QUARTERLY REVIEWS

ASYMMETRIC TRANSFORMATION AND ASYMMETRIC INDUCTION

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Asymmetric Transformation : Introductory

ASYMMETRIC transformation involves no synthetic factor and is concerned with stereochemical changes only. The term was used by H. Leuchs and J. Wutke [1] in 1913 to describe the observed fact that addition of brucine to *dl*-2-*o*-carboxybenzyl-α-hydrindone (VII) in acetone solution resulted in an " asymmetric transformation " of the initially formed *and dissolved* base.*dl*-acid into *solid* base.*d*-acid, in yield showing that practically all the base.*l*-acid in solution had been transformed into solid diastereoisomeric base.*d*-acid. Removal of the brucine gave a dextrorotatory acid which readily racemised. Other workers discovered analogous cases, and occasionally the words " optical activation " were used : thus the brucine was said to have activated the inactive Leuchs acid. Attention was concentrated on what came out of solution rather than what was happening in solution.

An important experimental observation of a different kind was made by J. Read and A. M. McMath,[2] who found that the *l*-hydroxyhydrindamine salts (I) of *l*- and of *dl*-chlorobromomethanesulphonic acid exhibited in dry acetone solution a rotational change which could only be explained on the assumption of the existence of an equilibrium :

$$l\text{-Base}.l\text{-Acid} \rightleftharpoons l\text{-Base}.d\text{-Acid}$$

which was greatly in favour of the *l.l*-salt. Again the idea of activation of a potentially active molecule (that of the acid) by a stably active molecule (that of brucine) was put forward, although it was found impossible to isolate an optically active specimen of the free acid. In 1928, W. H. Mills and K. A. C. Elliott [3] observed the partial " activation " of *N*-benzenesulphonyl-8-nitro-1-naphthylglycine (XII) by means of an approximate equivalent of brucine in chloroform solution ; in the same research these authors obtained by processes depending on asymmetric transformation both the *d*- and the *l*-acid, which had low, but appreciable, optical stability.

[1] *Ber.*, 1913, **46**, 2420. [2] *J.*, 1925, **127**, 1572. [3] *J.*, 1928, 1291.
* (*née* Jamison.)

The discovery that the salt of 4 : 4′-dinitrodiphenic acid (XXIII) with the lævorotatory base quinine was strongly dextrorotatory in solution and moreover was apparently a single individual, but that all attempts to liberate an active acid failed, led R. Kuhn [4] in 1932 to introduce the expression " asymmetrische Umlagerung erster Art " to describe this and other cases which seemed to him similar (Read and McMath ; [2] P. Pfeiffer and his co-workers [5]). This expression was translated " asymmetric transformation of the first order," but " sort " or " kind " or " type " would have been a happier rendering of " Art " since " order " raises thoughts of reaction kinetics. R. Kuhn proposed the term " asymmetric transformation of the second order " for cases such as that of Leuchs, where one diastereoisomeride was obtained in preponderating quantity and removal of the activating base led to the isolation of an optically active acid. H. King,[6] in 1933, made a useful survey of the subject up to that date.

M. M. Jamison and E. E. Turner [7] re-defined first-order asymmetric transformation as a phenomenon relating only to the attainment of an equilibrium, while second-order transformation denotes the appearance of a second phase. They showed that one essential condition for first-order transformation was the real existence of diastereoisomerides in solution, the cause of any observed mutarotation being the approach to an equilibrium such as :

$$d\text{-Base}.d\text{-Acid} \rightleftharpoons d\text{-Base}.l\text{-Acid},$$

where the base is optically stable and the acid optically labile : salts will only show the effect in solutions in which ionic dissociation is largely absent. There are, however, numerous examples of diastereoisomerism apart from those concerned with salts ; thus α- and β-sugars are, in the present sense, diastereoisomeric, and their examination can be extended to aqueous solutions, in which salt-diastereoisomerides would as a rule be ionically dissociated. In fact, the " mutarotation " of sugars, which has been long studied, must now be reconsidered in the light of the conception of first-order transformation, as must also the interesting studies of " asymmetric catalytic racemisation " made by A. McKenzie and his co-workers [8] which can be more clearly interpreted now that first-order transformation has been investigated using compounds deliberately synthesised for the purpose.

Before discussing individual examples of asymmetric transformation, it is pertinent to consider the kind of molecule which possesses unstable dissymmetry. (Up to the present most experiments have been made in the normal range of temperatures, but, at temperatures considerably higher than the ordinary, many optically stable molecules would become optically labile, and the investigation of derivatives of such compounds as tartaric acid at temperatures at which they racemise readily offers interesting problems.) A large proportion of the experimental evidence in connection with asymmetric transformations has been obtained from a study of molecules

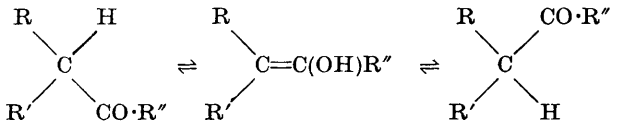
[4] *Ber.*, 1932, **65**, 49. [5] *Ibid.*, 1931, **64**, 2667 ; 1932, **65**, 560 ; 1933, **66**, 415.
[6] *Ann. Reports*, 1933, **30**, 261. [7] *J.*, 1942, 437.
[8] A. McKenzie and I. A. Smith, *J.*, 1924, **125**, 1582 ; *Ber.*, 1925, **58**, 894.

owing their dissymmetry to restriction of rotation about a single bond. A second class of molecule which has contributed is that in which interconversion of antipodal forms is rendered possible by the operation of prototropic changes, this class including some sugars. To these can be added a number of rather miscellaneous compounds, among which are certain complex salts. The total number of compounds the configuration of which can readily be inverted is relatively small; what might be called the average asymmetric carbon atom offers considerable resistance to inversion. (We are not concerned in the present article with inversion during replacement reactions of the type associated with the name of Walden, although cases can be foreseen where the steric aspects of "aliphatic substitution" and first-order asymmetric transformation may well have common experimental material.)

Compounds owing their optical activity to restriction of rotation about a single bond provide the most convenient material for a study of the two types of asymmetric transformations. They are suitable material for examination because their racemisation is of purely physical origin and therefore spontaneous, that is, not generally subject to acceleration by the action of catalysts. Some members of this class give active forms of very high optical stability, *e.g.*, 6 : 6′-dinitrodiphenic acid, while the optically least stable compounds yet known to show measurable mutarotation are certain alkaloidal salts[9] of *N*-benzoyl-2 : 4-dichlorodiphenylamine-2′-carboxylic acid (*B*, p. 325) and *N*-benzoyl-2 : 4-dimethyldiphenylamine-2′-carboxylic acid (*C*, p. 325). These acids belong to one of the most convenient and accessible series of compounds in the restricted rotation class. Substituted diphenyls offer a large field, but particular individuals are difficult to prepare in any quantity. *peri*Disubstituted naphthalenes, of which the Mills–Elliott acid mentioned above is the best example, provide a useful but limited field and are tedious to synthesise.

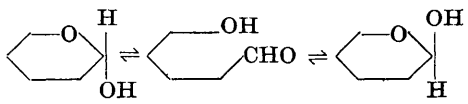
Enantiomeric pairs which racemise by a tautomeric mechanism are interconvertible in ways such as the following :

(*a*)



Inactive intermediate

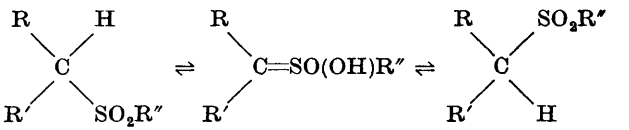
(*b*)



α β

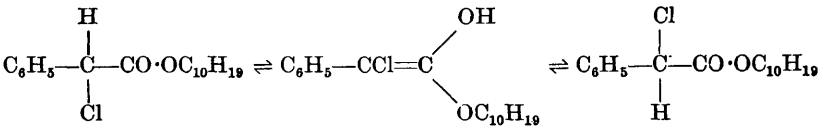
Skeletal forms of a sugar

(*c*)



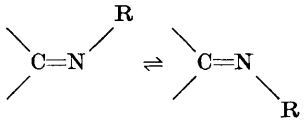
[9] *J.*, 1938, 1646.

These processes are subject to influence by catalysts and in some cases, *e.g.*, the (as it is now classified) first-order transformation :



the equilibrium process is too slow for measurement in absence of suitable catalysts.[8] The sugars provide examples of both types of asymmetric transformation.

Among substances which do not fall under either of these two headings are the oxime (V) (p. 310) and benzoylphenylhydrazone of *cyclo*hexanone-4-carboxylic acid ;[10] here the inversion mechanism is purely a configurational change, depending on the stereochemical instability of the system :



In complex salts, particularly the chromioxalates (II) (p. 308),[11] the mechanism of inversion is unknown, although various obvious possibilities can be conjectured. It may be that optical instability arises from sheer chemical instability, since asymmetric transformation was not observed by Werner in his exhaustive treatment of complex salts of the ammine type, where the chemical stability is considerable. The " asymmetric tin " compounds of W. J. Pope and S. J. Peachey [12] must owe their optical instability largely to ease of inversion in the ion, $MeEtPrSn^+$, or a solvated modification. Optical instability of a molecule owing its dissymmetry to " folding " was described by I. G. M. Campbell [13] in the case of 10-*p*-carboxyphenyl-2-methylphenoxstibine (VI) (p. 310).

If a structure contains two " centres of asymmetry ", X and Y, each centre can have either a dextro- or a lævo-configuration, so that under favourable conditions two pairs of diastereoisomerides are possible :

(*A*) *d*-X.*d*-Y and *d*-X.*l*-Y (*B*) *l*-X.*d*-Y and *l*-X.*l*-Y.

In the present discussion we are concerned either with (*A*) or with (*B*) : what applies to the one equally applies to the other with all signs changed. Taking (*A*), therefore, three classes are possible :

Class I. Both centres, X and Y, are configurationally stable under experimental conditions. This presents no problem, since although *d*-X.*d*-Y and *d*-X.*l*-Y must have different free energies, the energy barrier which would have to be surmounted in order to bring the two compounds into mobile equilibrium is too high for attainment.

[10] W. H. Mills and A. M. Bain, *J.*, 1910, **97**, 1866 ; 1914, **105**, 64.
[11] A. Werner, *Ber.*, 1912, **45**, 3061.
[12] *Proc.*, 1900, **16**, 42, 116. [13] *J.*, 1947, 4.

Class II. One centre, say X, has a high configurational stability, while Y can undergo configurational inversion at a measurable rate under the experimental conditions. An equilibrium can now be established: *d*-X.*d*-Y $\rightleftharpoons$ *d*-X.*l*-Y, and its establishment may be capable of observation as a mutarotation.

Class III. Both centres, X and Y, have low optical stability under experimental conditions. Starting with either *d*-X.*d*-Y or with *d*-X.*l*-Y the final result of equilibration will be a mixture of (*A*) and (*B*), the ratio of *d*-X.*d*-Y to *d*-X.*l*-Y (equal to that of *l*-X.*l*-Y to *l*-X.*d*-Y) being determined by the relative free energies of the diastereoisomerides.

We are here concerned only with Class II. Most of the known examples of asymmetric transformation relate to salts, either the acidic, or much more usually the basic, part containing X, the fixed asymmetric centre. In the sugar series, Y represents the CH·OH group which can adopt either the α- or the β-configuration, X representing the rest of the molecule and usually containing several asymmetric centres of high optical stability which can be thought of as acting together as one unit. The cases dealt with under "asymmetric catalytic racemisation" are esters. For second-order asymmetric transformation to occur with a Class II compound, the two diastereoisomerides need have no real existence in solution: what is necessary is that one salt should crystallise from solution. Thus if *d*-X is a stably active base and *dl*-Y is an optically labile acid, even if in solution there are merely the ions corresponding to base and acid, then, provided, *e.g.*, *d*-X.*d*-Y begins to crystallise, the acid *ion l*-Y can *racemise* and in this way provide continually more of the *d*-Y ion and so more *d*-X.*d*-Y. For first-order transformation, however, the two optical centres concerned must be in combination and this means that the solvent must be one in which little ionisation occurs: in particular a non-hydroxylic one. This condition fulfilled, let us suppose the *d*-form of an optically stable base to be in solution. On adding an equivalent of the *dl*-form of an optically unstable acid, there is formed at once, in solution,

$$\underset{50\%}{d\text{-Base}.d\text{-Acid}} + \underset{50\%}{d\text{-Base}.l\text{-Acid}} \quad (1)$$

Owing to the different free energies of the two diastereoisomerides, equilibration (first-order asymmetric transformation) will occur until we reach the composition:

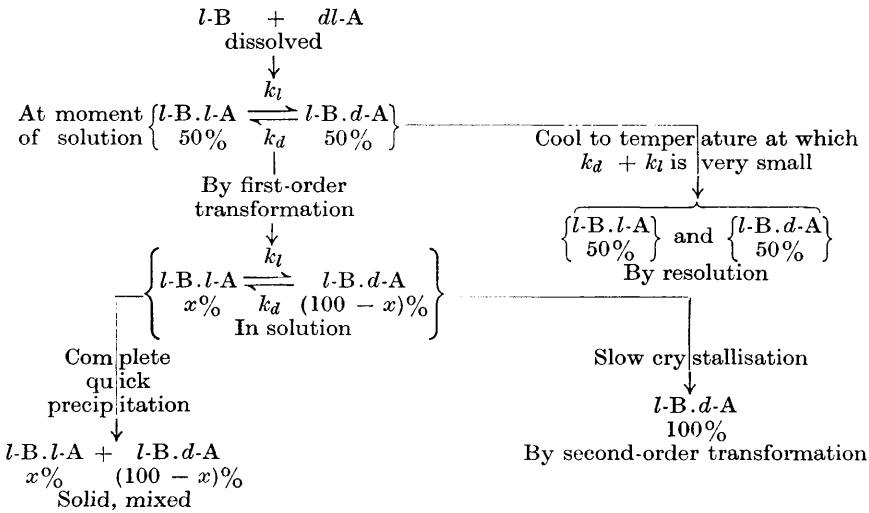
$$\underset{x\%}{d\text{-Base}.d\text{-Acid}} \rightleftharpoons \underset{(100-x)\%}{d\text{-Base}.l\text{-Acid}} \quad (2)$$

This can sometimes be followed polarimetrically, considerable rotational changes being observed. In other cases the equilibrium may be reached too quickly for observation; or the difference between the rotation of the partial racemate and that of the equilibrium mixture may be very small. Since first-order transformation depends on a difference of free energy between diastereoisomerides in a particular solvent, and the difference *d*-X.*l*-Y $-$ *d*-X.*d*-Y may not be the same as *d*-X′.*l*-Y $-$ *d*-X′.*d*-Y, using a second base X′, the stereochemist varies both activating agent and solvent in attempting to bring first-order asymmetric transformation

involving a specific labile group within the measurable range of magnitude and velocity.

In one instance [7] it was possible to prepare the pure *l*-base.*l*-acid and determine the rate constant for the change into the equilibrium mixture, in addition to determining the rate constant for the "activation" process, *viz.*, the change of the 50 : 50 mixture of *l*-base.*d*-acid and *l*-base.*l*-acid into the same equilibrium mixture. The two rate constants were found to be equal, k, the measured value, being the sum of two rate constants k_d and k_l, for the *partial inversion* of base.*d*-acid and base.*l*-acid. (By "partial inversion" we mean the change *l*-base.*d*-acid → *l*-base.*l*-acid or *l*-base.*l*-acid → *l*-base.*d*-acid.) These changes have been described as "partial racemisation", but this term is misleading, since the partial racemate, composed of equivalent weights of *d*-X.*d*-Y and *d*-X.*l*-Y, is not the equilibration product. In *partial racemisation* the values of k_d and k_l are equal : it is their difference that accounts for first-order transformation. In the case raised above in which second-order asymmetric transformations involve crystallisation of diastereoisomerides which become ionised in solution, first-order transformation is excluded and *partial racemisation* accurately describes what happens in solution.

To summarise the practical aspects of resolution, second-order transformation, and first-order transformation, it is convenient to consider a hypothetical case in which a *dl*-acid (optically unstable) and a *l*-base (optically stable) are dissolved in a solvent in which the salts formed are not dissociated, and to predict the results of applying various conditions on the solution and what crystallises or is precipitated from it :



This scheme, which is based on practical experience,[9,14] shows that the appropriate treatment of an optically labile substance, with one activating

[14] M. M. Jamison, *Trans. Faraday Soc.*, 1945, **41**, 696.

agent and one solvent only, can produce an interesting variety of results. There may be greater variety than is here indicated : the difference in free energy between the two diastereoisomerides may be so slight that in second-order transformation one form or the other may crystallise without there being an apparent difference in procedure. Ordinary resolutions, in which the question of optical stability does not normally arise, are sometimes complicated [15a, b] by the separation of the partial racemate in crystalline form, and similarly partial racemates sometimes separate as alternatives to the normal products of second-order asymmetric transformation.

It is understandable that decomposition of an optically pure salt obtained by second-order asymmetric transformation might give an optically inactive, *i.e.* racemised, acid. How, in that case, can the crystallisation be classed as second-order transformation ? Obtaining an active acid is the only entirely satisfactory proof of second-order transformation, but it may be suspected when a solution made up to contain a g. of an optically stable base *d*-X is mixed with one containing the equivalent, b g., of an acid *dl*-Y and crystallisation produces considerably more than $(a + b)/2$ g. of solvent-free, apparently homogeneous salt with a molecular rotation different from that " calculated " for the partial racemate. The suspicion is heightened if crystallisation appears to be progressive rather than sudden and if it is accelerated by gentle heating. It becomes very nearly a certainty (1) if several crops are obtained each with the same rotation and which together weigh nearly $(a + b)$ g., (2) if a solution of the salt in the same or a different solvent exhibits mutarotation, or (3) if when the salt is dissolved in a different solvent a new and uniform salt crystallises, which in turn gives rise to mutarotational changes when dissolved in the same or a different solvent. A striking difference, even of sign, between the rotation of *d*-X and that of the salt which crystallises is not enough to justify the assumption of asymmetric transformation.

Second-order transformations have often been called resolutions : this mistake has led to the judgment that diphenyl compounds are easy to resolve, when in fact it has been found easy to obtain *one* antipodal form only, by second-order transformation.

A problem of great interest is this : if *d*-X.*d*-Y and *d*-X.*l*-Y (X stable, Y unstable, optically) are brought together in equivalent amounts in solution, and first-order asymmetric transformation leads to the equilibrium :

$$d\text{-X}.d\text{-Y} \rightleftharpoons d\text{-X}.l\text{-Y}$$

so that more *d*-X.*l*-Y is finally present in solution than *d*-X.*d*-Y, then, if crystallisation begins, which of the two diastereoisomerides will separate ? With a pair of solids such as are met with in a study of allotropy or polymorphism, we should usually have a *stable* form and an *unstable* form (as distinguished from a pair of diastereoisomerides in equilibrium). Generally

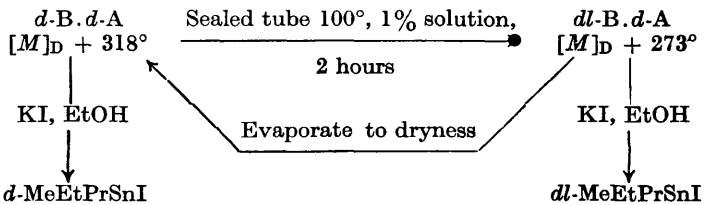
[15a] J. Meisenheimer and O. Beisswenger, *Ber.*, 1932, **65**, 32.

[15b] J. Meisenheimer, W. Theilacker, and O. Beisswenger, *Annalen*, 1932, **495**, 249.

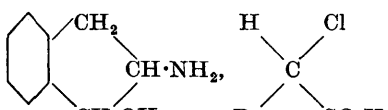
speaking, the stable form would be less soluble than the unstable form, so that, apart from chance inoculation, the stable form would be the one to separate if time were given for stability to assert itself thermodynamically over instability. We should have to hesitate, however, before answering the above question by (apparent) analogy. The answer can be given: " the stable form is the more soluble " in the case of some diastereoisomeric sugars,[26, 31, 32] some esters investigated by McKenzie,[8] and the only example known [7] in which both first- and second-order asymmetric transformations have been observed with one pair of diastereoisomeric salts in one and the same solvent.

Examination of Experimental Material

Two cases of second-order asymmetric transformation appear in Pope and Peachey's demonstration of optical activity in tin compounds.[12] Methylethyl-*n*-propyltin *d*-camphorsulphonate crystallised from water in one form only, $[M]_D + 95°$ in water; $[M]_D + 45°$ is the calculated value for the basic radical from this: the dextrorotation was retained when the camphorsulphonate was converted into the iodide.[12] Secondly, the specific rotations of successive crops of methylethyl-*n*-propyltin *d*-α-bromocamphorsulphonate from acetone solution were constant ($[M]_D + 318°$ in water [12]). Since the acid radical was known to have $[M]_D + 270°$, the authors attributed $+ 48°$ to the basic part and confirmed it by conversion into *d*-methylethyl-*n*-propyltin iodide as before. The aqueous solution, $[M]_D + 318°$, was heated to 100° in a sealed tube for two hours, by which time its rotation had fallen to $+ 273°$: decomposition of this solution with potassium iodide gave the inactive iodide, but evaporation to dryness gave the original *d*-α-bromocamphorsulphonate, $[M]_D + 315°$. They ascribed the fall in rotation on heating to partial racemisation, so that the whole series of changes can be expressed:



Read and McMath [2] were able to carry out a second-order asymmetric transformation using *dl*-chlorobromomethanesulphonic acid in either the *d*- or the *l*-direction by using the *d*- or the *l*-hydroxyhydrindamine. The *l*-hydroxyhydrindamine *dl*-chlorobromomethanesulphonate (I), $M[\alpha]_D - 72°$ in methyl alcohol, crystallised from acetone containing a little methyl alcohol to give a salt which, while it had eventually the rotation $-72°$, had $M[\alpha]_D - 173°$ when first observed.



(I.)

Proof of the activity of the acid part of the salt could only be obtained by the expedient of mixing equal quantities of the *d*-base.*d*-acid and *l*-base.*dl*-acid salts ; a residual $[M]_D$ of + 49° was then observed : attempts to replace the optically active base by benzidine or α-naphthylamine gave inactive salts.

When the salt *l*-base.*l*-acid was dissolved in specially purified anhydrous acetone it had $[M]_D$ — 256° three minutes after first wetting with solvent, a value which changed to — 187° in less than an hour (Fig. 1). This change might have been considered as consequent on partial racemisation had it not been that the partial racemate itself, *l*-base.*dl*-acid, when dissolved in the same solvent had $[M]_D$ — 71° initially, changing to — 187° on standing. This latter observation has become the classical case of first-order asymmetric transformation. If the salts are not dissociated in solution and their rotations are constant over the concentration ranges employed, the composition, as a simple calculation shows, at equilibrium is

$$\begin{matrix} \text{B}.l\text{-A} & \rightleftharpoons & \text{B}.d\text{-A} \\ 81\% & & 19\% \end{matrix}$$

It was, of course, desirable to remove the *l*-hydroxyhydrindamine from the equilibrated solution to prove that the mutarotation was due to optical activation of the acid (particularly as *l*-hydroxyhydrindamine benzenesulphonate shows (unexplained) mutarotation in methyl alcohol, $[M]_D$ changing from — 100° to — 76° in 8 hours), but the authors were unable to accomplish this. The experiments described are not suitable for correlation of the directions of first- and second-order transformation since the first-order transformation was carried out in specially purified and dried acetone and the second-order from acetone–methyl alcohol : also, the alternative crystalline solid which can be obtained is not the diastereoisomeride but the partial racemate, *l*-B.*dl*-A. An interesting recorded observation which would be worthy of further investigation is that " an acetone solution " of the salt deposits crystals the acetone solution of which has $[M]_D$ — 93° mutarotating to — 154° and yet depositing on evaporation the crystals with $[M]_D$ — 93°.

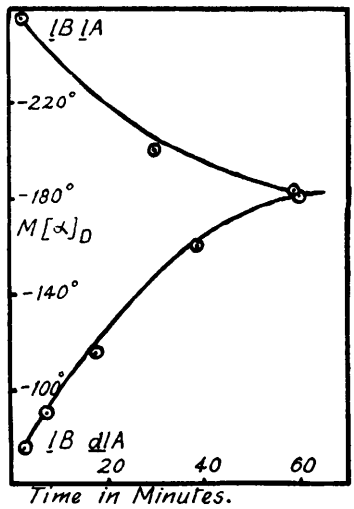


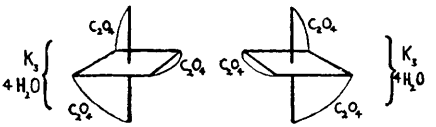
FIG. 1

A second series of experiments was made with the same base and chlorobromoacetic acid.[16] A solution of equimolecular quantities of the *l*-base and *dl*-acid was made in chloroform containing a little methyl alcohol ; slow crystallisation gave *l*-base.*dl*-acid, $[M]_D$ — 50° in the same solvent, while quick cooling of a hot solution to supersaturation gave *l*-base.*d*-acid in 75% yield, $[M]_D$ changing from the first observed 0° to — 50° on standing :

[16] *J.*, 1926, 2183. See also H. J. Backer and H. W. Mook, *J.*, 1928, 2125.

l-base.*dl*-acid was deposited from the mother liquor. Although the antipodal forms of the above pair of salts, *d*-base.*l*-acid and *d*-base.*dl*-acid, were prepared, attempts by mixing to observe a rotation which was due to acid only failed—an inconclusive observation of $-0{\cdot}1°$ was made 1·5 minutes after wetting with solvent. The naming of the various types of crystal is therefore conjectural.

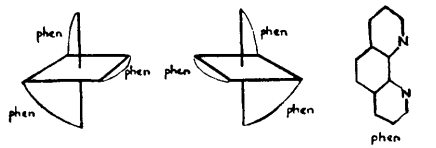
The crystals deposited from a hot solution of potassium distrychnine chromioxalate in ethyl alcohol were shown by Werner [11] to contain asymmetrically activated chromioxalate ion. The rotation of the salt, a tetrahydrate, was $[\alpha]_G + 430°$ in water, the part due to the chromioxalate ion ($+ 0{\cdot}43°$ observed) mutarotating to zero in $1\frac{1}{4}$ hours; the tripotassium salt obtained from a sample of it before mutarotation was dextrorotatory. A dilute solution of potassium distrychnine chromioxalate in water deposited



(II.)

crystals of tristrychnine *l*-chromioxalate ($+ 4H_2O$), all the crops measured being lævorotatory: the specific rotation $[\alpha]_G$ was $-300°$ in water, and decomposition with potassium iodide gave *l*-potassium chromioxalate (II). Werner investigated the mother liquor from which crystallisation was taking place and found it "practically inactive"; this is what might be expected if asymmetric transformation of the second order were taking place, whereas resolution would result in an increase of rotation in solution of the opposite sign from that of the solid coming out.

This work of Werner's enabled P. Pfeiffer and K. Quehl [5] to put an interpretation on some results they obtained in crystallising zinc β-camphorsulphonate from water in presence of *o*-phenanthroline. A solution of zinc



(III.)

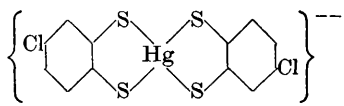
β-camphorsulphonate itself had $\alpha_D + 0{\cdot}92°$ (1/1000-mol. in 25 c.c. of water), while the salt $Zn(phen)_3O{\cdot}SO_2{\cdot}C_{10}H_{15}O,7H_2O$ (as III) obtained in 80% yield by crystallising zinc β-camphorsulphonate from water containing 3·5 mols. of *o*-phenanthroline had α_D 0·0°.

When 3 mols. of *o*-phenanthroline were added to a solution of zinc β-camphorsulphonate, the rotation fell immediately from $+ 0{\cdot}92°$ to $+ 0{\cdot}09°$: neither ammonia, pyridine, nor ethylenediamine produced this diminution. Replacement of the β-camphorsulphonate ions by nitrate or

bromide gave inactive products; nevertheless Pfeiffer and Quehl accounted for their observations by assuming formation of *l*-$[Zn(phen)_3]^{++}$ under the influence of the β-camphorsulphonate ions. The quinate and α-bromo-π-camphorsulphonate ions [5] appeared to cause similar activation (first order) of zinc complexes, large changes in rotation being observed on adding *o*-phenanthroline or 2 : 2′-dipyridyl to aqueous solutions of these zinc salts. One feels a little hesitant at accepting the interpretation of these experimental observations in solution as first-order changes, since the salts $[Zn(phen)_3]X_2$ must be completely ionised, that is, the transforming agent is separated from the complex it is activating. In comparison with examples of similar phenomena in other fields of molecular dissymmetry, it is more surprising that a cation should be able to activate a cation, as the authors suggest in the following cases: a solution of cinchonine hydrochloride and zinc sulphate in water showed $\alpha_D + 5{\cdot}29°$ before the addition of 3 mols. of *o*-phenanthroline, after which it changed immediately to $-1{\cdot}89°$ and to $-2{\cdot}46°$ on standing. Precipitation of the cinchonine by means of alkali left an optically inactive zinc salt. Results of the same type were obtained using strychnine sulphate instead of cinchonine hydrochloride, and indeed there are many similar examples in the work of Pfeiffer and his collaborators. It is possible that these mutarotations are not first-order transformations at all, but result from the replacement of alkaloid by *o*-phenanthroline in a metal complex, with consequent mutarotation.

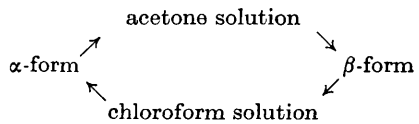
The activation of the ferrioxalate ion by means of *d*- or *l*-α-phenylethylamine recorded by W. Thomas [17] rests on more slender evidence but would be worthy of repetition. J. J. Woldendorp [18] records a crystallisation of strychnine hydrogen chromimalonate $(C_{21}H_{22}O_2N_2{\cdot}H)H[Cr(malonate)_3]$ resulting in deposition of *l*-base . *l*-acid only.

W. H. Mills and R. E. D. Clark's [19] work on the complex anion of mercury with 4-chlorobenzene-1 : 2-dithiol (IV) is particularly interesting on account of the arguments the authors use in favour of a tetrahedral disposition of the mercury valencies. The diquinine salt was formed and on crystallisation from chloroform solution produced an α-form which on crystallisation from acetone deposited a β-form, a process which could be repeated indefinitely: each crystalline form has solvent of crystallisation, but the two forms remain different after the solvent is removed. The fact that no two forms of *metallic* salts were discovered may be taken as excluding the possibility that the α- and β-forms are *cis*- and *trans*-forms of a flat mercury cation. In spite of the fact that the authors were unable



{Quinine, H}$_2^+$

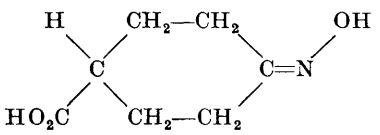
(IV.)



[17] *J.*, 1921, **119**, 1140. [18] *Vers. K. Akad. Wetensch. Amsterdam*, 1919, **27**, 1212.
[19] *J.*, 1936, 175; see on a practical point T. S. Patterson, *J.*, 1927, 1717.

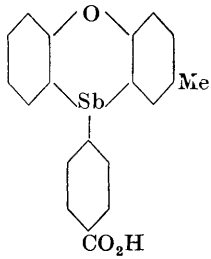
to observe mutarotation of the substances in solution at temperatures as low as — 35° they present the evidence of solubility changes as indicating optical activation of a tetrahedral mercury cation by the quinine, and assume that the mutarotations accompanying the transformations were too quick to measure. Zinc and cadmium salts were prepared which showed similar behaviour.

The oxime of *cyclo*hexanone-4-carboxylic acid (V) was prepared by Mills and Bain [10] in order to investigate the stereochemical configuration of the group $\rangle C{=}N{-}OH$. When they attempted its resolution with quinine in 30 parts of water, a salt, quinine *l*-acid, $2\frac{1}{2}H_2O$, crystallised in 80% yield of the *total* quantity present; the mother liquor, instead of containing the diastereoisomeride, as would have been expected in resolution, was inactive, and decomposition of the salt with sodium hydroxide yielded a sodium salt, $[M]_D$ — 91° (morphine effected a dextroasymmetric transformation similarly, giving a salt from hot ethyl alcohol which could be decomposed by aqueous ammonia to give dextrorotatory ammonium salts). The authors explained their results as being due to the configurational instability of the oximino-group which is involved in the dissymmetry of the whole molecule: the aqueous solution contains the partial racemate, and as the less soluble quinine *d*-acid salt is removed by crystallisation, equilibrium is rapidly re-established by racemisation of the quinine *l*-acid salt remaining in solution. Similar behaviour was encountered in the crystallisation of the quinine and morphine salts of the *N*-benzoylphenylhydrazone of *cyclo*hexanone-4-carboxylic acid; [10] with a mixture of methyl alcohol and water as a solvent the *l*-quinine *d*-acid salt crystallised first and was converted into the sodium, potassium, or ammonium *d*-acid salt. The authors stated that this crystallisation was an asymmetric transformation and not a resolution although the percentage of the salt crystallising was not recorded in support: they did not obtain any of the *l*-base.*l*-acid salt, which makes resolution appear unlikely. In the same way the semicarbazone of the parent acid was activated by crystallising its morphine salt from aqueous methyl alcohol and converted into a dextrorotatory ammonium salt.



(V.)

A strychnine salt of 10-*p*-carboxyphenyl-2-methylphenoxstibine (VI) having $[\alpha]_D$ — 18° in chloroform was converted almost completely by boiling with alcohol for 30 minutes into a salt with $[\alpha]_D$ + 17°. This was regarded by the author [13] as a case of second-order asymmetric transformation.

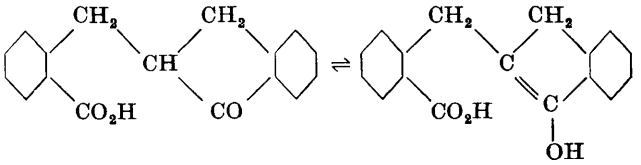


(VI.)

2-*o*-Carboxybenzylindan-1-one (VII) and brucine

crystallise from acetone to give a 94% yield of a single salt : the acid part of the salt, in its ketonic form, shows molecular dissymmetry, and decomposition of this salt with sulphuric acid gave a dextrorotatory acid, $[\alpha]_D^{20°} + 64°$, which mutarotated in chloroform solution. Leuchs and Wutke,[1] who carried out this work, gave the explanation that the optically active forms of the ketonic acid were interconvertible through the inactive enolic form, thus providing a mechanism for asymmetric transformation by the agency of the brucine :

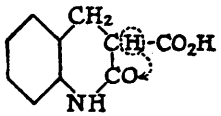
B.*l*-Acid ⇌ B.*enolic* Acid ⇌ B.*d*-Acid ⟶ Crystals



d- or *l*-Form Inactive enolic form

(VII.)

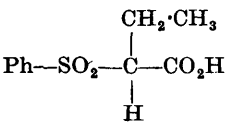
By the use of another compound owing its optical instability to keto–enol tautomerism, hydrocarbostyril-3-carboxylic acid (VIII), Leuchs [20] has provided a very clear example of a second-order asymmetric transformation. The accompanying table shows the weights of three crystalline fractions obtained from 2·4 g. of hydrocarbostyril-3-carboxylic acid and 4·07 g. of anhydrous quinidine in 40 c.c. of methyl alcohol. The dihydrated salt crystallised and was shown to be one form only by removing the quinidine in hydrochloric acid at − 10° and watching the mutarotation of the residual acid in glacial acetic acid solution at 18° ; the rotations of the separate preparations of acid are given



(VIII.)

Fraction.	Weight (g.).	α_D (l = 0·5).
1	4	+ 1·08°
2	1·5	+ 1·09
3	0·7	+ 1·04

in the third column, extrapolated to the time of wetting with solvent. The total weight of salt is seen to be 6·2 g. out of a possible 6·9 g.



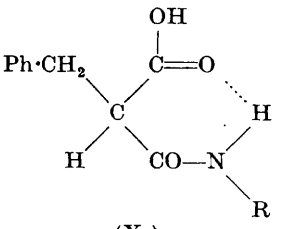
(IX.)

W. C. Ashley and R. L. Shriner [21] found that α-phenylsulphonylbutyric acid (IX) underwent almost theoretical asymmetric transformation of the second order under the influence of brucine in acetone solution to give the brucine *l*-acid salt.

[20] *Ber.*, 1921, **54**, 830. [21] *J. Amer. Chem. Soc.*, 1932, **54**, 4410.

Decomposition gave the *l*-acid, a tautomeric mechanism being envisaged for the optical inversion.

An 83% yield of optically pure brucine *l*-benzylmalonoanilic acid (X) separated from an alcoholic solution of brucine and the *dl*-acid, a second-order asymmetric transformation which the discoverers, E. M. Davidson and E. E. Turner,[22] found to be accelerated by heating. (One of the most impressive things about a crystallisation which is taking place with asymmetric transformation is that the beaker of filtered solution can be left in a warm place rather than in a cold to accelerate deposition.) Cinchonidine in chloroform solution converted the *dl*-acid in 90% yield into the optically pure base.*d*-acid salt. First-order asymmetric transformations were not observed in spite of very careful searching. The analogous benzylmalono-*o*-toluidic acid was activated similarly by cinchonidine from acetone solution to give an 83% yield of the base.*d*-acid salt. This was amply proved to be a second-order transformation by removal of the base to give the *d*-acid, which had very considerable optical stability in formic acid solution and did not racemise at a measurable rate in cold ethyl-alcoholic solution.



(X.)

The papers of A. McKenzie and his school contain much interesting experimental work which is valuable in a study of first-order asymmetric transformation, that classified as " asymmetric catalytic racemisation " in particular. The *l*-menthyl esters of various acids, *dl*-phenylbromoacetic, *dl*-phenylchloroacetic, and *dl*-mandelic, when dissolved in ethyl alcohol and given a very small concentration of alcoholic potash, undergo mutarotation.[8] Evidently the ethoxide ion acts as a catalyst for the inversion of the acid part of the ester and thereby provides a mechanism for the optical activation or first-order asymmetric transformation, under the influence of the *l*-menthyl residue. In these cases the transforming agent and the labile group are in chemical combination. McKenzie and Smith,[8] for example, studied in detail the changes in rotation undergone by *l*-menthyl phenylchloroacetate, starting from the *l*-menthyl *d*-acid, *l*-menthyl *l*-acid, and *l*-menthyl *dl*-acid esters : they came to the conclusion that " the velocity of the catalysis is greater with the *l*-menthyl *d*-phenylchloroacetate than with its diastereoisomeride " by making a calculation based on the measurement of the percentage of the original ester left after a certain time of mutarotation. This calculation assumes that the system is moving towards the partial racemate, whereas in fact the reactions in which the speed of the two diastereoisomerides differ is partial inversion. The rate constant for approach to equilibrium from either diastereoisomeride is the same, being the sum of two rate constants of partial inversion, which are different. McKenzie and Smith's figures for the mutarotations, although they were measured without temperature control, show fairly good agreement when used to calculate the rate of

[22] *J.*, 1945, 843.

approach to equilibrium from either side. The equilibrium composition, calculated on strict proportionality, is 57% of *l*-menthyl *l*-phenylchloroacetate and 43% of *l*-menthyl *d*-phenylchloroacetate.[23]

$$\underbrace{\left\{\begin{matrix}\bar{\text{C}}\text{HCl}\cdot\text{CO}_2\text{C}_{10}\text{H}_{19}\\ 50\%\end{matrix}\right\} + \left\{\begin{matrix}\overset{+}{\text{C}}\text{HCl}\cdot\text{CO}_2\text{C}_{10}\text{H}_{19}\\ 50\%\end{matrix}\right\}}_{\left\{\begin{matrix}\bar{\text{C}}\text{HCl}\cdot\text{CO}_2\text{C}_{10}\text{H}_{19} + \overset{+}{\text{C}}\text{HCl}\cdot\text{CO}_2\text{C}_{10}\text{H}_{19}\\ 57\% \qquad\qquad 43\%\end{matrix}\right\}\text{equilibrium mixture}}$$

$$\left\{\begin{matrix}\bar{\text{C}}\text{HCl}\cdot\text{CO}_2\text{C}_{10}\text{H}_{19}\\ 100\%\end{matrix}\right\} \qquad\qquad \left\{\begin{matrix}\overset{+}{\text{C}}\text{HCl}\cdot\text{CO}_2\text{C}_{10}\text{H}_{19}\\ 100\%\end{matrix}\right\}$$

It was not possible to saponify the equilibrium mixture of esters in order to prove that first-order transformation was the cause of the mutarotations, because of their sensitivity to alkali and also because they are saponified at unequal rates and on this account also would lose their equilibrium composition during the reaction.

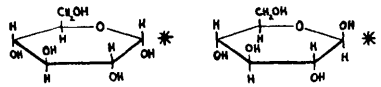
As a result of their experience of many crystallisations carried out in the resolution of *l*-menthyl *dl*-phenylchloroacetate using rectified spirit as the solvent, McKenzie and Smith found that the *l*-menthyl *d*-acid ester was the less soluble diastereoisomeride. This is interesting to note in connection with the direction of mutarotation, towards an excess of the methyl *l*-acid ester, in the same solvent.

I. A. Smith [24] has shown that similar mutarotation phenomena can be observed with amygdalin, where the transforming agent is the gentiobiose residue.

It is interesting to correlate the first- and second-order transformations with mutarotation and crystallisation behaviour in the sugar series. Most of the work to be discussed here is long established as describing the properties of the various sugars, but was not accepted by stereochemists as of general application, probably because it is not possible to remove the " activating agent " from a sugar molecule—it is the whole molecule apart from the labile group—and therefore to *prove* optical activation in any one case. Thus an investigation incorporating many of the features described under restricted rotation compounds was carried out by Hudson and his collaborators [25, 26] for several sugars but owing to the strict formulation of the sugars and their mechanism of partial inversion being in doubt the results could not take a pioneer place in a study of optically labile compounds.

d-Glucose has been the subject of the most extensive experiments, presumably because it crystallises well and is not difficult to obtain. Its composition in aqueous solution at equilibrium has for a long time been

[23] P. D. Ritchie, " Asymmetric Synthesis and Asymmetric Induction ", 1933, p. 83.
[24] *Ber.*, 1931, **64**, 1115.
[25] C. S. Hudson and L. K. Yanovsky, *J. Amer. Chem. Soc.*, 1917, **39**, 1013.
[26] C. S. Hudson and J. K. Dale, *ibid.*, p. 320.



α-*d*-Glucose β-*d*-Glucose

(XI.)

calculated from the rotations of the α- and β-forms (XI) and of the equilibrated mixture, a calculation which seems to be justified as any other form must be present in negligible quantity [27, 25] (so long as the sugars are in the ring form the diastereoisomerides are " real " : the carbon atom marked is the unstable centre of asymmetry and the configuration of all the other carbon atoms is fixed).

Some of the latest published figures [27, 25] for the rotations are :

α-*d*-Glucose.	Equilibrium.	β-*d*-Glucose.
$[\alpha]_{5893}^{22\cdot2^\circ}$ + 110·0°	+ 52·56°	+ 19·7° at 20°

the equilibrium composition of 64% β- and 36% α-form being unaltered between 0° and 40°.[28] Crystallisation from cold water invariably produces the α-form as the monohydrate,[29] but if the operation is carried out between 35° and 40° the anhydrous α-*d*-glucose crystallises. The α-form therefore crystallises out from a solution containing excess of the β-form. [In order to obtain the β-form, C. Tanret left the α-form for some hours at 105° : R. L. Whistler and B. F. Buchanan [30] obtained it by evaporating an 85% solution containing 50 g. of glucose in a vacuum at 100° to a solid mass of crystals. " Second-order transformations " to α- or to β-*d*-glucose can be obtained in various other ways ; Hudson and Dale,[26, 31] for example, found that if an aqueous acetic acid solution was allowed to crystallise slowly in the cold 75—80% pure anhydrous α-glucose was produced, while a hot quick crystallisation resulted in 93% of β-glucose.] Hudson and Dale [28, 31] recognised that the measured velocity constant k for approach to equilibrium from α- or from β-glucose was the same and that it was the sum of two constants k_α and k_β. Certainly it would seem that α-glucose is the less soluble of the two forms, although they are both too soluble in water for accurate measurement to be made.

The solubilities could, however, be measured in 80% ethyl alcohol,[25] 100 c.c. of which dissolved 4·9 g. of the β-form and 2·0 g. of the α-form : the α-form is the one crystallising as the hydrate, while the rotation values show that the β-form is in excess at equilibrium :

$$[\alpha]_D^{20^\circ} \quad \left.\begin{matrix} \alpha\text{-glucose} + 115\cdot5^\circ \\ \beta\text{-glucose} + 20\cdot3^\circ \end{matrix}\right\} \text{equilibrium} + 59\cdot3^\circ$$

In absolute methyl alcohol Andrews and Worley [27] find that there is excess of the β-compound at equilibrium :

$$[\alpha]_D^{20^\circ} \quad \left.\begin{matrix} \alpha\text{-glucose} + 138\cdot4^\circ \\ \beta\text{-glucose} + 26^\circ \end{matrix}\right\} \text{equilibrium} + 75\cdot8^\circ$$

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[27] J. C. Andrews and F. P. Worley, *J. Physical Chem.*, 1927, 1880 ; J. C. Kendrew and E. A. Moelwyn Hughes, *Proc. Roy. Soc.*, 1940, *A*, **176**, 353.

[28] E. A. Moelwyn Hughes, " Kinetics of Reactions in Solution ", 1933 edn., p. 45.

[29] C. Tanret, *Compt. rend.*, 1895, **120**, 1061.

[30] *J. Biol. Chem.*, 1938, **125**, 557. [31] *J.*, 1904, **85**, 1551.

T. M. Lowry [31] found the α-form crystallising from methyl alcohol, and showed that the solubilities in this solvent were small enough not to interfere with the relationship

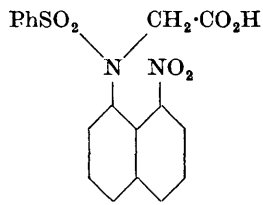
$$K \text{ (the equilibrium constant)} = \frac{k_\alpha}{k_\beta} = \frac{S_\infty - S_\alpha}{S_\alpha}$$

which was also propounded by Hudson and Dale, where S_α is the initial solubility of the α-form and S_∞ the solubility at equilibrium. This relationship was used to calculate the rotations of missing β-compounds.

d-Mannose was sufficiently insoluble in water for Hudson and Yanovsky [25] to use the solubility–rotation relationship to calculate the rotation of the then unknown α-mannose; they obtained the value + 30°, knowing that for β-*d*-mannose to be − 17° and that for the equilibrated solution to be + 14·6°. P. A. Levene, six years later,[32] confirmed their prediction on isolating α-mannose: he records that mannose crystallises in the α-form under conditions in which glucose appears in the β-form and *vice versa*, a fact which we should link with the equilibrated *d*-mannose solution containing excess of the α-form while glucose contains excess of the β-form.

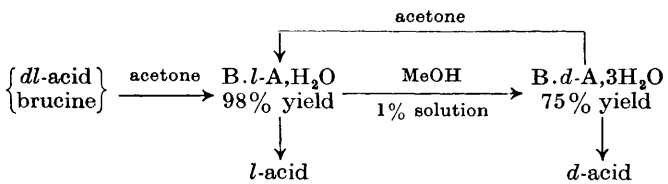
Hudson and Yanovsky also predicted the rotation of α-mannose in 80% ethyl alcohol to be + 35°, which Levene confirmed later. Taken together with a value $[\alpha]_D^{20°}$ − 14·9° for the β-form and + 25·7° for the equilibrium, this means an excess of α-form at equilibrium in a solution under which the β-form is stable.

Similar relationships hold for the α- and β-forms of lactose and galactose, the hydrated α-forms crystallising from aqueous solutions in which the β-forms are present in excess.[33, 25]



(XII.)

N-Benzenesulphonyl-8-nitro-1-naphthylglycine (XII), which owes its optical activity to restriction of rotation of the substituted amino-group by the nitro-group, was shown by Mills and Elliott [3] to undergo second-order asymmetric transformation with brucine in either direction according to the solvent used. It was the first acid found to show the two transformations in this way: decomposition of each of the diastereoisomeric salts gave an active acid:



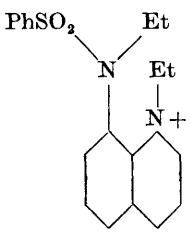
The *effect*, although not the process, was as if a resolution had been performed.

[32] *J. Biol. Chem.*, 1932, 329. [33] C. Tanret, *Bull. Soc. chim.*, 1871, **15**, 195.

From the point of view of the subject of this article, the most important work which these authors carried out on this acid was to *prove* their interpretation of the mutarotation of the brucine *dl*-acid salt as an optical activation (or first-order asymmetric transformation). This they did as follows: 0·183 g. of the *dl*-acid was dissolved in 25 c.c. of chloroform, and 0·221 g. (1·18 mols.) of brucine in a further 25 c.c. of chloroform, and the two solutions were mixed. The initial α_{5461} observed immediately changed from $-0·78°$ to $-0·22°$ ($l = 4$; $T = 0·7$—$1·5°$) as the *l*-base.*d*-acid $\rightleftharpoons$ *l*-base.*l*-acid equilibrium established itself with the former in excess. A similar solution, but containing 0·211 g. of brucine only, after being left for 3 hours, was extracted with ice-cold dilute sulphuric acid, the brucine being thus removed. The remaining solution (to which a little acetone had to be added to keep the acid in solution) had an unmistakable dextrorotation which mutarotated almost to zero at 1·2°. This dextrorotation could only be due to the acid which had been activated in solution by the brucine.

At a later date, other workers [34] were attracted to this acid and prepared the cinchonidine *l*-salt which mutarotated in chloroform from $[\alpha]^{15°}_{5461}$ $-255·5°$ to $-87·3°$, and the cinchonidine *dl*-salt which mutarotated from $-35·5°$ to $-87·3°$; this means a composition at equilibrium of 62% *l*-base.*l*-acid and 38% *l*-base.*d*-acid, neglecting dissociation or the possibility of a change of specific rotation over the concentrations involved in the calculation.

The 8-benzenesulphonethylamido-1-ethylquinolinium ion (XIII) is structurally very like the substituted glycine which has just been considered, and its range of optical stability is such that it can be made to perform the crystallisations associated with second-order asymmetric transformations. W. H. Mills and J. G. Breckenridge [35] found that 8-benzenesulphonethylamido-1-ethylquinolinium *d*-α-bromocamphor-π-sulphonate crystallised as the *d*-base.*d*-acid,$2H_2O$ salt, from a mixture of ethyl acetate and acetone. This salt could be converted into the *d*-quinolinium iodide by shaking the chloroform solution with aqueous potassium iodide, and it mutarotated in the lævo-direction in water, chloroform, and ethyl alcohol.

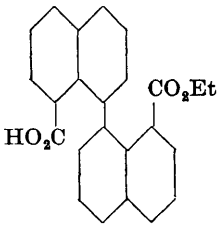


(XIII.)

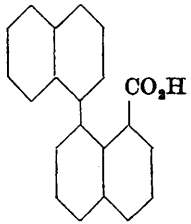
No first-order asymmetric transformation was detectable with the bromocamphorsulphonate, and from the rotations of the two diastereoisomerides and that of their equilibrated solution it would appear that the equilibrium solution has the composition of the partial racemate. We should now explain this difference in behaviour from the alkaloidal salts of *N*-benzenesulphonyl-8-nitro-1-naphthylglycine as being due to the fact that in the latter case the diastereoisomerides are "real" in non-dissociating solvents, while the quinolinium salts must be dissociated into ions even in chloroform solution. Such diastereoisomerides are "real" in this sense only on crystallisation.

[34] M. M. Jamison and E. E. Turner, *J.*, 1940, 264. [35] *J.*, 1932, 2209.

Some members of the dinaphthyl series bear a certain skeletal resemblance to these compounds. Meisenheimer and Beisswenger [15a] found that when ethyl hydrogen 1 : 1′-dinaphthyl-8 : 8′-dicarboxylate (XIV) was crystallised with brucine from ethyl acetate containing a little methyl alcohol, the brucine *l*-acid,$3H_2O$ salt appeared in almost 100% yield: the



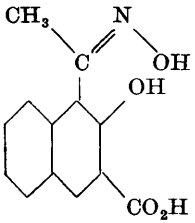
(XIV.)



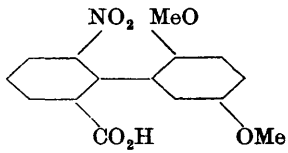
(XV.)

l-acid could be obtained by decomposing the salt with dilute mineral acid. A similar acid (XV), lacking only the carbethoxyl group, formed a monohydrate with brucine, crystallising from ethyl acetate solution as base.*d*-acid or base.*l*-acid on inoculation with the appropriate crystal. Meisenheimer, Theilacker, and Beisswenger [15b] again describe activation by alkaloids of the *β*-oxime of 2-hydroxy-3-carboxy-1-naphthyl methyl ketone (XVI).

The diphenyl nucleus has formed an obvious framework for investigating the effective sizes of groups by observing their influences on the optical stability of potentially active structures. There are therefore several



(XVI.)



(XVII.)

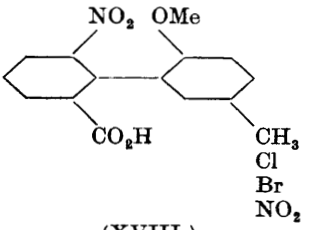
examples of what must be asymmetric transformations to be found in reading accounts of such work. Brucine *dl*-2-nitro-2′ : 5′-dimethoxydiphenyl-6-carboxylate (XVII) dissolved in water crystallised in three fractions, 90% of the total weight, all with the same specific rotation; on decomposition with ice-cold hydrochloric acid they all yielded the *l*-acid.[36] The base.*l*-acid salt prepared by this second-order transformation mutarotated in chloroform from $[\alpha]_D$ $-167°$ to $+3{\cdot}2°$ in 100 minutes: extrapolation of the recorded readings to zero time (time of wetting salt with chloroform) gave $-180°$ as the proper initial value of $[\alpha]_D$. A solution of brucine and the *dl*-acid in chloroform had an initial $[\alpha]_D$ $-8{\cdot}6°$, changing to $+3{\cdot}3°$ in 80 minutes. This latter mutarotation has all the appearance

[36] H. C. Yuan and R. Adams, *J. Amer. Chem. Soc.*, 1932, **54**, 2966.

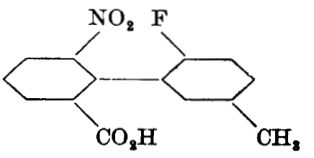
of a first-order transformation, but Yuan and Adams after performing a precipitation experiment on the equilibrated solution conclude that it is not. Examination of their figures [14] shows that if the mutarotation is due to first-order transformation the equilibrium composition by the simple calculation is 53·5% *l*-base.*d*-acid and 46·5% *l*-base.*l*-acid; precipitation of such a solution in chloroform with light petroleum, which would not be quantitative, might well give a product which was indistinguishable from the partially racemic mixture.

The same acid underwent second-order transformation with cinchonidine also.

The whole series (XVIII) of 2-nitro-2′-methoxydiphenyl-6-carboxylic acids with methyl, chlorine, bromine, and nitro-groups in the 5 position have been shown by the same authors[37] to undergo what are clearly second-order



(XVIII.)



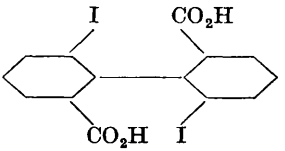
(XIX.)

asymmetric transformation with brucine from alcohol containing varying quantities of water. The authors, who were interested in obtaining specimens of optically active acids for another purpose, describe these crystallisations as *resolutions*: it seems a pity to use this term, which is best reserved for the separation of a racemic mixture into its stereoisomeric forms, to imply conversion of it all into one of them. Brucine or quinine brings 2′-fluoro-2-nitro-5′-methyldiphenyl-6-carboxylic acid (XIX) out of ethyl-alcoholic solution as the base.*d*-acid salt.[38] If the fluorine atom is replaced by chlorine or bromine the optical stability is so raised that the crystallisation process with brucine from the same solvent *is* resolution, the rotations of the crops increasing from negative to positive in the order in which they are deposited.

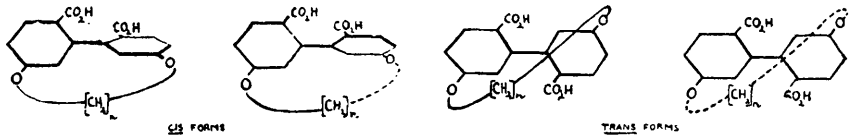
The following evidence may be interpreted as showing that a first-order transformation takes place with the fluoro-acid in chloroform by the agency of brucine. The first crop in the crystallisation of 2·75 g. of the acid and 3·94 g. of brucine weighed 5·1 g. and was identified as the salt *l*-B.*d*-A,$\frac{1}{4}H_2O$. The rotation in chloroform ($[\alpha]_D^{20°}$) was − 3·2°, but, if the solution was made up at 0°, $[\alpha]_D^{20°}$ was + 13° when first observed, and mutarotated to − 3·4°. This may, of course, be due to a large temperature coefficient of rotation, but if it is not, then it would seem that + 13° is nearer to the rotation of the base.*d*-acid salt, while − 3·4° represents an equilibrium composition which is unlikely to be that of the racemic mixture.

[37] H. C. Yuan and R. Adams, *J. Amer. Chem. Soc.*, 1932, **54**, 4434.
[38] R. W. Stoughton and R. Adams, *ibid.*, p. 4426.

The *l*-acid could be obtained [39] from each of three fractions crystallised from 95% ethyl alcohol of dibrucine 2 : 2′-di-iododiphenyl-6 : 6′-dicarboxylic acid (XX) which weighed together 83% of the possible total of salt. When a similar crystallisation was carried out using methyl alcohol as solvent, both diastereoisomeric forms crystallised out, but not as an intimate mixture. They formed discrete crystals which could be separated by hand-picking. R. Adams and N. Kornblum [40] found two cases of what now appears to be second-order asymmetric transformation in diphenyl compounds (XXI) having the 5 : 5′-positions joined by ether linkages to a hydrocarbon chain. When *n* is 10, brucine in methyl alcohol gives a 77% yield of a dibrucine salt in one fraction and a further quantity from the

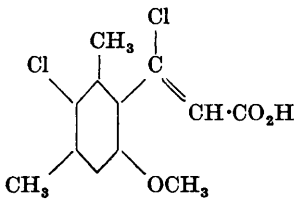


(XX.)



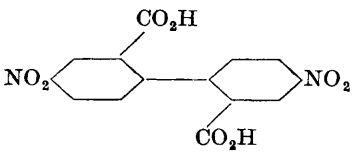
(XXI.)

mother liquor, all of which yielded dextrorotatory acid on decomposition and removal of the brucine. When *n* is 8, cinchonine in ethyl alcohol produces the *l*-acid salt in 3 fractions totalling 91% of the theoretical quantity, as proved by preparation of the *l*-acid from it. The substituted benzene derivative of R. Adams and J. Gross [41] deposited a quinine salt from ethyl acetate in a series of fractions all of which had the same specific rotation and were decomposed to yield *d*-β-chloro-β-(5-chloro-2-methoxy-4 : 6-dimethylphenyl)acrylic acid (XXII).



(XXII.)

R. Kuhn and O. Albrecht [42] claimed an asymmetric transformation of 4 : 4′-dinitrodiphenic acid (XXIII) by quinine on crystallisation from 96% ethyl alcohol, although removal of the base from the deposited salt gave an acid in which they were unable to detect optical activity. The evidence which they used to support their conclusion was as follows. The deposited crystals, all the same substance, represent 80% of the theoretical yield—1st crop, m.p. 207—208°, $[\alpha]_D^{20°}$ + 108·4° in chloroform ; 2nd crop,

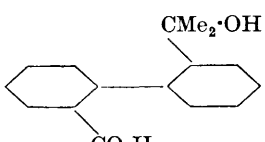


(XXIII.)

[39] N. E. Searle and R. Adams, *ibid.*, 1933, **55**, 1649. [40] *Ibid.*, 1941, **63**, 188.
[41] *Ibid.*, 1942, **64**, 1786. [42] *Annalen*, 1927, **435**, 272.

m.p. 207—208°, $[\alpha]_D^{22°}$ + 110·3° in chloroform. Secondly, the acid is one of a series with two, one, and no nitroxyl in the 6 : 6′-positions in the diphenic acid : 6 : 6′-dinitrodiphenic acid is resolvable with brucine and is optically stable ; 4 : 6-dinitrodiphenic acid is resolvable with quinine and shows racemisation at an observable rate ; 4 : 4′-dinitrodiphenic acid shows (supposed) asymmetric transformation with quinine, and the acid is too unstable to be active. Thirdly, quinine *m*-nitrobenzoate and quinine phthalate have the specific rotations — 163·5° and — 168·2° in the same circumstances, rotations very different from the salt under investigation and of the opposite sign. This last piece of evidence, largely owing to the work of M. S. Kharasch, J. K. Senior, D. W. Stanger, and J. A. Chenicek [43] on the anomalous rotation of quinine salts, has been shown not to afford the support it appeared to at first.

A. Corbellini and A. Angeletti reported in 1932 [44] that 2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid (XXIV) crystallised as the brucine salt from ethyl alcohol in the *lævo*-form in 83% yield. Jamison and Turner,[7] who were looking for a representative optically unstable diphenyl compound which could be prepared relatively easily, raised this figure to 97·6% and found also that a second-order transformation could be effected by evaporating a chloroform solution of the brucine *dl*-acid salt to dryness with stirring on a boiling water-bath. This salt yielded the lævorotatory acid on removal of the brucine by means of dilute acid. Thus second-order transformation takes place in the *lævo*-direction from chloroform at the boiling point, and first-order transformation in the same solvent at 25·15° takes place in the opposite direction. The brucine salt of the *dl*-acid (*i.e.*, a mixture of brucine and the *dl*-acid in equimolecular proportions) in chloroform mutarotates from $[\alpha]_{5461}^{25·15°}$ — 5·08° to + 1·90°. The brucine *l*-acid salt (obtained by second-order asymmetric transformation from ethyl alcohol solution) mutarotates from — 47·04° to + 1·46°. The velocity constants for these mutarotations, $k_{\log_{10} \text{hours}^{-1}}^{25·15°}$, were, respectively, 0·0280 and 0·0277, the agreement being taken to show that the same process is being observed in each case. Assuming no dissociation, the equilibrium composition calculated from these figures is 58% of the *d*-acid salt and 42% of the *l*-acid salt. Unless the equilibrium composition varies sensibly between room temperature and the boiling point of chloroform it appears that the base.*d*-acid is more stable in solution while the base.*l*-acid has the greater tendency to come out of solution.



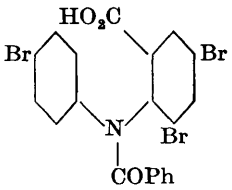
(XXIV.)

N-Benzoyl-4 : 6 : 4′-tribromodiphenylamine-2-carboxylic acid (XXV), a member of a useful series showing optical activity due to restricted rotation, was the first of its kind to be submitted to a thorough stereochemical

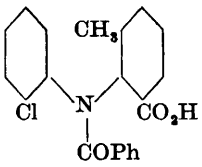
[43] *J. Amer. Chem. Soc.*, 1934, **56**, 1646. See also M. S. Lesslie and E. E. Turner, *J.*, 1934, 347 ; M. S. Lesslie, E. E. Turner, and E. R. Winton, *J.*, 1941, 257.

[44] *Atti R. Accad. Lincei*, 1932, **15**, 968.

investigation. With cinchonidine (1 mol.) in acetone solution it can be made to show first- and second-order transformation and resolution, by appropriate choice of conditions. In the second-order transformation, which can be accelerated by heating, the crystals deposited are 94% of the theoretical quantity and consist of the optically pure cinchonidine *d*-salt. The *d*-acid can be obtained from this by treatment with pyridine followed by dilute hydrochloric acid.[9] The velocity constant of mutarotation of this salt was measured at several temperatures, the value of the Arrhenius constants B and E calculated, which showed that k ($k = Be^{-E/RT}$) might be small enough for resolution to be possible at − 15°. This was put to the test by dissolving *dl*-acid and cinchonidine in warm acetone and chilling to − 15° as soon as crystallisation began. The deposition of crystals, instead of continuing until all was out of solution as in the second-order transformation, stopped when almost exactly 50% of the total weight had come down. The salt deposited was *l*-base.*d*-acid, while the mother liquor on cold evaporation under reduced pressure showed a rotation indicating that it contained two thirds of the *l*-base *l*-acid salt.



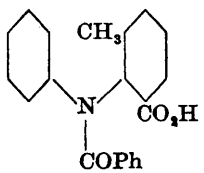
(XXV.)



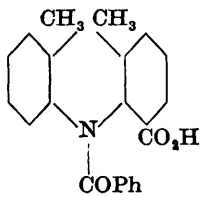
(XXVI.)

dl-*N*-Benzoyl-2′-chloro-2-methyldiphenylamine-6-carboxylic acid (XXVI) is converted by crystallisation as the brucine salt from a mixture of ethyl alcohol and ether into the *l*-form. The *l*-acid was obtained free from brucine on decomposition of the salt by dissolving it in formic acid and stirring with ice-cold dilute hydrochloric acid.

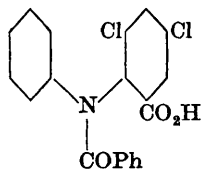
With varying substituents, the *N*-benzoyldiphenylamine-6-carboxylic acids provided material for many more first-order asymmetric transformations.[9] *N*-Benzoyl-2-methyldiphenylamine-6-carboxylic acid (XXVII) in chloroform containing 2·5% of ethyl alcohol by volume underwent mutarotation when 1 mol. of *d*-nor-ψ-ephedrine was present. The related acid



(XXVII.)



(XXVIII.)



(XXIX.)

substituted in the 2 : 2′-positions by methyl groups (XXVIII) mutarotated with cinchonidine in the same solvent, and provided proof that the mutarotations were not due to slowness of salt formation in this way—the originally lævorotatory cinchonidine solution became immediately more lævorotatory

on addition of the acid and then mutarotated in the dextro-direction. *N*-Benzoyl-2 : 4-dichlorodiphenylamine-6-carboxylic acid (XXIX) showed mutarotation with *d*-nor-ψ-ephedrine in chloroform and with cinchonidine in chloroform containing 2·5% of ethyl alcohol by volume. The assumed optical activation was proved by extracting the equilibrated solution with mineral acid, leaving a dextrorotatory acid in the chloroform solution. *N*-Benzoyl-2′-chloro-2-methyldiphenylamine-6-carboxylic acid (XXVI) showed mutarotation with quinidine and brucine in the same chloroform–alcohol solvent.

First-order transformation was observed with cinchonidine in chloroform solution, in the lævo-direction. It was possible to observe the approach to equilibrium from all three starting points, base.*d*-acid, base.*l*-acid (the optically impure mixture from the mother liquor in the — 15° experiment), and base.*dl*-acid :

Starting material.	$[\alpha]^{18\cdot0°}_{5461}$ (initial).	$[\alpha]^{18\cdot0°}_{5461}$ (final).	$k^{17\cdot7°}_{\log_{10}\text{min.}^{-1}}$.
Base.*l*-acid . . .	— 105°	— 44·5°	0·0200
Base.*d*-acid . . .	+ 194 (extrap.)	— 44·5	0·0206
Base.*dl*-acid . . .	— 40·4	— 44·5	(range too small for measurement)

The measured velocity constant k is the sum of the two velocities of inversion, k_d and k_l, of the diastereoisomerides : neglecting the possibility of dissociation in solution,

$$\frac{k_d}{k_l} = \frac{\text{concentration } l\text{-B}.l\text{-A at equilibrium}}{\text{concentration } l\text{-B}.d\text{-A at equilibrium}}$$

whence $k_d = 0{\cdot}0105$ and $k_l = 0{\cdot}0101$; the difference is very small but there is no doubt that it is real.

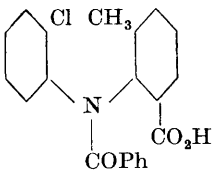
First-order asymmetric transformation of this acid was also observed in the dextro-direction with *d*-nor-ψ-ephedrine in chloroform.

Investigation of the First-order Transformation Equilibria

When it was first observed that the rotation of an equilibrated solution containing equivalent quantities of acid and base, the acid being optically unstable and the base optically stable, was changed by adding an excess of the *dl*-acid, the authors' immediate thought was to attribute the effect to suppression of dissociation of the salt. But this explanation was quickly disproved,[9, 34] and so far no satisfactory one has been put in its place. The added acid may enhance or diminish the existing rotation in different cases, and the effect has been used to explore realms of optical instability which were hitherto unattainable.

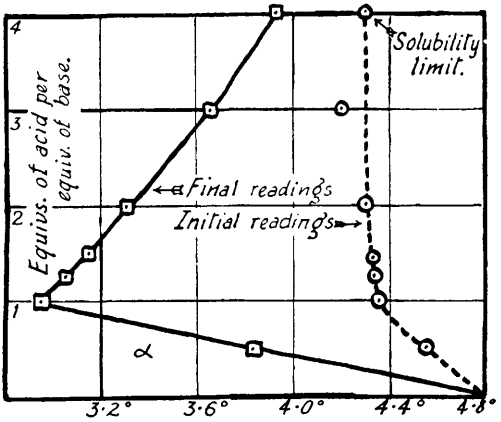
N-Benzoyl-2′-chloro-2-methyldiphenylamine-6-carboxylic acid (XXX) and quinidine in chloroform containing 2·5% of ethyl alcohol by volume behave as follows :

0·1620g. of quinidine in 20 c.c. of solvent showed a rotation $\alpha_{5461}^{20°}$ of + 4·8°, $l = 2$. On the addition of 1 equivalent of the *dl*-acid this rotation changed immediately to + 4·35° and then mutarotated to + 2·99° ; 2 equivalents of



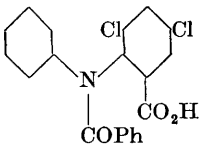
and quinidine in $CHCl_3$–EtOH

(XXX.)



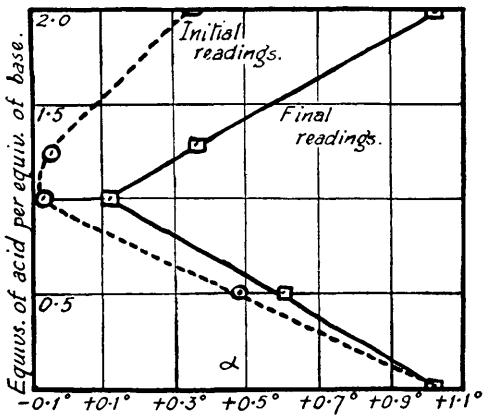
acid caused an immediate change to + 4·30°, mutarotating to + 3·32° ; with 3 equivalents, + 4·32° changed to + 3·67°. All these solutions on decomposition with mineral acid afforded the lævorotatory acid : equilibrium was attained more quickly the greater the excess of acid.

Another example selected from many showing this type of behaviour is *N*-benzoyl-2 : 4-dichlorodiphenylamine-6-carboxylic acid (XXXI) which with *d*-nor-ψ-ephedrine in chloroform mutarotates towards the value of the rotation of the base instead of away from it. In a case such as this the



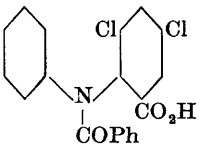
and *d*-nor-ψ-ephedrine in $CHCl_3$

(XXXI.)



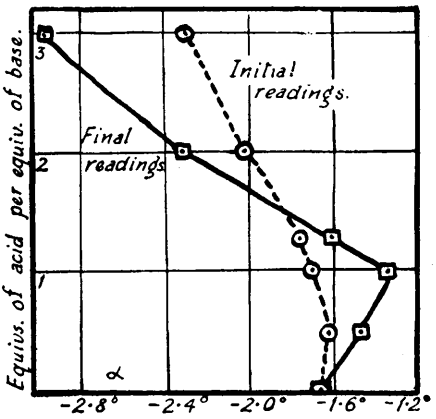
difference between the curves of initial and final readings is considered to be due to optical activation : the departure of the initial curve from the vertical shows that there are other reasons (such as increased concentration) for a static change in rotation present also. (The initial curves described are obtained by extrapolating the observed mutarotations back to zero time.)

The whole subject would have been much less intriguing had not some of the initial and final curves crossed over : that is to say, at certain acid : base ratios first-order transformation was in the *lævo*-direction, and at other ratios in the *dextro*-direction. This was a new phenomenon, and as it is well substantiated although not explained, worthy of further quotation. *N*-Benzoyl-2 : 4-dichlorodiphenylamine-6-carboxylic acid (XXXII) with

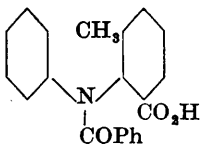


and cinchonidine in chloroform–ethyl alcohol

(XXXII.)

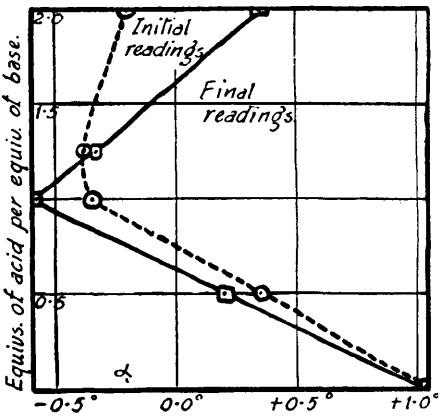


cinchonidine in chloroform–ethyl alcohol mutarotated in the *dextro*-direction at the 1 : 1 ratio and in the *lævo*-direction at the 3 : 1 ratio ; the equilibrated solutions on decomposition yielded *d*- and *l*-acid (not optically pure) respectively. The experiments do not, of course, indicate whether the activated acid is free, or combined as salt. Very similar results were obtained with (XXXIII) and (XXXIV).

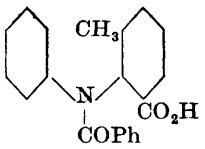


and *d*-nor-ψ-ephedrine in chloroform

(XXXIII.)

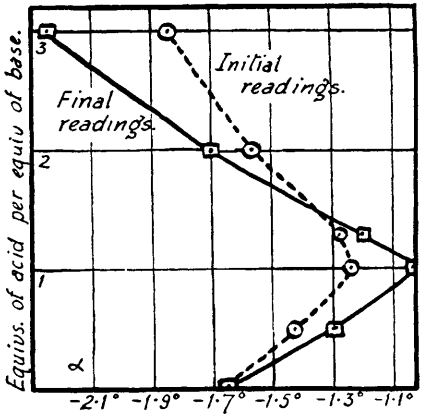


A further point of interest is added in another case in which decomposition of the 1 : 1 and 2 : 1 solutions gave lævorotatory acid, the 3 : 1 solution inactive acid, and the 4 : 1 dextrorotatory acid—the curves for *N*-benzenesulphonyl-8-nitro-1-naphthylglycine (XXXV) and cinchonidine in chloro-

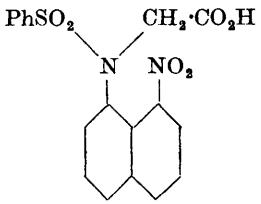


and cinchonidine in chloroform–ethyl alcohol

(XXXIV.)

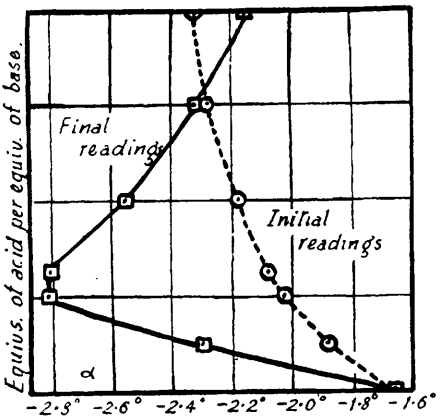


form–ethyl alcohol show how this comes about. This means then, that, without the separation of a salt, both *d*- and *l*-acid could be obtained—not optically pure, but distinctly active, through optical activation in the same solvent and by the same alkaloid.

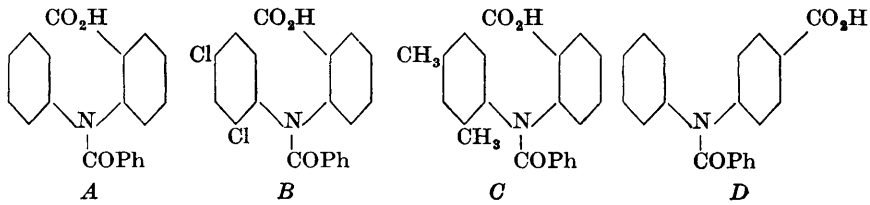


and cinchonidine in chloroform–ethyl alcohol

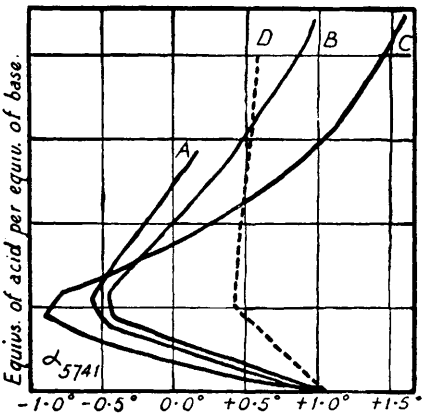
(XXXV.)



The plotting of a series of these "addition curves" served to demonstrate the potential optical activity of a series of acids which were too unstable for the observation of it at ordinary temperatures. The blocking which causes dissymmetry in these acids is very slight, so that they will tolerate neither resolution nor observable first-order transformation under normal conditions.



The curves obtained by addition to *d*-nor-ψ-ephedrine in chloroform—they are "final" curves, the "initial" ones presumably being too ephemeral for observation—are shown in the diagram. The salts of acids *A*, *B*, and *C* have equilibrium rotations which are highly sensitive to excess of the acid: the curve for acid *D*, which has an effectively symmetrical molecule, shows it to be in a different class. Experiments at − 31° justified this distinction: 4 equivalents of acid *C* and one of *d*-nor-ψ-ephedrine in chloroform solution showed a mutarotation α_{5461} changing from − 4·03° to + 2·15°, half-life period 2·4 minutes. Acid *B* mutarotated more quickly in the same circumstances: acid *A* showed no such mutarotation, and its claim to optical activity, until a lower-temperature technique is developed, rests on the curve in the above diagram in conjunction with those of the other acids in the series.



(0·1051 g. *d*-nor-ψ-ephedrine in 14·5 c.c. $CHCl_3$; $l = 2$.)

In a review of these excess acid phenomena W. H. Mills [45] said that they might "affect the diagnostic value of the activation process". But as has already been pointed out [14] there is no indication that proper use of the method would lead to fortuitous results, while it has materially extended the field of investigation of labile optically active compounds.

Asymmetric Induction

The term "asymmetric induction" was introduced by E. Erlenmeyer, Jun., in 1912 in explanation of his alleged successes in "inducing" optical activity in various unsaturated compounds the molecules of which were not dissymmetric on classical theory. He claimed to have induced optical activity in such substances as benzaldehyde and cinnamic acid by heating them with tartaric acid either in presence or in absence of a solvent. E. Wedekind,[46] and L. Ebert and G. Kortüm [47] were unable to confirm Erlenmeyer's results, the references to which are given in the Obituary Notice [48] to Erlenmeyer.

Although Erlenmeyer had attempted the induction of activity in molecules which to us clearly could not be dissymmetric, other workers were concerned with a different matter, the more legitimate inquiry as to the possibility of inducing optical *resolution* of racemates not by the standard methods but by differential solvent action say of a dextrorotatory solvent on the two enantiomeric forms of a second substance. This was examined

[45] Presidential Address, *J.*, 1943, 194.
[46] *Ber.*, 1914, **47**, 3172.
[47] *Ibid.*, 1931, **64**, 342.
[48] *Ibid.*, 1921, **54**, 107.

in two ways : (1) by determining the solubility of the two enantiomeric forms separately in an active solvent, and (2) by crystallising or extracting the racemate by means of an active solvent. In spite of much careful work, no differentiation of the kind sought was found.[23, 49] An interesting set of results was obtained by A. McKenzie and his co-workers,[50] although, owing to the rather complex mixtures used, their significance cannot yet be properly assessed. *l*-Malic acid (1 mol.) was added to an aqueous solution of potassium racemate (1 mol.), and a crop of crystals obtained consisting of potassium hydrogen racemate and potassium hydrogen *d*-tartrate, similar results being obtained with sodium, rubidium, and cæsium salts. No other active acid than malic produced the same kind of result, and no acid that was examined, other than racemic acid, could be " activated ". The reality of these observations cannot be doubted, and a thorough phase-rule study of one of the systems would no doubt repay the effort.

Generally speaking, racemates cannot be even partially resolved by crystallisation from an optically active solvent. This is what might be expected, unless one antipode crystallised with solvent of crystallisation. An example remains to be discovered in which association with an optically active solvent, by hydrogen bonding for example, is responsible for solubility differences in a pair of optical isomerides, although it may well be that McKenzie's case can be interpreted in this way. Some such loose association, with preference for one isomeride, must be responsible for cases of partial resolution by adsorption on optically active adsorbents.

Another type of experiment to which the name asymmetric induction was attached was the attempted conversion of a symmetrical into a dissymmetrical molecule in solution in an optically active solvent. As long ago as 1896, D. R. Boyd [51] reduced benzoylformic acid in an aqueous solution of tartaric acid, and four years later F. S. Kipping [52] performed the benzoin synthesis in presence of *d*-camphor. In these and many subsequent investigations, no activity was induced by the non-reacting asymmetric material which had been added.

In 1932, G. Kortüm gave his interpretation of the meaning of the term " asymmetric induction " as follows : the action of a force exerted by asymmetric molecules on molecules capable of changing from a symmetrical into an asymmetrical configuration. He further noted the division of the effect into inter- and intra-molecular types. The examples we have just dealt with are intermolecular, and we now turn to the intramolecular ones.

In 1936, A. McKenzie,[53] commenting on Walden's dismissal of the Erlenmeyer conception of asymmetric induction, said : " Nevertheless, whether the idea of asymmetric induction is right or wrong, it has since proved itself of service in the study of asymmetric synthesis, and to-day it ought not to be at once dismissed as both useless and superfluous." The

[49] Kortüm, " Samml. chem. und chem.-tech. Vortrage ", Stuttgart, 1932.

[50] A. McKenzie, *J.*, 1915, **107**, 440 ; A. McKenzie and N. Walker, *J.*, 1922, **121**, 349 ; A. McKenzie, H. J. Plenderleith, and N. Walker, *J.*, 1923, **123**, 2875.

[51] Inaug. Dissert., Heidelberg. [52] *Proc.*, 1900, **16**, 226.

[53] *Ergebn. Enzymforsch.*, 1936, **5**, 49.

view " that in optically active esters of α-ketonic acids the carbonyl group in the α-position might assume a dissymetrical configuration under the influence of an optically active radical " enabled him to correlate the steric course of a long series of reactions between *l*-menthyl benzoylformate or *l*-menthyl pyruvate on the one hand and Grignard reagents on the other, with the direction of mutarotation observed when the two esters mentioned were dissolved in ethyl alcohol. McKenzie suggested that these mutarotations might be due to the establishment of an equilibrium of the type :

$$\underset{(-)}{\mathrm{R{\cdot}CO{\cdot}CO{\cdot}}}\underset{(-)}{\mathrm{OC_{10}H_{19}}} \rightleftharpoons \underset{(+)}{\mathrm{R{\cdot}CO{\cdot}CO{\cdot}}}\underset{(-)}{\mathrm{OC_{10}H_{19}}}$$
$$(A) \qquad\qquad (B)$$

whilst in ethereal solution (in which the Grignard additions were carried out) equilibrium was established too quickly for observation, but that nevertheless the two above forms were present in unequal amounts, this accounting for the success of the asymmetric synthesis and also for the sign of rotation of the resulting α-hydroxy-acids, all the benzoylformate reactions giving lævorotatory acids and all the pyruvate reactions dextrorotatory ones. It seems clear that it would also have been necessary to assume that the rate of addition of the Grignard reagent to the carbonyl group was greater than the rate of equilibration. Nevertheless, the detailed experimental evidence deserves close scrutiny. M. M. Jamison and E. E. Turner,[54] although their evidence did not justify a precise interpretation, preferred to regard the mutarotations in the alcoholic solutions of the esters as due to first-order transformation between the diastereoisomeric hemiacetals formed by the very probable reversible combination of the esters with the solvent :

$$\underset{(l)}{\mathrm{R{-}CO{-}CO{\cdot}OC_{10}H_{19}}} \overset{\mathrm{EtOH}}{\rightleftharpoons} \underset{(d)}{\mathrm{R{-}\overset{\mathrm{OH}}{\overset{|}{C}}(\mathrm{OEt}){-}CO{\cdot}OC_{10}H_{19}}} + \underset{(l)}{\mathrm{R{-}\overset{\mathrm{OEt}}{\overset{|}{C}}(\mathrm{OH}){-}CO{\cdot}OC_{10}H_{19}}}$$

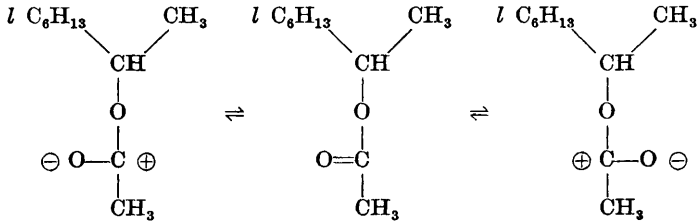
At the same time, the absence of mutarotation in ether was ascribed to the lack of any real distinction between (*A*) and (*B*), the partial stereo-specificity of the many Grignard reagent syntheses then being attributed to first-order asymmetric transformation of optically unstable intermediates. The idea of asymmetric induction, in the sense of a double bond made dissymmetric previous to approach of the reagent, as the cause of an " asymmetric reaction " was not accepted.

Without apparently realising the mass of experimental material which McKenzie and his co-workers, as well as others, had accumulated in their studies of asymmetric synthesis and related matters, T. M. Lowry and E. E. Walker [55] suggested " that an unsaturated group in an asymmetric molecule, *e.g.*, the carbonyl group in camphor, may acquire an induced asymmetry and thus itself become optically active ". This conclusion, which was reconsidered by T. M. Lowry and J. O. Cutter,[56] was based on " the fact that

[54] *J.*, 1941, 538. [55] *Nature*, 1924, **113**, 565. [56] *J.*, 1925, **127**, 604.

the dispersion-equations for camphor and its derivatives are haunted by a low-frequency term *the period of which is definitely characteristic of the ketonic group* ". Lowry and Cutter further said : " We therefore assign this partial rotation to the ketonic group, which is proved to be asymmetric by the unequal yields of two stereoisomeric (diastereoisomeric ?) products which are obtained when the double is converted into two single bonds. This absence of symmetry in a double bond has already been proved in the camphor series by the unsymmetrical reduction of camphor to borneol and *iso*borneol and of its oxime to bornylamine and neobornylamine. . . . Since the two links of a double bond in an asymmetric compound are clearly unequal from the chemical point of view, it would be absurd to pretend that they must be equal from the physical point of view, and no additional justification need therefore be given for using this conception in order to explain the optical properties of camphor or of . . . certain other unsaturated compounds."

H. Phillips [57] saw in the then freshly discovered (but since abandoned) semi-polar sulphoxide bond a means of giving the optical activity of a carbonyl group a physical meaning ; he pictured *l*-β-octyl acetate as the equilibrium :



T. M. Lowry and G. Owen,[58] following S. Sugden, J. B. Reed, and H. Wilkins,[59] pointed out that a semi-polar bond with carbonyl would represent the activation limit of a polarisation and not the normal state of the group. They saw in such an activation the origin of the ultra-violet ketonic band shown by camphor. C. E. Wood and S. D. Nicholas,[60] in a study of anomalous rotatory dispersion, concluded that the carbonyl group " need not be regarded as an asymmetric centre but rather as causing a deflecting and disturbing action on the electronic system round the asymmetric centre ". Lowry's view that the two bonds of a double bond in an asymmetric compound are unequal from the chemical point of view is untenable because it over-simplifies the picture of addition reactions.

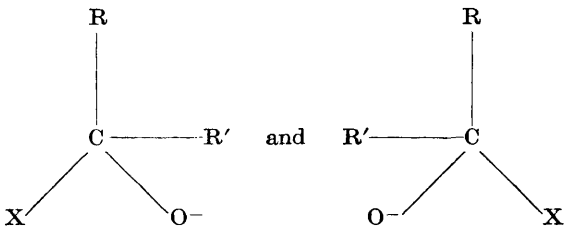
Part of the present problem is discussed by M. P. Balfe and J. Kenyon.[61] The use of the term " induced anisotropy " instead of " induced asymmetry " is an advantage, since it avoids the implication that the optical and the alleged chemical mechanisms are intimately related. As W. C. Price [62] has pointed out, the π-molecular wave functions are responsible for the production of the optical anisotropy ; they are also concerned with chemical

[57] *J.*, 1925, **127**, 2552. [58] *J.*, 1926, 606. [59] *J.*, 1925, **127**, 1525.
[60] *J.*, 1928, 1671. [61] *Ann. Reports*, 1942, **39**, 125. [62] *Ibid.*, 1939, **36**, 52.

addition reactions. In the optical sphere they function as part of the *permanent* state of the molecule ; in the chemical sphere, for all we know to the contrary, they play their normal part in permitting electronic activation of the double bond prior to its two-stage saturation. It seems probable that, at any rate at the moment, only confusion will result from correlating the chemical reactivity (" asymmetric induction ") of a carbonyl group with the rotatory dispersion effects (" induced asymmetry ") associated with it. Until the two effects have been more closely investigated no useful conclusions can be drawn.

In order that a fixed centre of asymmetry shall influence the steric course of an addition reaction at an unsaturated centre in the same molecule in an asymmetric synthesis, there must be some stage at which either stereo-selective addition occurs as an irreversible process or first-order asymmetric transformation takes place. There are at present insufficient experimental data upon which to base an analysis of even the simplest " asymmetric reaction ", but some general lines of argument can be foreseen. Thus, in the addition of XY to a carbonyl group of a molecule already containing a fixed centre of asymmetry (in group R), the first stage may be regarded as the approach of X^- towards the positive end of the polarised carbonyl group:

The two tetrahedral arrangements represented by the plane diagrams:



are possible before the addition of Y^+. If the energy changes concerned in the formation of these two structures are equal, there is no immediate asymmetric addition. If they are unequal (*i.e.*, influenced by existing asymmetry), then we have *asymmetric addition*, which appears to take place even in non-reversible asymmetric reactions of this type (*e.g.*, Grignard reactions). On the other hand, addition which is known to be chemically reversible (*e.g.*, when X^- is CN^-) could be accompanied by first-order asymmetric transformation of the newly forming molecule at this stage, and it would be rash to say, without further experiment, whether the new asymmetry is introduced during or after the first addition or at both stages.

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