'-dicarboxylic acid is but slightly stable in its active form.

Finally, the observations of R. Kuhn (19) on diaminodinaphthyl (formula IX) are of interest. This compound shows no tendency whatever toward racemization. When heated it goes over into the optically inactive dibenzocarbazole (formula X). The inactivity of dibenzocarbazole was quite as expected on the basis of all present knowledge of the stereochemistry of aromatic ring systems.

IX   X   XI
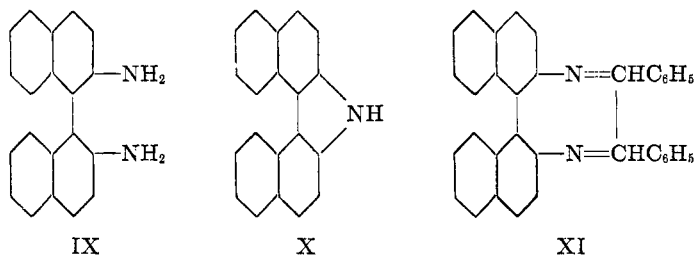
Its formation also shows that the breaking of the bond between carbon and nitrogen is more readily effected than is the racemization of diaminodinaphthyl. Furthermore, one would expect that when diaminodinaphthyl is hydrogenated the substituents in the ortho positions would have an opportunity to diverge somewhat from each other. In fact, an investigation using diacetyldiaminodinaphthyl revealed inactive reaction products, though these were not studied further. Of very especial interest is the formation of a highly active ring compound (formula XI) by the condensation of diaminodinaphthyl with benzil, the activity of which is also lost through hydrogenation.

The disappearance of optical activity in the formation of condensed ring systems has also been observed by Meisenheimer and Höring (16) in the following reaction sequence:

active   active   inactive
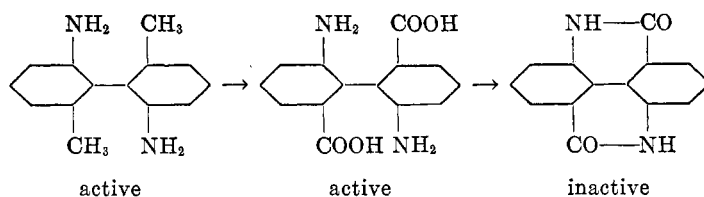
II. THE STEREOISOMERIC DECAHYDRONAPHTHALENES

The underlying hypothesis of stereochemistry was expressed by its originators in somewhat different forms. Pasteur, on the basis of the organic chemistry of his day, considered dissymmetry of molecular structure as requisite for optical isomerism. LeBel's conception is similar to that of Pasteur; he conservatively applied the formal principles of symmetry theory to the molecule postulated by structural chemistry. On the other hand, van't Hoff

sought the cause of optical isomerism in the dissymmetry of one element of the molecule, and thus devised the conception of the asymmetric carbon atom. Later investigators, namely Aschan (51), F. M. Jaeger(52), and Mills (53), have rightly considered Pasteur's point of view as the more general and more serviceable. Their opinion was based on compounds of the type of spirane and of certain optically active complex salts, which had been discovered by that time, and which demand very artificial auxiliary constructions if an asymmetric central atom, as conceived by van't Hoff, is to be assumed. We have met an excellent example of this kind in the above case of the diphenic acids. Although the special concept of an asymmetric atom has not proved in the course of time to be especially fortunate, we must not forget that the tetrahedral carbon atom, considered simply as a model, was actually an extraordinary advance beyond the happy intuition of Pasteur, for it was this conception which made it possible to construct molecular models to which the criterion of molecular dissymmetry could profitably be applied.

There is therefore even today notable interest in new experimental material for the verification of a tetrahedrally symmetrical carbon atom. As is well known, Baeyer (54) suggested in his strain theory the possibility of the deformation of the carbon tetrahedron and thence drew important conclusions which have received attention even very recently (55). One of the postulates of Baeyer's strain theory was the planisymmetrical structure of cyclohexane, for which there seemed to be overwhelming stereochemical evidence. Not until the fine work of Böeseken and his school on the configuration of the cyclic glycols (56) was there occasion to return to non-planar models of cyclohexane (56a). The proof that it is possible to construct a strain-free model of cyclohexane from regular tetrahedrons had been provided by Sachse (57) in 1890. Decisive arguments against the plane structure of hydroaromatic rings of six and more members were, however, first furnished by the surprising discoveries of W. Hückel in the decalin series and of Ruzicka on the higher-membered carbon rings.

The previous development of this work has been described by

Hückel (58) himself, so that but few words are needed here. It
was shown originally by Mohr (60) that two forms of decahydro-
naphthalene can be constructed from tetrahedral models. One
is the so-called *trans* form (figure 1), which shows the symmetry
of a cubic lattice (diamond), and the other is the *cis* form (figure
2), which has hexagonal symmetry (Wurtzite lattice). Both
forms seem to be stable and can be converted into one another
only with some difficulty. We would therefore predict the
existence of two decalins and would expect four racemic forms of a
monosubstitution product, derived in pairs from the *cis* and the
trans forms. These deductions were brilliantly confirmed by
experiments. It turned out that the two known β-decalols, with
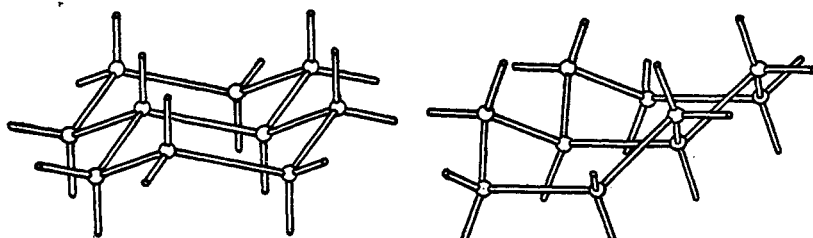
Fig. 1   Fig. 2

Fig. 1. *Trans* Form of Decahydronaphthalene
Fig. 2. *Cis* Form of Decahydronaphthalene

melting points of 75° and 105°, which had been considered as
cis-trans isomers analogous to borneol and isoborneol, actually
belong to two different steric series, for they may be oxidized to
two different decalones, which can in turn be reduced to the
original decalols. The decalols can be disintegrated by oxidation
to a mixture of cyclohexanediacetic acid and cyclohexane-1-pro-
pionic-2-carboxylic acid, whereupon the corresponding acids
again appear in pairs of *cis-trans* isomers. The configuration of
the *trans*-cyclohexanediacetic acid was established by its resolution
into optical isomers. Finally, the *cis*- and *trans*-β-decalones
were synthesized from *cis*- and *trans*-cyclohexane-1-acetic-2-
propionic acid. Further work identified the two missing β-de-
calols and the four possible β-decalylamines were also prepared.
The following diagram summarizes the relationships.

CH_2COOH

CH_2CH_2COOH

cis-Cyclohexane-1-acetic-2-propionic acid m.p. 109°

CO CH_2 CH_2

α-Hydrindone

CH_2COOH

CH_2CH_2COOH

trans-Cyclohexane-1-acetic-2-propionic acid m.p. 116°

=O

cis-Decalone

$COOH$ CH_2CH_2

cis-Cyclohexane-1-propionic-2-carboxylic acid m.p. 103°

$COOH$ CH_2CH_2

trans-Cyclohexane-1-propionic-2-carboxylic acid m.p. 143°

=O

trans-Decalone

OH

cis-Decalol m.p. 105°

CH_2COOH CH_2COOH

cis-Cyclohexanediacetic acid m.p. 160°

CH_2COOH CH_2COOH

trans-Cyclohexanediacetic acid m.p. 167°

OH

trans-Decalol m.p. 75°

Willstätter

Pt

$Ni + H_2$ (gives among other products)

OH

ac-Tetralol

OH

ar-Tetralol

Investigation of the analogous α-derivatives gave one important result, namely, an easy transition from the *cis* to the *trans* series. *Cis*-α-decalone is converted to the *trans* form under the action of several reagents and even spontaneously on standing or under distillation. Probably the enol form is an intermediate step. Similarly, the *cis*-α-decalol in the form of the sodium compound is converted to the *trans* form on heating. As to the rest, disintegration by oxidation gives a picture similar to that of the β-series.

In addition, the two parent hydrocarbons have been obtained, apparently in homogeneous condition. They may be prepared by reduction of the crystallized decalones by Clemmensen's method or by the splitting of water from the decalols followed by hydrogenation of the resulting octalins. Finally, they have also been separated from technical decalin by fractional distillation. The hydrogenation of naphthalene in glacial acetic acid according to Willstätter gives exclusively the *cis* form, while hydrogenation by Sabatier's method gives predominantly the *trans* form. The following table shows the marked differences in their physical constants.

	MELTING POINT	BOILING POINT	D_4^{20}	n_D^{20}	HEAT OF COMBUSTION
					calories per gram
cis-Decalin	about −51°	193°	0.895	1.480₅	10,858
trans-Decalin	about −36°	185°	0.869	1.469₅	10,824

The energy difference per molecule is 4.7 kg-cal. in the case of the decalins and 2.3 kg-cal. in the β-decalones. It is well known, however, that heretofore it has seldom, if ever, been possible to prepare liquid organic substances in a sufficient degree of purity to utilize the possible accuracy of the combustion method (about 0.02 per cent). It is therefore hardly possible to judge definitely the significance of these figures.

The facts which have been reported certainly show that the cyclohexane rings in decalin cannot lie in one plane. At the

very least this is true for *trans*-decalin, for it is impossible to construct a model of it out of two planar cyclohexane rings. It is therefore difficult to understand how Haworth (61) reaches the the conclusion that these phenomena of isomerism are compatible with the assumption of planar cyclohexane rings. The stereochemical deductions from Mohr's models of decalin have been tested further by Rao (62) and have been entirely confirmed. Yet we can hardly follow Rao in regarding his researches as a support of Ingold's well-known theory of "valency-deflexion." This theory[3] has been convincingly refuted by Hückel (55).

The stereochemistry of the decalins presents another problem of considerable interest, namely, what happens when a double bond is introduced into the molecule. Assuming van't Hoff's model of a double bond with four valences in a single plane, it is possible, but not certain, that isomerism would be eliminated by flattening of the rings. In the model of *trans*-decalin the van't Hoff double bond cannot be used at all. On the other hand, we do have reason to think that our conceptions of the space-structure of the double bond are in need of revision. Consequently, we have in this case a problem with two unknowns. W. Hückel (63) has attacked this problem too. The manipulation of these hydrocarbon mixtures is naturally one of considerable difficulty, and hence no conclusive results have been obtained. One important result nevertheless seems certain,—the existence of a *trans*-Δ^2-octalin which on oxidation gives *trans*-cyclohexanediacetic acid, and of *cis*-$\Delta^1 + \Delta^2$-octalin, the homogeneity of which is not yet established, and which on oxidation gives *cis*-cyclohexanediacetic acid and *cis*-cyclohexane-1-propionic-2-carboxylic acid. Thus at least a part of this interesting problem seems to be solved. The constitution of $\Delta^{9,10}$-octalin (formula XII) is worthy of note and has been thoroughly investigated (64).

[3] Compare also Ingold and Thorpe (J. Chem. Soc. **1928**, 1318); Desai (J. Chem. Soc. **1932**, 1047); Ives, Linstead, and Riley (J. Chem. Soc. **1932**, 1093). Special interest in this connection should be given to the work of Qudrat-I-Khuda (J. Indian Chem. Soc. **8**, 277 (1931); Chem. Zentr. **1932**, I, 221) who has found four isomers of 4-methylcyclohexane-1-carboxylic-1-acetic acid. This result, should it be confirmed, agrees only with a non-planar cyclohexane ring.

XII

Two stereoisomeric ring systems have also been established in the series of perhydrogenated indenes (hydrindans). Hückel and Friedrich (65), starting with cis- and trans-cyclohexane-diacetic acid, have prepared the corresponding β-hydrindanones which in turn were converted by oxidation into cis- and trans-cyclohexane-1-acetic-2-carboxylic acids. One deduction from the structural considerations is in this case readily subject to experimental proof, namely, that the cis-hydrindanone must give rise to two stereoisomeric cis-hydrindanols on reduction, while the trans form can give only one such alcohol. This has been experimentally confirmed.
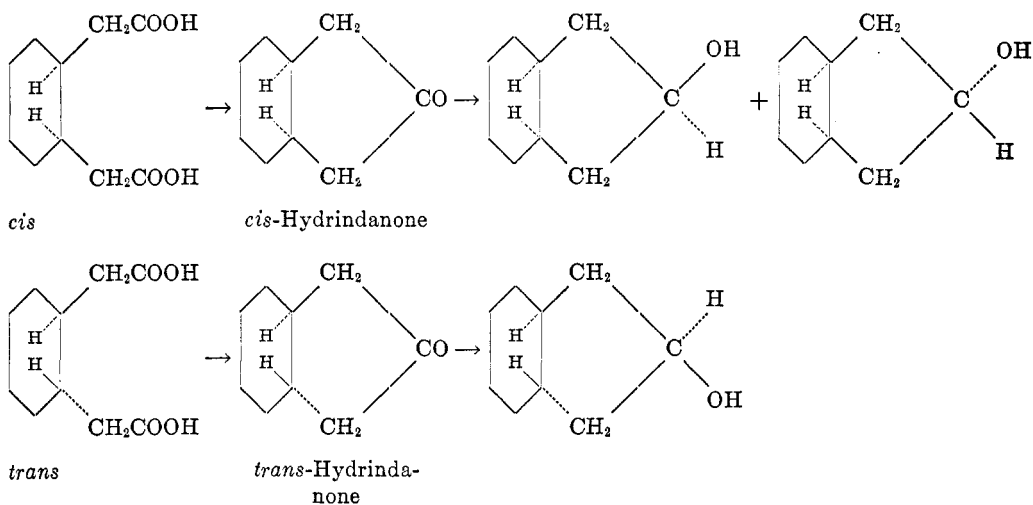
Although the structural model of trans-hydrindanone reveals a certain strain, yet the cis compound, judging by the heats of combustion, has the higher energy content. The energy difference (with the limitations mentioned above) amounts to 2 kg-cal.

This type of isomerism is not restricted to isocyclic compounds; heterocyclic substances show analogous phenomena. The cases

that have been most thoroughly investigated are those of decahydroisoquinoline (66), decahydroquinoline (67), and octahydroacridine (68).

For the judgment of Baeyer's strain theory, Ruzicka's discovery of many-membered carbon rings and the proof of their considerable stability toward chemical influences is of great importance. On Baeyer's assumption a seventeen-membered ring should be under about the same tension as a three-membered ring. Actually, however, cyclopentadecane and cycloheptadecane resist the action of hydriodic acid and phosphorus at 250°. Cycloheptadecanone can be passed over thorium oxide at 400° without change except for a slight carbonization. The difficulty of preparing the rings containing a large number of carbon atoms is therefore not explained by their instability, although the latter is often assumed.

According to Ruzicka's hypothesis the tendency to ring formation is determined by two factors which are independent of each other. The first (factor a) is the distance between the reacting terminal groups in the acyclic starting material; the second (factor b) is the tension in the ring system produced. The resultant (c) of both factors determines the yield. The probability that the reacting terminal groups will come into a position favorable to ring-closure decreases with the increase of the length of the chain. The ring tension reaches its minimum at five members and remains constant thereafter. The resulting yield-curve is shown diagrammatically in figure 3.

The physical properties of these unique homologous series present an interesting picture. As figure 4 shows, the melting points of the ketones from cyclooctanone to cyclotriacontanone oscillate in a very peculiar manner. It can hardly be doubted, if only on the basis of their irregularity, that these oscillations are not comparable with those that occur, for instance, in the homologous series of the aliphatic carboxylic acids. This is quite comprehensible, since the addition of a CH_2 group to a zigzag chain has an entirely different effect on the spatial structure from its entrance into a ring of moderate size. The density curve of the ketones and of the hydrocarbons is quite without analogy, for it

shows a definite maximum.   This may be interpreted to mean
(70) that as the number of members in the rings increases the
plan of structure is altered.   While the lower members have an
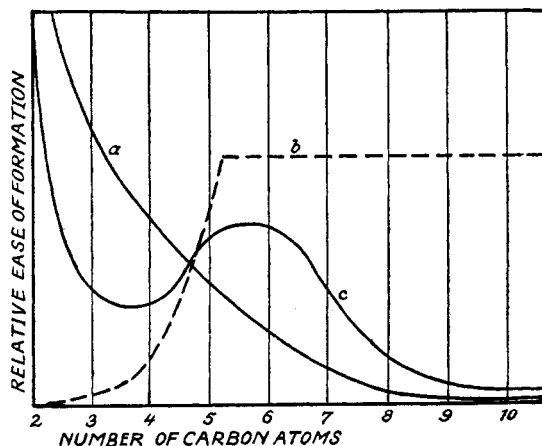
FIG. 3. EASE OF FORMATION OF CARBON-ATOM RINGS
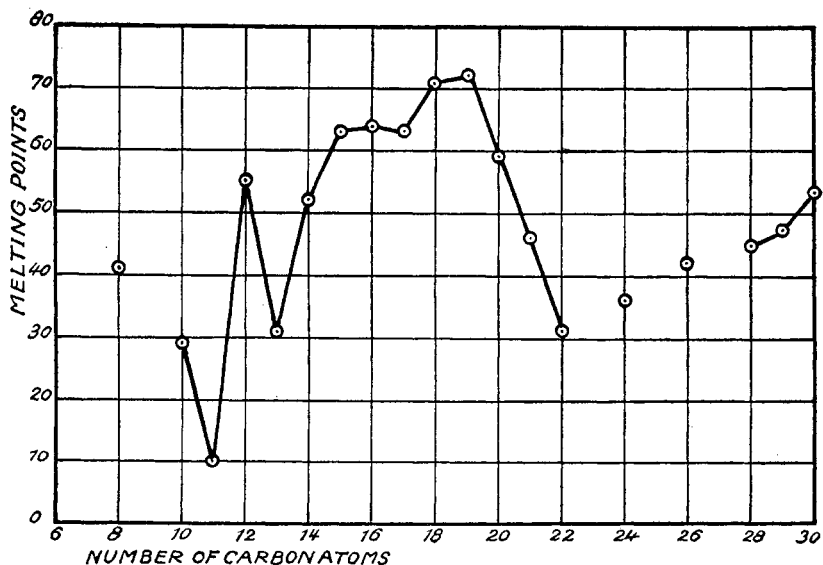
FIG. 4. MELTING POINTS OF KETONES FROM CYCLOÖCTANONE TO CYCLOTRIA-
CONTANONE

approximately circular distribution of the carbon atoms, these atoms in the higher membered rings may group themselves in two parallel chains connected at the end (figure 5).[4] The investigations of Katz (71) on the x-ray patterns of these substances in liquid form and on their spreading on a water surface are also interpreted from this point of view.

In recent years attempts have frequently been made to compare the heats of combustion of polymethylene compounds with the predictions of Baeyer's strain theory (55).   It is more than doubtful whether the conclusions have even qualitative significance. The heats of combustion of cyclopropane as determined by Thomsen and by Berthelot differ by almost 8 kg-cal. per mole.   In the opinion of thermochemists, Thomsen's values
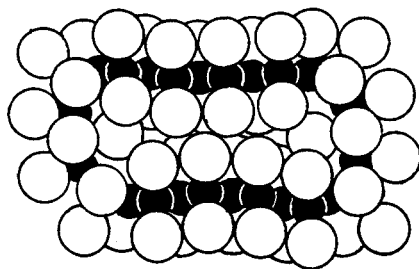
FIG. 5. POSSIBLE ARRANGEMENT OF CARBON ATOMS IN LARGE RINGS

for gases are the more reliable, as has been shown again recently by von Wartenberg and Krause (72).   But since the cyclopropane used in both cases was presumably very impure (73), we must leave the question open.   The author has recently shown that the methylcyclobutane which was used for combustion by Subow and which served as the basis of calculations for the four-membered ring, was incorrectly listed in the literature as a cyclobutane derivative.   It had been recognized by Rosanow and Filipow (74) as an impure cyclopentane.   Consequently there is no reliable foundation for the three-membered and the four-

[4] The black spheres in figure 5 represent carbon atoms, the white spheres hydrogen atoms. The size of the latter is exaggerated in order to give a correct picture of the effective space requirement of the methylene group.

membered rings, the very cases where the predictions of Baeyer's strain theory are the most definite. The heats of combustion of the polymethylenecarboxylic acids are better known. Apart from the fact that a comparison of some of their substitution products instead of the polymethylenes themselves is objectionable, there is the difficulty that the heats of sublimation must be known in order to recalculate to the gaseous condition. We cannot here have recourse to any schematic assumptions, as was shown by the studies of A. Wassermann (75) on the heats of combustion of fumaric and maleic acids. The clarification of these questions requires above all new experimental determinations.

Verkade (76) rightly demands "a penetrating insight into the energy relationships and the stability relationships of a large number of successive members of the homologous series of the cycloparaffins and of the homologous series of their derivatives, including the rigid small rings as well as the large ones." He has already published a lengthy series of measurements on hydroaromatic glycols. We refrain from reproducing his data at this point in order not to anticipate his intended theoretical discussion. His very interesting data once more demonstrate that the heats of combustion of solid substances cannot be schematically compared.

III. SOME OPTICALLY ACTIVE COMPOUNDS WITH INORGANIC GROUPS

Several especially interesting cases of optical isomerism have recently been found among this type of compounds. They deserve special attention because previous structural formulas did not seem to permit such isomerism.

Most notable is the discovery by H. Phillips (77) in 1925 of an optically active sulfinic acid ester. By treating active octanol-2 with toluenesulfinyl chloride he obtained octyl p-toluenesulfinate, $C_7H_7 \cdot SO \cdot O \cdot CH(CH_3) \cdot C_6H_{13}$, which was separated by fractional distillation at very low pressure into fractions of different rotations and which apparently represented a mixture of the two diastereoisomeric esters of active toluenesulfinic acid and the active octanol. Similarly the action of active octanol on ethyl p-toluenesulfinate gave an active ethyl p-toluenesulfinate. The

examination of these very unstable compounds is not simple, for they are all uncrystallizable. The octyl esters showed decided mutarotation effects, the cause of which has by no means been established. The surest evidence for the actual existence of optically active sulfinic acid esters is the fact that it is possible to oxidize the active ethyl ester *quantitatively* to the crystallizable, optically *inactive* ethyl *p*-toluenesulfonate.

On the basis of the structural model the activity of the sulfinic acid molecule may be interpreted in several ways. Phillips himself proceeds from the fact that according to the electron theory of valence the sulfinic esters contain an oxygen atom united by a semipolar bond; he therefore writes their electronic formulas as follows (formula I):

$$
\begin{array}{ccc}
\mathrm{R} & \left[\begin{array}{c} \mathrm{R_2} \\ \overset{..}{\mathrm{R_1{:}\overset{..}{S}{:}}} \\ \mathrm{R_3} \end{array}\right]^{+} & \mathrm{R_2} \\
\overset{..}{\mathrm{{:}\overset{..}{O}{:}\overset{..}{S}{:}}} & & \overset{..}{\mathrm{R_1{:}\overset{..}{N}{:}\overset{..}{O}{:}}} \\
\overset{-}{~}{}^{+}\mathrm{OC_2H_5} & & \overset{+}{\mathrm{R_3}}{}^{-} \\
\mathrm{I} & \mathrm{II} & \mathrm{III}
\end{array}
$$
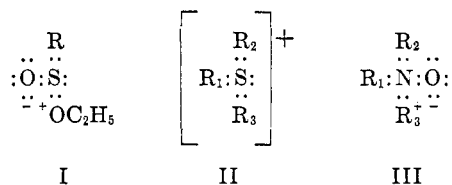
This formulation has the advantage that it clearly reveals the formal analogy with the optically active sulfonium salts (formula II), as well as with the amine oxides (formula III) which can be formulated in the same manner. In each case the determining circumstance is the "positive charge" of the central atom. This charge is necessary, according to Phillips, because otherwise the tertiary amines of analogous structure should also be active. Nevertheless this argument does not seem to the author to be absolutely conclusive. The question of the possibility of resolving the tertiary amines into isomers has not yet been finally settled. It is probable that they are merely racemized with unusual ease, as is indicated by the relatively high instability of the isomers with C=N linkages. Such an instability also would seem to be required by the quantum theory for derivatives of trivalent nitrogen (78). We must therefore, for the present, be content with the conclusion that the presence of three groups attached to sulfur permits, on principle, the possibility of an asymmetric space-distribution. P. Goldfinger (79) has attempted to deduce

such a distribution on the basis of ionic radii, determined by means of x-rays, and on the basis of the principle of the closest packing of spheres. Attention should also be directed to an interesting, though not convincing, attempt of F. M. Jaeger (80) to give an explanation. If we attribute to the sulfur atom the form of a rhombic bisphenoid on the basis of the crystal structure of rhombic sulfur (81), then the plane which contains the doubly bound oxygen atom makes an angle different from 90° with the plane that contains the R and the OC_2H_5 groups. The molecule is therefore asymmetric.

The resolution of the sulfoxides and the sulfonylimines rests on the same assumption as the resolution of the sulfinic esters. Harrison, Kenyon, and Phillips (82) resolved m-carboxyphenyl methyl sulfoxide, $CH_3SOC_6H_4COOH$, and 4'-amino-4-methyldiphenylsulfoxide, $NH_2C_6H_4SOC_6H_4CH_3$. The resolution of m-carboxyphenylmethylsulfine-p-toluenesulfonylimine $CH_3S(C_6H_4COOH):NSO_2C_7H_7$ was accomplished by Clarke, Kenyon, and Phillips (83). Both the optically active sulfoxides and the sulfonylimine are crystalline compounds and show a very distinct specific rotation. This gives additional strong support for the work of Phillips on the active sulfinic esters.

For compounds containing several sulfoxide groups in the molecule, the theory predicts diastereoisomerism or cis-trans isomerism. Such cases have been studied by Bell and Bennett (84), and it is possible that the isomers of the sulfoxides of trithioformaldehyde can be explained in the same manner.

A new type of optically active compounds is represented by the aci-nitro compounds, the first of which was resolved by R. Kuhn and Albrecht (85). From the classical formula (IV) it would not be expected that an optically active nitro compound would retain its activity on conversion to a salt.

IV   V
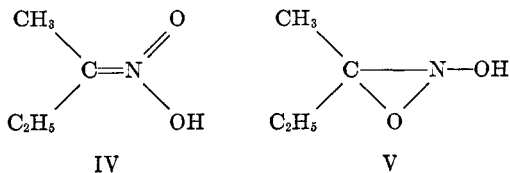
This is, however, actually the case, as was shown with 2-nitrobutane by these authors. A solid sodium salt is obtained with a definite, though weak, activity and the action of mineral acids upon it restores the partially racemized nitro compound. Furthermore, the addition of bromine to the optically active alkaline solution gives an active bromonitrobutane. It was shown many years ago by Hantzsch and Veit (86) that only the *aci* forms of nitro compounds react with bromine. Hence an active bromo-nitro compound can arise only from an active *aci* compound. Recently the experiments of Kuhn and Albrecht have been repeated by Shriner and Young (87), who used 2-nitroöctane and obtained the same results.

Formula V, suggested by Hantzsch and Schultze (88), provides an explanation for the activity of *aci* compounds. This formula has been given little attention, however, because no compounds are known to which this structure could be attributed with certainty and because a proof of the formula by chemical or physico-chemical means does not appear to be a very promising venture. Consequently attempts have been made to provide an explanation here, as in the case of the sulfinic esters, on the basis of the electron theory. It is in fact possible to construct a formula, based on the postulate of complete shells of eight electrons and on semipolar bonds, which shows the necessary asymmetry and also reveals the analogy with the active sulfonium compounds and the sulfinic esters.

$$\left[\begin{array}{cc} R_1 & \ddot{O}\cdot \\ R_2 : \ddot{C} : & \ddot{N} : \quad \underset{+}{\ddot{O}} \cdot \end{array}\right]^{-}$$
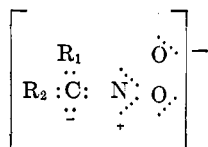
It is essential in this formula that carbon be the center of asymmetry, i.e., the same atom which determines the activity of nitrobutane itself. It would be very desirable to have experimental proof for this point of view, which for the present is purely hypothetical. The active nitro compounds and the active diazo compounds, which are to be discussed forthwith, are for the

present the only cases in which the carbon atom can produce activity when it is combined with three different groups and carries a charge.

Optically active diazo compounds were reported ten years ago by Levene (89) and by W. A. Noyes (90). Recently Lindemann (91) has also worked with them. According to Chiles and Noyes optically active aliphatic amino acids are converted by diazotization into diazo compounds of weak activity. These results were confirmed with diazosuccinic ester by Lindemann and by the researches of Levene, which were distinguished by the use of large quantities of material. Nevertheless, none of these researches provides so striking a proof that one can be conclusively convinced of the existence of optically active diazo compounds. Kendall and Noyes (92) obtained a crystalline, optically active, diazo compound from methyl aminocamphonanate, and attributed formula VI to it. It contains an asymmetric carbon atom. Ray (93) continued this investigation and believed that he obtained a diastereoisomer of this compound, to which he assigned formula VII.

$$
\begin{array}{cc}
\mathrm{CH_3} & \mathrm{CH_3} \\
| & | \\
\mathrm{CH_2-C-COOH} & \mathrm{CH_2-C-COOH} \\
| \quad | & | \quad | \\
\mathrm{C(CH_3)_2} & \mathrm{C(CH_3)_2} \\
| \quad | & | \quad | \\
\mathrm{CH_2-C:N:::N:} & \mathrm{CH_2-C:} \\
& \qquad :N:::N \\
\text{VI} & \text{VII}
\end{array}
$$
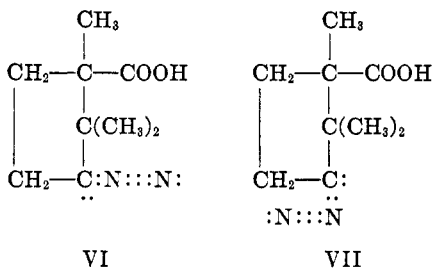
Aside from the fact that these researches cannot as yet be regarded as conclusive from the experimental point of view, another theoretical difficulty exists in the case of the active diazo compounds. According to the parachor determinations of Lindemann (94), the aliphatic diazo compounds in the majority of cases contain a three-membered ring (formula VIII), whereas only the chain formula (IX), containing semipolar bonds, can explain the

$$>C\begin{smallmatrix}N\\\|\\N\end{smallmatrix} \qquad >\bar{C}-\overset{+}{N}\equiv N$$

VIII   IX
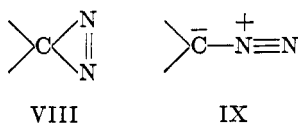
occurrence of optical activity. Now it is not possible to avoid this difficulty by assuming an equilibrium between the two forms, as was originally done. For in that case the diazo compounds should be speedily racemized (95), or, what is even more probable, they should not be obtainable at all in the active condition. Progress is possible only through further investigations. The fact is that neither is the existence of active diazo compounds established with certainty nor do we have a theoretical basis for the constitutional significance of the parachor which would permit us to draw reliable conclusions from parachor measurements.[5]

IV. THE PROBLEM OF THE WALDEN INVERSION AND RELATED QUESTIONS

Since the time of Emil Fischer (96) the Walden inversion has been understood to mean the conversion of an optically active compound into its antipode, or opposite isomer, by means of substitution reactions but not by way of the racemate. The so-called "optical cycle" is characteristic of this type of inversion. The configurational changes which take place in the making and breaking of double bonds and of ring structures are essentially related to these inversions. It has therefore recently become customary to include them in the broader use of that term.

One of the most important questions in this field of investigation has been expressed by E. Fischer (97) in the following often-quoted words: "Since two different substitutions are always required for proof of a Walden inversion, there is a question as to which one is responsible for the change in configuration. It has heretofore in no case been possible to answer this question with

[5] *Note added to proof:* As to diazosuccinic acid ester, Weissberger (Ber. **64**, 2896 (1931); **65**, 265 (1932)) has in the meantime proved that its activity is caused by impurities. At the same time Ray (J. Am. Chem. Soc., **54**, 295 (1932)), in one of his very interesting articles, has described a crystallized oxynaphthyl-phenyl diazomethane of considerable activity. These questions need further research.

certainty." Some progress, though not much, has been made in the twenty years since this was written. Among addition reactions there were even in Fischer's time several cases in which the course seemed quite clear. "The conversion of fumaric and maleic acids into racemic acid or mesotartaric acid, respectively, seems to be quantitative and is recognized as a nice confirmation of the steric formula of fumaric and of maleic acid." In 1911 Holmberg (98) and McKenzie (99), almost simultaneously, succeeded in determining the configuration of the dichloro- and dibromo-succinic acids by separating them into optical isomers. Thus the well-known conversion of fumaric acid into meso-dichloro- or mesodibromo-succinic acid was revealed as anomalous and as involving an inversion (100). Nevertheless this type of argument remains unsatisfying, for the formulas of maleic and fumaric acids cannot be conclusively determined by purely chemical methods. This recent conclusion of R. Kuhn and Ebel (101) still seems entirely justified, although parts of their argument have rightly been questioned (102).

Certain ring splittings in which the alteration of configuration occurs in a single step of the reaction are free from these objections. A preliminary case was found by Holmberg (103), who demonstrated that the malic acid lactone obtained from levorotatory bromosuccinic acid gave predominantly *d*-malic acid in an alkaline medium, while in an acid medium *l*-malic acid was in excess. In one of the two cases an inversion must therefore have taken place. In 1919 Böeseken and van Loon (104) found that the cyclopentanediol-1, 2, which is formed by the hydrolysis of cyclopenteneoxide, can be separated into isomers by the use of *l*-menthylisocyanate. It therefore has the *trans* configuration and must have been formed from the oxide by inversion. An analogous *trans*-splitting of a three-membered ring was also observed by Kuhn and Ebel: *cis*-ethyleneoxide dicarboxylic acid is converted quantitatively into racemic acid by boiling with water. The configurations of the reactant and of the product are established optically by non-resolvability and resolvability, respectively. Here again is a definite case of a change of configuration in the course of a single reaction.

In spite of the deep theoretical interest in these reactions, they do not throw much light on the nature of the Walden inversion. The success of the methods used by these investigators depends upon the use of compounds containing two similar asymmetric carbon atoms. Actually, the mere fact of resolvability or non-resolvability gives sufficient evidence with regard to the configuration. But the range of such compounds is too small and the scope of the chemical reactions to which they can be subjected is too limited to permit any hope of thus penetrating deeply into the real problem of the Walden inversion, for this latter has been studied primarily only with compounds which contain only one asymmetric carbon atom.

The most successful attempt to advance into this territory on a purely chemical basis was recently made by Phillips (105) and Kenyon (106). These investigators start with a fundamental principle of stereochemical research which was expressed with astonishing insight by A. von Baeyer (107) in 1888—i.e., seven years before the discovery of the Walden inversion—as follows: "The stability of the arrangement of the four atoms combined with a carbon atom, which permits the existence of geometric isomerism, is known to be destroyed by heating. The same is true in every chemical reaction which attacks the asymmetric carbon atom itself. The first of these two statements is not correct; the stability of the tetrahedral configuration toward thermal influences is very considerable (108). The second, on the other hand, has become a fundamental principle of modern stereochemistry. If one wishes to escape "the sword of Damocles of the Walden inversion" one must avoid substitution on the asymmetric carbon atom. Nevertheless whenever inversions have been observed, it has been possible to show in most cases that the asymmetric center had participated in the reaction. By this means E. Fischer (109) was enabled to construct the steric system of the sugars, and Freudenberg (110), using this principle, established the steric connection between tartaric acid, malic acid, isoserine, glyceric acid, and lactic acid.

A reaction which in its net effect has been shown experimentally to avoid the Walden inversion is the esterification of

optically active alcohols. This has recently again been shown in specific experiments for this purpose by Verkade (111) and W. Hückel (112). Pickard and Kenyon also always obtained the original alcohol in the saponification of a large number of esters. However, if the p-toluenesulfonic ester of methylbenzylcarbinol is prepared and is boiled in alcoholic solution with potassium acetate, an acetate is obtained which is the isomer of the one formed from the same carbinol by direct esterification. In the same way the treatment of the sulfonic ester with potassium carbonate and alcohol gives an ethyl ether which is the isomer of the ethyl ether that is obtained from the potassium compound of methylbenzylcarbinol and ethyl bromide.

$C_6H_5CH_2$ \ / OH
        C   →
CH_3 / \ H
$\alpha_{546}^{23} + 33.02°$

$C_6H_5CH_2$ \ / $OSO_2C_7H_7$
        C
CH_3 / \ H
$[\alpha]_{546} + 31.11°$ (Benzene; c = 5)

$\xrightarrow[K_2CO_3]{C_2H_5OH}$

$C_6H_5CH_2$ \ / H
        C
CH_3 / \ OC_2H_5
$\alpha_{546}^{23} - 19.90°$

$C_6H_5CH_2$ \ / OC_2H_5
        C
CH_3 / \ H
$\alpha_{546} + 23.50°$

$\xleftarrow{C_2H_5Br}$

$C_6H_5CH_2$ \ / OK
        C
CH_3 / \ H

$\xrightarrow{C_7H_7SO_2C_2H_5}$

$C_6H_5CH_2$ \ / OC_2H_5
        C
CH_3 / \ H
$\alpha_{546} + 19.84°$

$C_6H_5CH_2$ \ / H
        C   →
CH_3 / \ OH
$\alpha_{546} + 33.02°$

$C_6H_5CH_2$ \ / H
        C
CH_3 / \ $OSO_2C_7H_7$
$\alpha_{546} + 31.11°$

$\xrightarrow{CH_3COOK}$

$C_6H_5CH_2$ \ / $OCOCH_3$
        C
CH_3 / \ H
$\alpha_{546} - 7.06°$ →

$C_6H_5CH_2$ \ / OH
        C
CH_3 / \ H
$\alpha_{546} - 32.18°$
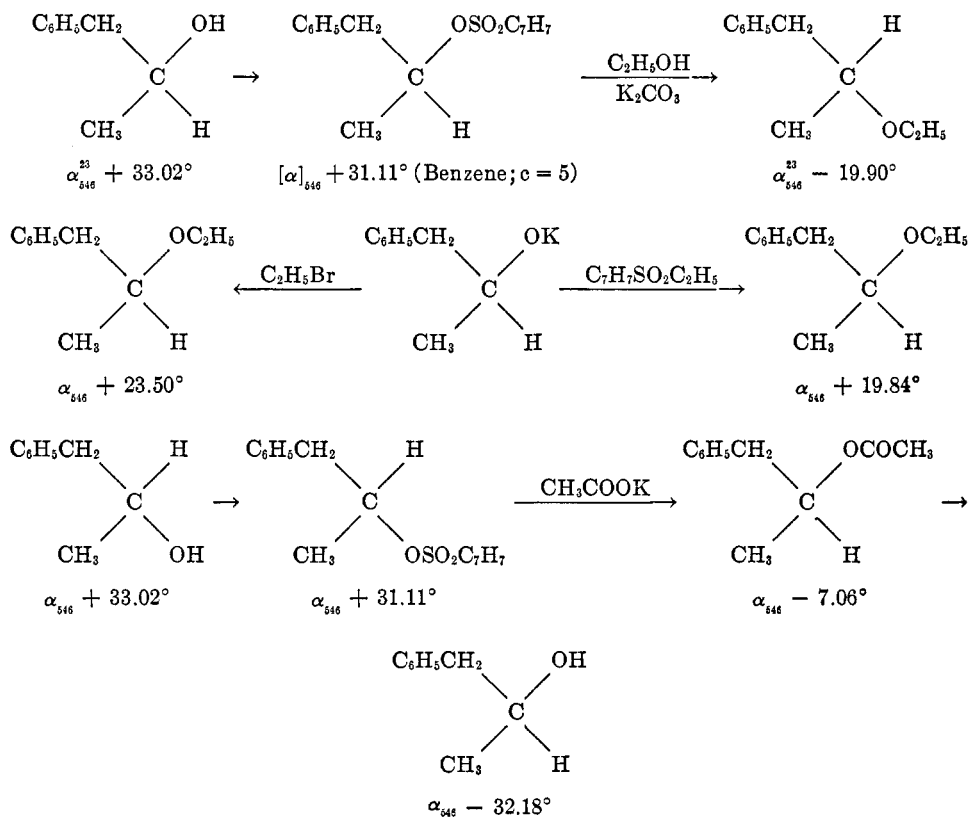
Since the asymmetric carbon atom remains untouched in the formation of the toluenesulfonic ester of methylbenzylcarbinol, it has been concluded with some justification that the inversion does not take place until the toluenesulfonic residue is detached. If so, a Walden inversion would be established for the first time in a single reaction step of a compound containing only *one* asymmetric carbon atom. The certainty of this conclusion rests entirely on the interpretation of the mechanism of saponification, or of alcoholysis, of the toluenesulfonic ester. The reactions of the esters of toluenesulfonic acid were thoroughly studied by Ferns and Lapworth (113) and agree with the interpretations of Kenyon and Phillips. A more exact study of these reactions would be important from several points of view, for we are also not sufficiently informed concerning the mechanism of saponification of the carboxylic esters. Skrabal (114) has concluded, on the basis of comparisons of the velocity of hydrolysis of the esters and of the mixed acetals, that both bonds of the central oxygen atom in the group $-C \cdot O \cdot CO-$ can be broken. But his arguments have been frequently questioned (115) because they are somewhat indirect and also rather schematic. In fact, according to his arguments, one should also expect cases of the Walden inversion in the hydrolysis of carboxylic esters; this, however, is not the case. Perhaps sulfur compounds would be suitable for investigations to this end. For instance, in reactions of the following types

$$C_6H_5OCOCH_3 + KSH = CH_3COSH + C_6H_5OK$$

$$C_6H_5COSC_2H_5 + KOH = C_2H_5SH + C_6H_5COOK$$
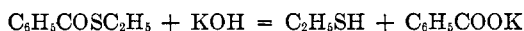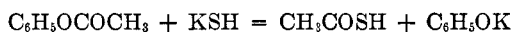
the point at which the bond is broken is obvious. It must be admitted that the analogy with the carboxylic esters is not rigorous because of the difference between the firmness with which sulfur and oxygen are bound.

Because of their high reactivity the toluenesulfonic acid esters, and also the sulfinic acid esters, are especially suitable for the study of the Walden inversion. The ease with which they are exchanged for halogen is particularly advantageous. The fol-

lowing reactions, in which the symbol $\leftarrow\!\!\overset{\circ}{\rule{1.2em}{0.4pt}}$ represents a Walden inversion, have been described by Houssa, Kenyon, and Phillips (116).

We must admit, however, that the interpretation of the course of this reaction, as given in the following quotation, abandons a firm factual basis and relies on dubious analogy: "The assumption is made that since the alcohol (or ester) and the halide are produced under similar experimental conditions, by reactions of the same type, they have the same configuration. Apart from the unsaturated nature of the acetate ion, as opposed to the saturated nature of the chloride ion, there is no obvious reason why the reaction of the ester with lithium chloride should follow a different course from that which it follows with potassium acetate."

We may therefore record as the real success of this work that we have a new and interesting case of Walden inversion. Nevertheless it does not contradict the opinion of most investigators

that a solution of the problem is not to be obtained by purely chemical methods. We therefore turn to the attempts which have been made to determine configuration by the aid of physical methods.

Here we must first consider the opinions of R. Kuhn (117), who chose compounds with two asymmetric carbon atoms as suitable for his work. He describes his course of reasoning as follows: "The method consists in combining the compound of unknown configuration with a second asymmetric carbon atom in order to obtain two substances which are not mirror images and which differ in a number of other physical properties, and finally in removing the auxiliary asymmetric atom. This method is in a sense comparable with that used by L. Pasteur for the resolution of racemates with the help of other optically active compounds. The asymmetric carbon atom is best handled by means of its mates." Kuhn then made the assumption that of the two racemic chloromalic acids, one would be found to lie between the racemic forms of tartaric acid and of dichlorosuccinic acid in its physical properties as a whole, while the other would form a series with the corresponding meso forms. It turned out, however, that in the large majority of cases the differences between the two chloromalic acids were so small that they could not be definitely arranged. Only in the case of the quotient of the dissociation constants, K_1/K_2, are there sufficient differences. On this basis Kuhn assigns the chloromalic acid with a melting point of 145° to the meso series (118). In table 4 these quotients are given for a number of racemic and meso forms of the succinic acid series. The chloromalic acids are arranged according to Kuhn's hypothesis. The configurations of the chlorobromosuccinic acids are not doubtful, as is shown by the melting points listed farther below.

A more thorough confirmation of these not altogether convincing conclusions would be of the greatest value, for the chloromalic acids occupy a key position among the substituted succinic acids. If their configuration were known, it could be directly determined which processes are normal and which proceed with inversion. On Kuhn's hypothesis the action of silver oxide on halogen compounds is normal, while inversion takes place with phosphorus pentachloride, thionyl chloride, and thionyl bromide.

This work shows very plainly the great difficulties involved in methods based on the comparison of physical properties. It is therefore necessary to be very circumspect in the choice of methods of comparison. It would seem, for example, that the comparison of constants based on the solid condition is but rarely permissible, because these constants are not exclusively dependent on the space-structure of the molecule. We need only to examine the melting points of the halogenated succinic acids (table 5) to recognize that the differences, $\Delta_{meso-racemic}$, do not themselves

TABLE 4

Values of K_1/K_2 for derivatives of succinic acid

ACIDS	K_1/K_2 RACEMIC	K_1/K_2 MESO
OH-OH.	20	48
OH-Cl.	24	48
Cl-Cl.	21	38
Cl-Br.	20	15
Br-Br.	51	15
C_6H_5-C_6H_5.	80	113

TABLE 5

Melting points of the halogenated succinic acids

ACIDS	RACEMIC	MESO	$\Delta_{meso-racemic}$
Cl-Cl.	171°	220°	49 ⎱ 4
Cl-Br.	162	215	53 ⎰ ⎱ 34
Br-Br.	170	257	87 ⎰

differ by a constant amount between the various series no matter how the chlorobromosuccinic acids are arranged. The occurrence of such a numerical relationship as was observed by Kuhn in the chloromalic acids is therefore a mere accident.

Table 6 records the melting points of a similar series which are especially instructive (119). The figures in parentheses represent the melting points of the corresponding active forms. In spite of a large difference in melting points, a definite arrangement of

the hydroxydiphenylethylamines is not possible. The active form of isohydrobenzoin has a higher melting point than the racemic form, while the two active hydroxydiphenylethylamines melt lower than do their racemic forms.

The determination of configurational relationships by means of optical behavior should probably suggest itself, since this is the primary characteristic of stereoisomers. Such attempts were made as early as 1909 by C. S. Hudson (120) in the study of the sugars, where conditions are especially favorable because of the very close relationship of the sugars to each other. van't Hoff's principle of optical superposition (121) was shown to be valid here, at least within certain limits. This permitted Levene (122), for instance, to determine the configuration of some hexosaminic acids. Naturally this principle is not applicable to

TABLE 6

Melting points of meso and racemic forms of some compounds

SUBSTANCE	MESO	RACEMIC
$C_6H_5CH(NH_2)CH(NH_2)C_6H_5$	120°	91°
$C_6H_5CH(OH)CH(NH_2)C_6H_5$	129 (115)	165 (143)
$C_6H_5CH(OH)CH(OH)C_6H_5$	138	120 (146)

compounds containing only *one* asymmetric carbon atom; instead it becomes necessary to make a general comparison of optical behavior. The researches of Clough (123) were pioneering in this field, although E. Fischer (124) and Frankland (125) had made suggestions in this direction. Using the simplest hydroxy and amino acids, Clough proved that compounds of similar configuration undergo analogous changes in rotation when they are subjected to the same influences of solvent, temperature, and added salts. He connected natural (+)-alanine with l(+)-lactic acid, just as is done today. However, the more thorough investigation of these phenomena by K. Freudenberg (126) showed that Clough's method is successful only under certain conditions. Thus it was found to be necessary to avoid altogether the use of solvents (127). Furthermore all those compounds which possess

a special tendency for association, owing to the presence of free hydroxyl, amino, or carboxyl groups, had to be excluded from optical comparison (128). Finally, each case had to be individually tested to determine which compounds might be considered as analogous and therefore suitable for optical comparison. "Since the concept of 'analogy' cannot be sharply defined, no simple scheme can ever be devised for such determinations of configuration" (129).

In order to present the data on which the work of Freudenberg rests, the molecular rotations of several derivatives of $d(-)$-lactic acid and of dextrorotatory bromopropionic acid are given in

TABLE 7

Molecular rotations of some derivatives of lactic acid

DERIVATIVE	TOLUENESULFONYL-d-LACTIC ACID	METHYL-d-LACTIC ACID	ACETYL-d-LACTIC ACID	BENZOYL-d-LACTIC ACID	d-BROMO-PRO-PIONIC ACID
Diethylamide	+15(t = 40°)			−94	−12
Dimethylamide	+51(t = 30°)	+84	+28	−82(t = 135°)	−28
Chloride	+145(t = 35°)	+112	+49	−121	+46
Methyl ester		+112	+74	−35	+92
Ethyl ester	+129	+122	+76	−49	+73
Propyl ester		+125	+79		+58

table 7. The significant point is not the absolute values, which differ markedly from group to group, but the direction and the magnitude of the *displacements* which occur with the shift from one group to another (for instance, from the dimethylamide to the chloride). In spite of many individual disagreements, the data as a whole testify that d-lactic acid and the dextrorotatory bromopropionic acid are similar in configuration.

On the basis of all the facts that have been cited, Freudenberg succeeded in connecting a number of the most important halogen, amino, and hydroxycarboxylic acids as is shown by the following diagram (130). (The abbreviation "opt." signifies a connection established optically; "chem.", one established chemically.)

$l(-)$-Azidopropionic acid $\xleftrightarrow{\text{opt.}}$ $l(-)$-Halopropionic acid $\xleftrightarrow{\text{opt.}}$ $l(-)$-Halosuccinic acid

$\searrow$ *chem.* $\;\;\updownarrow$ opt. $\;\updownarrow$ opt.

$l(+)$-Lactic acid $\quad\xleftarrow[\text{opt.}]{\text{chem.}}\quad l(-)$-Malic acid

$\updownarrow$ opt. $\;\updownarrow$ opt.

$l(+)$-Alanine $\quad\xleftarrow[\text{opt.}]{\text{chem.}}\quad l(+)$-Asparaginic acid
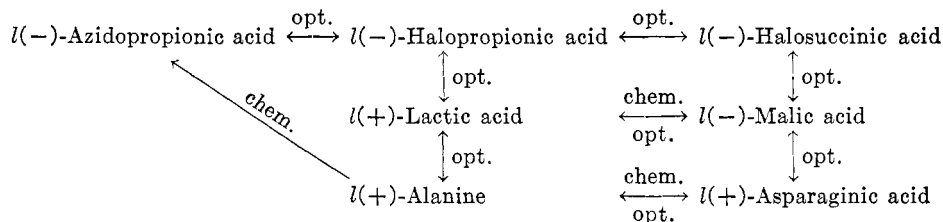
Accordingly, the configurational relationships of the propionic acids and the succinic acids can be represented as in table 8 (131).

In view of the great care with which these connections have been established we may assume that we are here on compara-

TABLE 8

Configurational relationships of propionic and succinic acids

	LACTIC ACID	CHLORO- AND BROMO-PROPIONIC ACIDS	ALANINE	ALANINE ESTER
	MALIC ACID	CHLORO- AND BROMO-SUCCINIC ACIDS	ASPARAGINIC ACID	ASPARAGINIC ACID ESTER
Ag_2O	←			
N_2O_3	←			
NOCl ⎫ NOBr ⎭		←	← ○	
PCl_5, $SOCl_2$ ⎫ PBr_5 ⎭	—— ○ →	○ →		
NH_3		○ →		
KOH	← ○			

tively firm ground. But if we consider the marked limitations which are imposed in the choice of substances and methods, then it seems desirable also to have a theoretical justification for the procedure employed, i.e., to investigate more closely the connection between rotatory power and chemical constitution. We shall return later to the investigations of W. Kuhn, which were undertaken with this in mind.

Extensive researches on configurational relationships and the problem of the Walden inversion were also undertaken by P. A. Levene. His efforts to classify the amino sugars and their acids

by the principle of optical superposition have been described by him in This Journal (132). An important consequence of this work was the observation that, in general, ionization (i.e., salt-formation) in acids of related configuration produces a shift of the rotation in the same direction (133). As table 9, taken from Levene (134), shows, both the hexonic and the hexosaminic acids are separable into two groups. In one group (designated with asterisks) the differences in rotation between the free acids and the salts are negative; in the other they are positive. These acids were shown to have the same configuration (i.e., the same orientation of the carbon atom 2).

Although this empirical rule was confirmed in numerous cases, it cannot alone form a solid foundation for the determination of configuration. Levene (135) therefore attempted to devise a second and independent method based on general considerations in regard to the relation between rotation and polarity of the substituents. The characteristic manner in which the rotatory power of compounds with the same configuration can be altered by the electrochemical character of the substituents has long been known and may be illustrated here by using the derivatives of the levorotatory amyl alcohol (136).

$$C_2H_5CH(CH_3)CH_2Br \rightarrow C_2H_5CH(CH_3)CH_2NH_2$$
$$[\alpha]_D^{20} + 3.7° \qquad\qquad [\alpha]_D^{25} - 5.9°$$

$$C_2H_5CH(CH_3)CH_2OH$$
$$d\text{-Amyl alcohol}$$
$$[\alpha]_D^{20} - 5.90°$$

$$C_2H_5CH(CH_3)COOH$$
$$[\alpha]_D + 18°$$
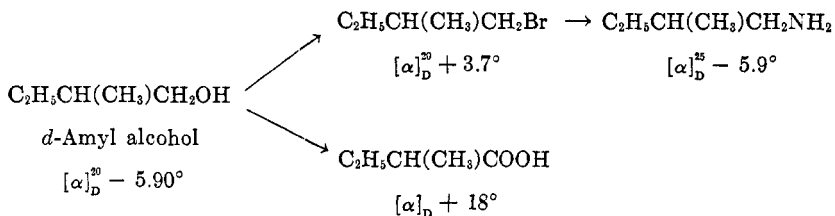
The oxidation of aliphatic mercaptans to sulfonic acids also involves a change in the sign, according to Levene:

$$C_2H_5CH(CH_3)SH \longrightarrow C_2H_5CH(CH_3)SO_3H$$
$$[\alpha]_D + 15.7° \qquad\qquad [\alpha]_D - 3.2°$$
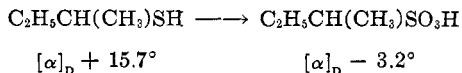
Levene then made the assumption, which is difficult to justify, that the differences in polarity between the OH group and the Cl group are qualitatively similar to those between the SH group

and the SO_3H group (137). This would lead to the conclusion that the chlorides, R_1R_2CHCl, obtained from the carbinols, R_1R_2CHOH, correspond in configuration to the carbinols, since they show rotations of the opposite signs. Using this assumption, Levene has developed a very elegant system for relating the simplest optically active carbinols with the hydroxymono- and hydroxydi-carboxylic acids and their corresponding halogen derivatives. The following diagram shows his connection of chlorosuccinic acid with malic acid and lactic acid (138).
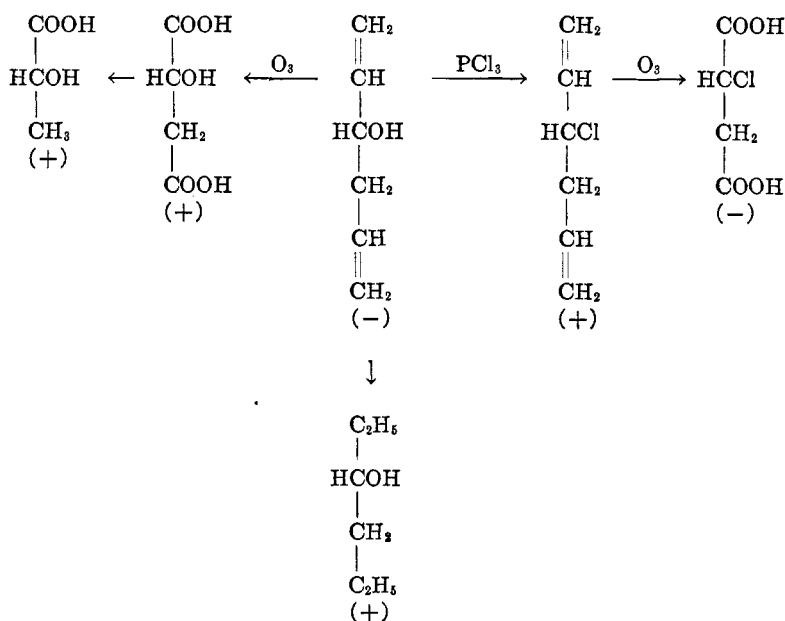
In many cases the configurations thus determined coincide with those derived from Levene's displacement rule. Nevertheless there are also contradictions (139). This is not surprising for, as we have already remarked, it is very doubtful whether halogen and hydroxy compounds of opposite rotations can have the same configuration (140). The concept of polarity[6] is still

[6] We are indebted to Rule and Betti for a thorough investigation of the relation between rotation and polarity; a full discussion of this interesting work would lead us too far afield.

very vague and has not been more sharply defined by Levene; it can therefore not be used to apply conclusions from the mercaptans and sulfo compounds directly to halogen compounds, as has already been pointed out by Houssa, Kenyon, and Phillips (141). It is also hardly permissible to draw general conclusions from the simple fact of change in rotation so long as all influences of the solvent have not been carefully excluded.   Hence it is quite compre-

TABLE 9

Specific rotations of hexonic and hexosaminic acids

	FREE ACID $[\alpha]_D^{\circ}$	SODIUM SALTS $[\alpha]_D^{20}$	PHENYL- HYDRAZIDES $[\alpha]_D^{20}$	AMIDES $[\alpha]_D$
* Gluconic acid	0.0°	+11.78°	+18.0°	+31.2°
Mannonic acid	+15.6	−8.82	−10.5	−17.3
Idonic acid	+	−2.52	−15.1	—
* Gulonic acid	−1.6	+12.68	+13.45	+15.2
* Galactonic acid	−8.0	+0.40	+12.2	+30.0
Talonic acid	+16.7	—	−25.4	—
* Allonic acid	−10.0	+4.30	+25.88	—
Altronic acid	+8.0	−4.05	−15.8	—

ACIDS	$[\alpha]_D^{\circ}$ in 2.5% HCl	$[\alpha]_D^{\circ}$ in 5% NaOH	
* Chitosaminic acid	−15.0°	+1.3°	c = 5.0
Epichitosaminic acid	+10.0	−5.0	c = 5.0
d-Xylohexosaminic acid	+14.0	−16.0	c = 2.5
* l-Xylohexosaminic acid	−11.0	+2.0	c = 2.5
* Chondrosaminic acid	−17.0	−15.0	c = 2.5
Epichondrosaminic acid	+8.0	+1.8	c = 2.5
d-Ribohexosaminic acid	+12.5	+2.0	c = 2.5
*l-Ribohexosaminic acid	−26.0	−15.0	c = 2.5

hensible that the results of Freudenberg and of Levene in regard to the arrangement of the halogen compounds contradict each other.   It can hardly be doubted that, for the present at least, Freudenberg's method has decidedly the greater probability.

   Finally we must make brief reference to the work of Ott (141a) who believes that he has discovered connections between the

Walden inversion and reaction velocities.[7] Since according to his investigations "it must appear doubtful whether in the future the representation of optical isomers as mirror images will be justifiable," we shall have to await experimental confirmation of his experiments, which were in part carried out with rather small amounts of liquid substances.[8] That powerfully rotatory impurities in such experiments may easily give rise to serious false conclusions is shown by the work of Erlenmeyer (141b) on the supposed optically active cinnamic acid and the alleged differences in the physical constants of the d- and l-mandelic acids (141c).

V. RELATIONSHIPS BETWEEN ROTATION AND CONSTITUTION

As is apparent from the above survey, the attack on the problem of the Walden inversion has been made chiefly with the empirically determined "displacement rule." In order to avoid this empiricism, the most important problem of the future would seem to be to clarify the quantitative relationships between chemical constitution and optical rotatory power. Until recently there has been no satisfactory theory of optical rotation. The hypothesis of the asymmetry-product proposed by Guye in 1890 was soon invalidated, especially by the work of Walden. Lindman (142) demonstrated very nicely that the masses of the substituents are not the determining factors, for four similar copper spheres at the corners of an asymmetric tetrahedron turn the plane of polarization of Hertzian waves, but four unequal spheres in a regular tetrahedron show no such effect.

Recently W. Kuhn (143), building on the older work of Born (144) and Oseen (145), has succeeded in drawing a quantitative relation between rotational dispersion and absorption. This

[7] Previous work of Ott had shown a connection between reaction velocity and *cis* or *trans* addition. Acetylene dicarboxylic acid gave maleic acid upon rapid hydrogenation with platinum; upon slow hydrogenation it gave fumaric acid. The experimental result is beyond question. The significance of the work would, however, become decisive only with the proof that maleic acid is not converted into fumaric acid by longer contact with the effective catalyst. If this were the case, fumaric acid would merely be the product of a *secondary* conversion.

[8] *Note added to proof:* In the meantime Ott (Ann. **491**, 287) has recalled a part of his statements.

experiment was suggested by Fresnel's conception of rotation as circular double refraction

$$a = \frac{\pi}{\lambda_{\text{vac.}}} (n_l - n_r)$$

and by the striking fact that the relationship between refraction-dispersion and absorption is analogous to that between rotational dispersion and circular dichroism (Cotton effect).

Refraction and absorption are connected in gases by the following equation:

$$n - 1 = \frac{Ne^2}{2\pi m} \sum \frac{f_k}{\nu_k^2 - \nu^2}.$$

N is the number of atoms in the unit volume, e the charge, m the mass of the electron, ν_k the absorption frequency, and f_k the intensity of the absorption band. Since for each substituent in the molecule there is always a corresponding value of ν_k, and since f_k and ν_k are in the first approximation independent of the other substituents, the result is the well-known additivity of molecular refraction.

In a similar way rotation in the visible region may be analyzed into the contributions of the individual substituents. Thus the following expression for rotational dispersion can be developed.

$$n_l - n_r = \frac{Ne^2}{2\pi m} \sum \frac{\nu}{\nu_k} \cdot \frac{f_k g_k}{\nu_k^2 - \nu^2}$$

A new factor here is g_k, the "anisotropy factor." It represents the relative difference of the absorption coefficients for left-hand and right-hand circular light inside the absorption band

$$\frac{\epsilon_l - \epsilon_r}{\epsilon}$$

It is therefore related to circular dichroism. However, while all the summational items in the equation for refraction have a positive sign, in the case of rotational dispersion

$$\sum f_k g_k = 0$$

because the individual values of g_k alternate in sign. Furthermore it may be shown that only weak absorption bands can have a high anisotropy factor. As a result summational items which come from the intense Schumann bands are partially cancelled and it is the weak bands lying in the near ultra-violet which give the important contributions to the total rotatory power. The anisotropy of these bands is due to the existence of coupling forces between one substituent (which we may call R) and the other substituents, $R_{1, 2, 3}$, which themselves possess intense bands in the Schumann region. Kuhn expresses the situation as follows: The intense bands $R_{1, 2, 3}$ "induce by vicinal function" an anisotropy in the weak band R. In agreement with experience it may be shown that optical activity occurs only when the molecule is composed of at least four different groups (146).

W. Kuhn has examined both absorption and rotation in the ultra-violet for a number of very simple compounds which offered especial interest in view of Freudenberg's determinations of configuration. In the case of methyl azidopropionate $CH_3CH(N_3)COOCH_3$, whose molecular rotation is 24°, the azido band furnishes 12°, i.e., fifty per cent, to the rotation, while the contribution of the same band to the total absorption is only 10^{-5}. The vicinal function is not appreciably changed by minor chemical changes in the substituents, $R_{1, 2, 3}$, producing it. For instance, while the total rotatory power of the dimethylamide of azidopropionic acid is strongly negative and that of the corresponding methyl ester is positive, the contribution of the azido band is in both cases negative. On the other hand, the anisotropy of a weak band due to the substituent R is extraordinarily sensitive to chemical changes in R. Under certain circumstances the sign may thus be reversed. If a substituent which possesses an absorption band in the near ultra-violet is removed from the asymmetric center, then the vicinal function, and therefore its contribution to the rotation, is rapidly decreased.

It may easily be seen that with approximate validity of these rules both the principle of "optical superposition" and the rules of displacement would attain a theoretical basis. It has recently been emphasized from various sides (147) that the principle of

optical superposition may at the most represent an approximate rule. An often neglected fact is important in this connection, namely, that "the optical rotatory power of an asymmetric carbon atom depends upon the composition, constitution and *configuration* of each of the four groups" (148). This is in fact already evident from the differences in the absorption spectra of tartaric acid and mesotartaric acid (as far as we can judge by the existing measurements). Kuhn's point of view leads to a very important consequence for the determination of configuration by the method of optical comparison. Only those compounds in which all groups which contribute essentially to the rotation are alike, may be compared with respect to their rotation. For instance, the rotation of lactic acid is essentially determined by the anisotropy of the carboxyl group, while that of mandelic acid is determined by the phenyl group. Lactic acid and mandelic acid therefore cannot be directly compared with each other.

VI. ABSOLUTE ASYMMETRIC SYNTHESIS

This term is applied to the production of optically active materials from racemic compounds without the aid of a substance which is itself optically active. It is therefore in a sense a question of equivocal generation of optical activity. The outstanding attempt to produce activity by purely physical means is that of Cotton (149), who discovered the circular dichorism of the copper-alkali tartrates in 1896. Since the solutions of these compounds decompose in the light, Cotton expected to find that the decomposition would proceed with different velocities in left- and right-handed circularly polarized light and that he could thus produce an optically active solution. The attempt however failed, and we know today that it could not have given positive results, for the region of photochemical sensitiveness of Fehling's solution lies in the ultra-violet, as Byk (150) showed, while Cotton studied circular dichroism only in the visible region. Actually Mitchell (151) has recently proved that Fehling's solution shows no dichroism in the region involved. There is still another condition essential for success in experiments of this sort, namely the validity of Einstein's photochemical equivalency law.

Positive confirmation of the correctness of Cotton's idea was provided in 1929 by W. Kuhn and Braun (152). In the study of the rotation of ethyl bromopropionate in the ultra-violet they found that this substance shows a high rotation anomaly in the near ultra-violet (2450 Å.), so that a considerable portion of the optical activity can be attributed to this band. They were actually able to produce a weak activity (maximum ±0.05°) of the expected sign by irradiating the racemic ester with circularly polarized light of wavelength 2800 Å. They soon found a substance which was more suitable for this purpose in the dimethyl-amide of azidopropionic acid, the azido band of which shows circular dichroism at 2900 Å. The relative difference in the absorption of right and left circularly polarized light amounts here to not less than 2.5 per cent. The activation produced by light of wavelengths 2800 Å. to 3200 Å. amounted to about 1° and agreed both in magnitude and in sign with the theoretical prediction.

Finally there is the very recent successful attempt of Mitchell to produce the effect in the visible region. Humulene nitrosite, a derivative of a terpene, shows circular dichroism in the red. It was activated by irradiation with light of wave length 7000 Å. The progress of the reaction was followed polarimetrically and the complete symmetry of the rotations produced by right- and left-handed circularly polarized light under similar conditions was nicely demonstrated.

VII. STEREOCHEMISTRY AND CRYSTALLOCHEMISTRY

Since its very beginning stereochemistry has stood in very close relationship with crystallography. "It was crystallographic researches that led Pasteur to the discovery of asymmetry in organic substances; crystallographic considerations served van't Hoff and LeBel as a foundation for the building of stereochemistry, and crystallographic measurements have up to the present time provided auxiliary means often consulted for the characterization of optical, racemic and pseudo-racemic individuals" (153). It is therefore not surprising that the recent development of crystallography under the influence of x-ray physics has presented new

problems in the stereochemistry of organic compounds. The dimensions of the elementary crystallographic unit,[9] as measured by x-rays, the space-group of the crystal, and the observed intensities combined with z, the number of molecules in the elementary unit, yield the minimum symmetry of the single molecule in a crystal. The assumption is made that the micro-unit of crystallographic structure is identical with the chemical molecule.

We thus have the interesting question as to whether the symmetry of the crystal molecule thus determined agrees with the symmetry of the molecule in vapor and solution as determined by the methods of classical stereochemistry. We can hardly expect in advance to find a complete agreement, for the regular tetrahedron can be considered only as a rough first approximation, certain deformations do not alter the character of the isomerism, and only the mirror-plane and the center of symmetry are taken into account from the classical point of view. Naturally it is possible to apply the geometrical structure theory to the chemical molecule and to ask which symmetries result in a molecule if one makes certain assumptions concerning the equivalence and the individual symmetry of the substituents. In its essence this question is involved in the geometrical considerations of LeBel, who started from the space-lattice theory of Bravais. If the group theory is applied to the simplest four-membered group, Ca_4 (methane and its derivatives), and if the question is then asked as to the number of ways in which four equal groups "a" can be equivalently arranged about a carbon atom, then we have the following results given in table 10 according to K. Weissenberg.

If "a" does not possess the symmetry of a trigonal axis (C_3, C_{3v}), then Ca_4 cannot be a regular tetrahedron. If the substituent "a" is asymmetric (C_1) or if its single element of symmetry is a mirror-plane (C_s), then the following configurations are available for Ca_4: tetragonal and rhombic bisphenoid (the so-called distorted tetrahedron) and, furthermore, quadratic and tetragonal pyra-

[9] It must be emphasized that the elementary unit represents a purely geometrical concept.

mids with the "central" carbon atom at the apex. From this formal point of view, which has recently become known through the work of K. Weissenberg (154), it thus appears, as was remarked above, that the regular tetrahedron is only a special case.

It would, of course, have been of the greatest stereochemical interest to have been able to prove experimentally with the aid of x-ray methods either planar or pyramidal configurations for the Ca_4 molecules. For a time it actually seemed that such an

TABLE 10

Possible arrangements of four equal groups about a carbon atom

SYMMETRY OF SUBSTITUENTS			MOLECULE Ca_4														
			Space-centered						Plane-centered				Pyramidal eccentric			
			a	i	a	i	a	i	a	i	a	i	a	i	a	i
C_i		l				S_4	v					C_{2h}	C_4			C_{3v}
		d					v						C_4			
C_2		l							D_4	V_d						
		d							D_4							
C_3		l	T													
		d	T													
C_s						V_d				C_{4h}	V_h	C_{4v}			
C_{2v}										D_{4h}					
C_{3v}				T_d											

The first column lists all the six possible forms of symmetry which four equal substituents, a, (either element or radical) may possess (monogonal, digonal, trigonal axes, etc.) when grouped equivalently about a carbon atom. The symbols are those of Schönfliess and the corresponding diagrammatic symbols are given in the second column. Right and left isomers are distinguished by d and l. The figures heading the remaining columns show the possible configurations of the substituents (represented by small circles) about the carbon atom, which is assumed to be at the center of the space, at the center of the plane, or at the apex of the pyramid, respectively. Optically active molecules are designated by a, inactive by i. For each of the six forms of symmetry of the substituents the table therefore gives the symmetry of the Ca_4 molecules *which can be constructed from them*,—represented by Schönfliess symbols. Vacant spaces in the table signify that the corresponding configuration cannot be constructed. For instance, the space-centered configuration is not possible with substituents C_{2v}.

anomalous configuration had been found in the case of penta-
erythritol, $C(CH_2OH)_4$. If the symmetry C_s is attributed to the
CH_2OH groups, as based on the tetrahedral model of van't Hoff,
then the molecule should, according to the above point of view,
have the configuration of a bisphenoid or of a pyramid. The
measurements of Mark and Weissenberg (155) actually showed
the symmetry of a quadratic pyramid (C_{4v}). However, the
further examination of this work which was undertaken by
several authors showed that the calculation had been based on a
false symmetry class, as might have been seen from the Laue
diagram of Haga and Jaeger (156).

A tetragonal bisphenoid, S_4, may today be regarded as the most
probable symmetry (158), on the basis of thorough x-ray and
crystallographic investigations by Nitta, Schleede, and coworkers,
Nehmitz, Ernst, Seifert, van Melle, and Schurink, as well as by
Mark and v. Susich (157). Thus the molecule has a fourfold
axis of rotatory reflection as its single element of symmetry and
the CH_2OH groups are asymmetrically constructed. According to
newer results, however, the symmetry is perhaps still lower, i.e.,
rhombic. A decision can be reached only when we have a perfect
single crystal of pentaerythritol. According to the work of
Friederich and Brün (159), as well as of Ebert (160), we must
assume that pentaerythritol which has been purified only by
crystallization always contains an anhydride, dipentaerythritol,
$C_{10}H_{22}O_7$, as an impurity.

A second case of pyramidal configuration was apparently dis-
covered by Gerstäcker, Möller, and Reis (161) in pentaerythritol
tetraacetate. Here too, however, the verification by Knaggs
(162) gave a different result, namely an approximately regular
tetrahedral symmetry (S_4). Finally Wagner and Dengel (163)
undertook an x-ray study of the halohydrins of pentaerythritol,
$C(CH_2Cl)_4$, $C(CH_2Br)_4$ and $C(CH_2I)_4$, and gave to them the sym-
metry C_{2h}, according to which the carbon atoms of the four sub-
stituents would lie in the same plane with the central carbon atom.
However, as long as the symmetry class is not determined with
certainty,[10] we must withhold final judgment on this discovery.

[10] *Note added to proof:* Meanwhile this has been done in a very careful work
by Wagner and Dengel (Z. physik. Chem. **16B**, 382).

Attempts have also been made to decide by chemical means between the various configurational formulas of pentaerythritol (164). These also gave no indication of the existence of a pyramidal configuration. Yet in any case no conclusive proof is possible by chemical methods (165).

Still another series of Ca_4 compounds has been investigated by means of x-rays. According to McLennan and Plummer (166) methane crystallizes cubically; the same is true of carbon tetrabromide and carbon tetraiodide (167) as well as of tetramethylmethane (168). In all these cases the molecule is a regular tetrahedron (T_d). Pentaerythritol tetraformate crystallizes in the space-group V_h^{15} and contains eight molecules in the elementary unit (169). The tetranitrate has the molecular symmetry S_4 (170). Tetramethyl methanetetracarboxylate, $C(COOCH_3)_4$, has the symmetry C_2, C_{2h}, or S_4 (171). It is apparent that there is so far no case of contradiction to van't Hoff's theory. The occasionally rather temperamental attacks from the standpoint of the geometrical structure theory have thus not been able to shatter the classical theory.

On the whole the x-ray analysis of structure has not been of as much service to stereochemical research in organic chemistry as was originally hoped. This is partly because even relatively simple molecules often do not enter into the crystal with the highest symmetry that their structural formulas would permit (172). As an example, several x-ray investigations on derivatives of ethane may be mentioned. Concerning the structure of ethane itself Debye photographs by Mark and Pohland (173) show only that it is either center-symmetrical or planisymmetrical. A series of isomorphous ethane derivatives was thoroughly investigated by K. Yardley (Mrs. Lonsdale) (174), namely, C_2Cl_6, C_2Br_6, $C_2Cl_4Br_2$, C_2Br_5F, $C_2Cl_3Br_3$, $C_2Br_4(CH_3)_2$. These compounds crystallize in the space group V_h^{16} and contain in the elementary unit four molecules which have one plane as their single element of symmetry. C_2Cl_6, C_2Br_6, and $C_2Br_4(CH_3)_2$ contain a pseudo-center besides. On the other hand, the rigorously tetrahedral C_2Cl_6 has only the following symmetries: $C_{3i}, D_3, D_{3h}, C_{3h}$.

According to the views of A. Reis (175), one would expect that

mesotartaric acid would show a symmetry center in the crystal, while tartaric acid would show a twofold axis of rotation. Experiments showed, however, that both molecules are asymmetric (176). The translation-cell of triclinic mesotartaric acid contains two molecules which are associated in a center-symmetrical micro-unit. The monoclinic-sphenoidic tartaric acid also contains two asymmetric molecules; but in this case the single molecules are the micro-units and are connected by a screw axis, as in cane sugar. The elementary cell of racemic acid, like mesotartaric acid, contains a center-symmetrical bimolecule (177).

And finally we must mention the x-ray investigations of Hassel and Kringstad (178) on solid cyclohexane and of Dickinson and Bilicke (179) on benzene hexabromide because they relate to the Mohr models of cyclohexane, which were discussed in section II.

VIII. SOME RECENT PHYSICAL INVESTIGATIONS AND THEIR STEREO-CHEMICAL CONSEQUENCES

Formerly the symmetry characteristics of organic molecules were studied primarily by optical methods. As, however, our conceptions of the electrical structure of atoms and molecules were refined, it was inevitable that considerations of electrical symmetry should enter into the study of stereochemistry. The property most suitable for this purpose proved to be the dipole moment (the charge multiplied by the distance between the centers of gravity of the charges in the molecule). It became apparent (180) that it was possible to attribute fairly definite moments to the individual substituents and that these could be vectorially added. The resulting moment of the aliphatic hydrocarbons was zero. Since this was to be expected from a tetrahedral configuration it provided an excellent and independent confirmation of van't Hoff's theory.

One of the basic postulates of van't Hoff's theory is the "principle of free rotation" in compounds of the type
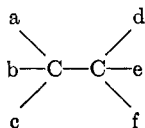
It leads to a single preferred configuration by the mutual action of the groups a, b, c on d, e, f (180a). The more detailed requirements of this principle were for many years not considered because experience had seemed to confirm it in every respect. It was not until the discoveries of J. Kenner, which have already been discussed, that cases were known in which free rotation was impeded so that the appearance of isomers became possible. Quite apart from stereochemical questions the principle also attained some interest in researches on the dipole moments of organic compounds. J. J. Thomson's introduction (181) of vectorial addition of individual moments with *ortho-*, *meta-*, and *para*-substituted benzene derivatives led to serious difficulties with the OH, OCH_3 and NH_2 groups. Different authors then showed (182) that the variations can be explained on the assumption that the valences of oxygen, or of nitrogen respectively, form constant angles. In that case the substituents do not lie in the plane of the benzene nucleus and therefore are able to take different positions with respect to each other because of the free rotation.

Williams made the first attempt to calculate the moment of symmetrically substituted ethanes. The resulting moment of ethylene dibromide must show a maximum with the *cis* position of the bromine atoms, while the *trans* position would give a moment of zero. Williams then made the assumption (which in this simple form is certainly not permissible) that all positions between these extremes possess equal probability and thus, on the basis of the experimental values then available, concluded that the angle between the vector and the C—C axis is reduced from a normal of 70° to about 35° in the halogenated ethanes (183). He attributed this effect to a mutual repulsion of the polar groups. But Stuart (184) has recently shown that such a deformation of the angle is certainly not involved. According to Eucken and Meyer (185) the mutual attraction and repulsion of the groups within the molecule result in a position of minimum energy which the molecule tends to attain. This hindrance of the free rotation, however, is opposed by the heat motion. Eucken and Meyer attempted a calculation of the distribution of potential in which they took into account only the C—Cl moments

and assumed the constancy of the bond moments and the valence
angles. They found thus that hindrance of the free rotation does
not occur when the intromolecular potential of the individual
moments in motion

$$\mu^2/r^3 < 0.1 \ kT.$$

A hindrance can be expected only at an order of magnitude of
kT, i.e., at an approach of the moments to about 3 Å. For
ethylene dichloride the potential amounts to 2 to 3 kT. With a
drop in the temperature the theory would demand a drop in the
moment. Such an effect has, however, not yet been observed
with any certainty. Of course, for the present only rough and
superficial calculations are possible (186).

One thing, however, is clear from the material which is now
available: symmetrical molecules in the liquid or gaseous condi-
tion do not by any means assume center-symmetrical positions
with a moment of zero. For instance, p-xylylene chloride
$ClCH_2C_6H_4CH_2Cl$ has a moment of 2.23 (187). Quite inde-
pendently of such assumptions Weissberger and Sängewald (188)
have demonstrated the hindrance of free rotation in the case of
stilbene chloride. If the two diastereoisomeric stilbene chlorides
possessed unhindered rotation, i.e., if the two halves of their
molecules did not affect each other electrically, then their dipole
moments would have to be the same, for the resulting vectors
of the two half-molecules are independent of whether or not the
respective groups are identical in configuration or are mirror
images. In fact, however, the two moments are quite different.
Wolf (189) made entirely analogous observations with tartaric
acid and mesotartaric acid. On the other hand, the moments of
hydrobenzoin and isohydrobenzoin differ only slightly (190).
This might, however, be due to the angle of the oxygen atom.
The moment in any meso form should be particularly small since
all the substituents can go into the *trans* form in pairs. This
has been experimentally confirmed in nearly all cases (191).
Bergmann and Engel (192) have published measurements of the
moments of diphenyl derivatives.

The results obtained by dipole measurements have found

desirable confirmation and extension by x-ray measurements. Keesom and de Smedt (193), as well as Debye (194), have shown that two processes overlap in the interference of monochromatic x-rays in liquids. There is, for one, the so-called "internal interference" which originates in the geometrical structure of the individual molecule. But, since the intermolecular distances are also comparable with the wave length, there is also an "external interference," from which a certain regularity in the molecular orienta-

TABLE 11

Distance between the chlorine atoms in chloromethanes

COMPOUND	DISTANCE Cl-Cl IN Å.
CCl_4	2.99
$CHCl_3$	3.11
CH_2Cl_2	3.23

TABLE 12

Dipole moments of halogenated methanes

SUBSTANCE	DIPOLE MOMENT
$CHCl_3$	1.18
$CHBr_3$	0.99
CHI_3	1.0
CH_2Cl_2	1.55
CH_2Br_2	1.4
CH_2I_2	1.1

tion in fluids can be deduced. In the study of the scatter radiation from gases only the internal interference is observed. By the use of the proper atoms in the molecule certain atomic distances can thus be directly measured. The measurements of Debye (195) on ethylene dichloride appear to show that the molecule is predominantly in the *trans* arrangement. Wierl (196) however came to a different conclusion in an investigation of the diffraction of cathode rays by ethylene dichloride. It is however possible that his result was falsified by the activation of the molecule (197).

There is unusual stereochemical interest in the interference

measurements of Debye and Bewilogua (195) made with simple substituted methane derivatives, for they permit a statement in regard to the form of the tetrahedron. As table 11 shows, the distance between the chlorine atoms increases with the decrease of their number, which may indicate a spreading of the valences (184). Wierl obtained practically identical figures from the diffraction of cathode rays. In view of the excellent agreement of the measurements a regular tetrahedral form is very probable for carbon tetrachloride. The length of the edge of the tetrahedron of carbon tetrabromide is 3.32 Å. according to Rumpf (198), and is 3.35 Å. according to Wierl.

Dipole measurements of the halogenated methanes are also interpreted as showing a spreading of the valences. Several measurements of Müller and Sack (199) are given in table 12. The values are smaller than those which would be calculated for the moments of a strictly tetrahedral structure. It is, to be sure, questionable whether the additivity rule is rigorously valid when strongly polarizing groups are attached to the same central atom. Measurements of dipole moments have also been applied to the solution of the question of the configuration of pentaerythritol derivatives. Here, too, no contradiction of the classical theory has been encountered (200).

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