STATIC AND DYNAMIC ISOMERISM IN PROTOTROPIC COMPOUNDS[1]

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A. THE DEFINITION OF TAUTOMERISM

1. A new definition of tautomerism

The discussion on tautomerism, at the Oxford Meeting of the British Association in August, 1926, seems likely to become of historic importance on account of the novel definition of this much-disputed term on which the discussion was based. Moreover, in view of the comments made upon it, there seems to be a very reasonable prospect that the admirable definition which was then put forward may be adopted generally, and may thus displace once for all the diverse interpretations of the term which are now in use. The definition in question describes the phenomenon of tautomerism as follows:

> This term is applied to the property exhibited by certain compounds of behaving in different reactions as if they possessed two or more different constitutions; that is, as if the atoms of the same compound or group were arranged in two or more different ways, expressible by different structural formulae.

The author of this definition has not been disclosed; but since it was cited from the Oxford Dictionary, and was circulated widely in the Preliminary Program of the Oxford meeting, it may very well be referred to as the "Oxford" definition. Its principal characteristics are (i) that it abolishes finally the distinction, upon

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[1] For earlier reviews of the subject see reports on "Dynamic Isomerism" (British Association Reports, Cambridge, 1904, pp. 193–224), on "Isomeric Change" (Science Progress, April and October 1909), and on "The Mechanism of Chemical Change" (Report of the Second Solvay Conference, 1925, pp. 135–178).

which Laar insisted so strongly, between "tautomerism" and "pseudomerism", (ii) that it defines tautomerism as a purely chemical phenomenon, and thus distinguishes it sharply from the physico-chemical phenomenon of dynamic isomerism, (iii) that it abolishes the former limitation of the term to prototropic compounds and extends it to mobile structures of other types.

2. Tautomerism and pseudomerism

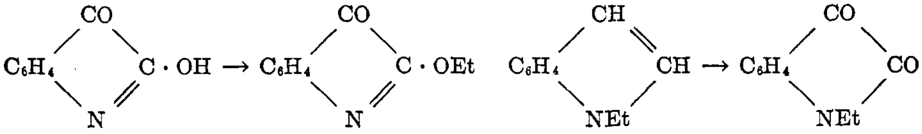
The term *tautomerism* was used for the first time by Laar in 1885, in a paper, "Ueber die Möglichkeit mehrerer Struktürformeln für dieselbe chemische Verbindung" (1). This paper was based on the observation of Zincke (2) that the phenylhydrazone derived from naphthaquinone was identical with the phenylazo-derivative of α-naphthol, with which it should have been isomeric:

$$C_6H_5 \cdot NH \cdot N : C_{10}H_6 : O \qquad C_6H_5 \cdot N : N \cdot C_{10}H_6 \cdot OH$$

Hydrazone Azo-compound

Since it was uncertain which of these formulae should be assigned to the identical product of the two reactions, Laar suggested that *both* formulae were equally correct, and described the supposed existence of a dual structure in the compound as "tautomerism."

The term *pseudomerism* was introduced by Laar in 1886, (3) in order to describe von Baeyer's discovery (4) that a substance, to which a perfectly definite structure could be assigned, might yield (or be prepared from) derivatives having a totally different structure. Thus, Baeyer's observations showed that, although isatin yields an O-ethylisatin by direct ethylation, an isomeric N-ethylisatin can be prepared indirectly from ethylindole by oxidation, although the pseudo-isatin from which it is derived is altogether unknown:

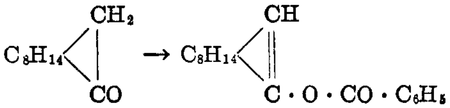


Isatin Ethyl-isatin Ethylindol Ethyl-ψ-isatin

The most familiar example of pseudomerism, however, is probably that of vinyl chloride, which on hydrolysis yields acetaldehyde instead of vinyl alcohol:

$$\underset{\text{Vinyl chloride}}{CH_2 : CHCl} \rightarrow \underset{\text{Vinyl alcohol}}{[CH_2 : CH \cdot OH]} \rightarrow \underset{\text{Aldehyde}}{CH_3 \cdot CHO}$$

A converse case is that of camphor which, when boiled with benzoyl chloride, yields the benzoyl-derivative of an unknown enolic isomeride:

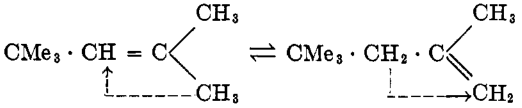


The Oxford definition, in obliterating finally the distinction which Laar made between the phenomena of pseudomerism and of tautomerism, has the advantage of being in agreement with the carefully-considered definition of Kurt Meyer (5) who uses "tautomerism" as a general term to describe the three phenomena of: (i) *desmotropy*, where the parent compound behaves as a mixture of two isomerides, (ii) *pseudomerism*, where the parent compound is of known structure, but gives rise also to a different structure in some of its derivatives, (iii) *cryptomerism*, where the nature of the underlying isomerism is still obscure. Since, after the lapse of 40 years, many of the examples cited by Laar can still only be described as "cryptomeric," there is an obvious advantage in making use of a definition which covers all these cases without attempting to classify them.

3. Tautomerism and dynamic isomerism

The necessity for a new definition of tautomerism arises from the fact that Laar embodied in his original definition a *theory* which is now universally recognized as being incorrect, at least in the cases to which he applied it, namely, that the various formulae which can be assigned to a tautomeric compound represent "not isomeric but identical substances" (6). The new definition has the advantage that there is *no* theory behind it, since it is limited to a mere statement of the *fact* of dual reactivity, and does not attempt any explanation of that fact. Its scope and meaning are therefore quite different from those of the term "dynamic isomerism," since tautomerism is now defined as a purely chemical phenomenon, whereas "dynamic isomerism" is a physico-chemical phenomenon which may or may not be the original cause of the dual reactivity of a tautomeric compound.

The phenomenon of dynamic equilibrium between isomers, which we now describe as dynamic isomerism[2] was discovered by Butlerow in 1877, eight years before the appearance of Laar's first paper (7). Butlerow had found the first example of a reversible isomeric change in the case of the isodibutylenes.



He therefore suggested that a similar condition might prevail in more labile compounds, and, in particular, that the isomeric esters of cyanic and hydrocyanic acid might be derived from real isomers, which had, however, been brought into a condition of dynamic equilibrium with one another, and could not therefore be isolated as separate entities:

$$CH_3O \cdot C \vdots N \leftarrow HO \cdot C \vdots N \rightleftharpoons H \cdot N : C : O \rightarrow CH_3 \cdot N : C : O$$

Methyl cyanate Cyanic acid Methyl isocyanate

$$CH_3 \cdot C \vdots N \leftarrow H \cdot C \vdots N \rightleftharpoons H \cdot N : C : \rightarrow CH_3 \cdot N : C :$$

Methyl cyanide Hydrocyanic acid Methyl isocyanide

Butlerow, unfortunately, was much more concerned with the facts which he had established than with the very important theoretical conclusions which he had derived from them. He therefore published his work under the modest title "Ueber Isodibutylen," and did not even invent a term to cover the condition of *dynamic equilibrium amongst isomers* which he had discovered. Laar, on the other hand, achieved immortality because he invented an

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[2] This term was first used in a paper on "Nitrocamphor as an Example of Dynamic Isomerism" Lowry: *J. Chem. Soc.* **75**, 211 (1899).

attractive name to describe the facts recorded by other workers, and, moreover, took the precaution of setting out the substance of his theoretical considerations in the title of his paper. As a result of this policy, the term which he introduced has come into general use, in spite of the fact that it was linked with an explanation which we know to have been incorrect, at least in the main group of cases to which he applied it.

A condition of dynamic equilibrium amongst isomers, similar to that which Butlerow discovered in 1877 in the alcohols and olefines of the C_8 series, had been postulated five years before by Kekulé (8) as a remedy for the most obvious weakness of his new formula for benzene, namely that it predicted an isomerism, which could not be realized in practice, between the 1:2 and the 1:6 diderivatives. Kekulé's dynamic hypothesis, however, had no other justification than his own reluctance to admit that carbon in aromatic compounds may perhaps be tervalent. It was therefore a mere "brain-wave," and was not supported by any trace of experimental evidence. On the other hand, since no serious chemist expects to be able to isolate isomeric compounds corresponding with all the diverse formulae which have been attributed to benzene during the last fifty years, it is clear that in this case at least we can without any hesitation apply Laar's carefully-worded definition ("Ueber die Hypothese der wechselnden Bindung" (9)), according to which the various formulae that can be assigned to a tautomeric compound represent "*not isomeric but identical substances.*" Whilst therefore it would be obviously unfair to transfer from Buterlow to Kekulé the merit of discovering the phenomenon of reversible isomeric change, we may nevertheless assign to him the credit of having put forward an example of tautomerism which approaches more nearly to Laar's definition than any other case that has been investigated since the problem was first discussed.

4. Tautomerism and prototropy

Another important feature of Laar's paper is the list of *substances* in which he claimed to have detected the dual structure of a tautomeric compound. Almost all of these substances owe their dual reactivity to a mobile hydrogen atom, the position of which is difficult to determine, either because different reactions appear to locate it in different positions in the molecule, or because it migrates very easily from one position to another even when it has been definitely located. It is clear that neither the phenomenon of dual reactivity, nor that of reversible isomeric change, need be limited to compounds containing a mobile hydrogen atom; nevertheless, the influence of Laar's original list of cases has proved so strong that this factor is frequently included in the definition of tautomerism. Thus, in the recent translation of Schmidt's "Text-book of Organic Chemistry," dated 1926, we read:

> A substance is tautomeric when it forms two series of derivatives. These are derived from two parent structures *which differ only in the position of a hydrogen atom and of one or more double bonds.*[3]

In the same way Kurt Meyer (5) (*loc. cit*). suggests that

> Substances are tautomeric, if they form two series of derivatives which are deduced from two isomeric formulae; *these formulae differ from one another in the position of a hydrogen-atom, and of one or more double bonds.*[3]

Since nobody now believes in Laar's theory of tautomerism, as he himself defined and applied it, this choice of an alternative characteristic from his schedule as the basis of a new definition is as lawful as any other; but the limitation which it imposes is out of harmony with the terms of the "Oxford" definition cited above, and, in my opinion, it should be abandoned, if only because it excludes the most characteristic of all cases of tautomerism, namely that of hydrocarbon benzene. On the other hand, the isomeric changes which depend on the mobility of a hydrogen atom are so special and so important that it is very desirable that they should be described by some less ambiguous word, especially since it is now proposed to assign to the term "tautomerism" a meaning in which this particular factor is entirely ignored. The

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[3] The italics are mine, T. M. L.

necessity for such a term, which is admitted in both of the preceding definitions, was recognized 40 years ago by Jacobsen, who introduced the word *desmotropy* for the express purpose of describing *"a rearrangment of bonds consequent upon the displacement of a hydrogen atom."*[4] When used by Jacobsen, therefore, (10) the word has nothing whatever to do with the possibility of isolating the various isomeric hydrides. The latter alternative meaning, which was suggested by Hantzsch and Hermann in 1887 (11) has however, rendered Jacobsen's term ambiguous, and therefore useless for its original purpose. As a result, there was, until recently, no word available to describe specifically the important group of balanced isomeric changes which Jacobsen sought to differentiate. Since Jacobsen's "bond-shifting" has thus been put out of action as a description of the migration of a proton and the rearrangement of bonds which accompanies it, I have fallen back on the other and more characteristic aspect of this dual process, and have described Jacobsen's phenomenon as "proton-shifting" or *prototropy* (12). In view of the interest attaching to this type of isomeric change, and the large amount of attention that has been given to it, the remaining sections of this report are devoted to a consideration of the mechanism of prototropic change, and to the experimental study of the conditions under which it can be arrested and promoted.

B. THE MECHANISM OF PROTOTROPIC CHANGE

5. *Butlerow's two types of prototropy*

The readiness with which isomeric hydrogen-compounds can be converted into one another varies very greatly. Thus, in many

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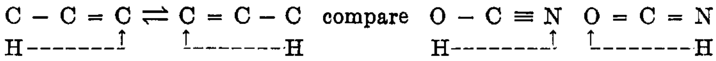
[4] The complete quotation is as follows:- "The word 'tautomerism' is based on Laar's view, which (I believe) is not shared by most chemists, that the molecules of compounds whose chemical behaviour is represented by two structural formulae differing in the point of attachment of a hydrogen atom never assume a definite constitution, but exist in a constant state of oscillatory change. The majority of chemists would explain the observations in question in this way, that the known forms of such compounds are to be represented by a definite grouping of atoms which in certain reactions passes over into an isomeric grouping by a rearrangement of bonds consequent upon the displacement of a hydrogen atom." *Ber.* **20**, 1732 (1887), footnote.

cases no conditions have yet been discovered under which isomeric change can be effected, whilst in others the interconversion proceeds so readily that it has not yet been found possible to isolate any one of the components of the equilibrium-mixture as a separate entity. This contrast was clearly brought out by Butlerow, who drew a sharp distinction between the isodibutylenes, which underwent isomeric change only in presence of strong sulfuric acid, and the cyanic and hydrocyanic acids, which appeared to undergo a similar isomeric change without the deliberate addition of a catalyst. Both types of change can be represented on paper by a precisely similar scheme, depending on a direct migration of a hydrogen atom from α to a β or γ position, with a consequent rearrangement of the intermediate bonds, thus:



$$\mathrm{\underset{H}{C}-C=C \rightleftharpoons C=C-\underset{H}{C}} \quad \text{compare} \quad \mathrm{\underset{H}{O}-C\equiv N \quad O=C=\underset{H}{N}}$$

but, in spite of this superficial analogy, I have felt for many years that there is a very real difference between the two groups of cases. Further consideration has confirmed this instinctive opinion, and has led me to conclude, not only that a definite mechanism is required to bring about isomeric change in all prototropic compounds, but also that there is an important difference in the mechanism by which isomeric change takes place in Butlerow's two types of cases.

6. Mobility and acidity in prototropic compounds

The term "prototropy" is based upon the view that the wandering of a hydrogen atom in a prototropic compound is an ionic reaction, in which the mobile atom migrates as a hydrogen ion or proton, i.e., as a *positively charged nucleus* and not as an electrically-neutral atom. Since the liberation of a proton as a hydrogen ion is specially characteristic of *acids*, it is obvious that prototropic change must be closely related to the property of *acidity*. Thus, according to modern views, an acid always exists in a condition of dynamic equilibrium, in which a proton is continually being exchanged between the acid and the solvent, e.g., $H_2O + HX \rightleftharpoons \overset{+}{H_3O} + \overset{-}{X}$. If, however, the ion X is "multipolar" (13), or is itself capable of undergoing isomeric change, so that the proton can be reattached at different points on the anion, thus giving rise to a series of isomeric hydrides, all the conditions for a reversible prototropic change are fulfilled. It is therefore probably not a mere coincidence that *prussic acid* from which, after the lapse of nearly half a century, isomeric forms have not yet been separated, is an *acid* of a more definite character than most of the compounds in which this separation has been accomplished. It is indeed obvious that a compound from which a proton can be separated by mere contact with water is in an exceptionally favourable condition for undergoing prototropic change, provided always that there are two alternative positions in which the proton can reattach itself to the anion. On the other hand, it follows from this hypothesis that, if in the future the "acidity" of the compound could be suppressed completely, e.g., by drastic drying, the mobility of the hydrogen atom would also be suspended.

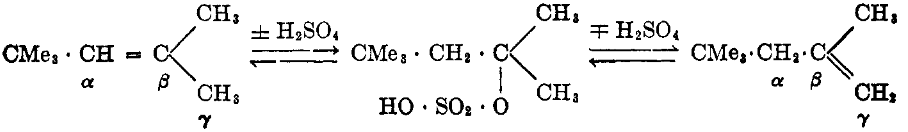
Evidence of this character is cited in a later paragraph, in which it is shown that, just as acidity can only be developed in presence of a *proton-acceptor* such as water, so also prototropic change in a methylated sugar can only take place *when the medium possesses both acidic and basic properties.* Similar evidence of the close relationship between acidity and mobility in prototropic compounds is found in their sensitiveness to alkaline catalysts, since it would be difficult to find an interpretation of this effect apart from the obvious influence of a base in developing the latent acidity of the compounds upon which it acts.

7. *Mechanism of isomeric change in olefines*

The fact that Butlerow's isodibutylenes are entirely inert towards alkalis, but undergo isomeric change in presence of a strong acid, is *a priori* evidence that these hydrocarbons do not contain a mobile hydrogen atom of the normal type. A clear explanation of their behaviour can, however, be given if we suppose that they *acquire* a mobile hydrogen atom when the olefine combines with the ions of sulfuric acid to form an isodibutyl sulfate.[5]

$$C_8H_{16} + H_2SO_4 \rightleftharpoons C_8H_{17} \cdot O \cdot SO_2 \cdot OH$$

According to this view, the hydrogen attached to the α and γ atoms of the 3-carbon system of the isomeric olefines is entirely immobile; but this state of affairs is altered completely when the sulfate radical is attached to the intermediate β-atom. This strongly negative radical then acts in the usual way to promote the separation of a positively-charged radical from the system; it therefore makes it possible to split off a proton from *either* of the adjacent atoms of carbon, and by a reversal of this process to promote the migration of a hydrogen from the α to the γ position, or conversely:



8. *Absolute and conditional tautomerism*

From a consideration of these examples it is clear that, whilst the tautomerism of prussic acid is apparently *absolute* (since we do not know any method of arresting the reversible isomeric change, and cannot therefore hope to find any reagent which will enable us to distinguish between the two components of the mixture) the tautomerism of the isodibutylenes is *conditional* upon the presence of a strong acid. It will be noticed that Laar regarded all cases of tautomerism as absolute, but that subsequent workers have succeeded in finding conditions and reagents which have enabled us to recognize in one case after another that the tautomerism is only conditional. Thus, Knorr (14) in addition

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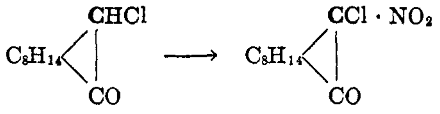
[5] Butlerow had proved that the conversion of amylene into amyl hydrogen sulfate was a balanced action; he had therefore strong experimental support for the view that the isomeric change of the isodibutylenes was effected through the reversible formation of a sulfate, and depended on the fact that *ter*-isodibutyl sulfate gave *two isomeric olefines* when sulfuric acid was eliminated from it.

to separating the two components of aceto-acetic ester, was able to prove that they reacted differently towards ferric chloride, and were therefore not tautomeric towards this reagent; and Kurt Meyer (15) was able to develop a general method whereby the ketonic and enolic forms of a prototropic compound can be estimated by titrating the latter form with bromine. There can, therefore, be little doubt that further experiments will provide evidence that other cases of tautomerism are conditional upon the presence of some suitable catalyst; but, since nearly all prototropic compounds are very sensitive to the action of alkali, the reagents used in this work must be free from alkali, and in general must be neutral substances.

An interesting example of conditional tautomerism is afforded by the α and α′ chlorocamphors and bromocamphors. Since these isomers are brought into equilibrium by alkalis, they must necessarily behave as tautomeric substances towards all alkaline reagents; but they are not necessarily tautomeric in acid solutions, where isomeric change is inhibited. It is therefore interesting to notice that, whilst the two chlorocamphors yield a pair of isomeric chloronitrocamphors on nitration (16)



α and α′ Chlorocamphors

αα′ and α′α Chloronitrocamphors

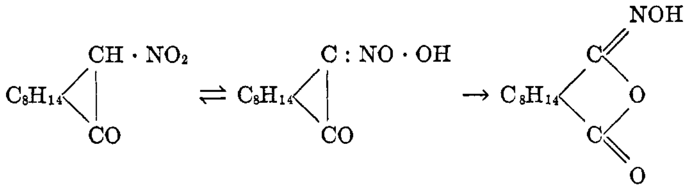
the two bromocamphors yield an identical product. Examples such as these suggest that the relationship between tautomerism and dynamic isomerism is not so close as has generally been supposed, since it is clear that dual reactivity may be developed under conditions which appear to rule out the possibility of reversible isomeric change.

C. PROMOTION AND ARREST OF PROTOTROPIC CHANGE

9. Catalysis of mutarotation by bases, acids and salts

At a date when the nature of the changes which give rise to mutarotation was still unknown, O'Sullivan and Tompson (17) recorded the fact that mutarotation takes place instantly on the addition of alkali to a solution of a reducing sugar. A similar effect was observed in the first experiments in which mutarotation was recorded as a sequel to isomeric change in a prototropic compound, since a solution of nitrocamphor, in alcohol to which sodium had been added in the proportion of 0.25 grams of metal per litre, already showed a steady rotatory power when the first reading was taken after an interval of only three minutes from the time when the solution was prepared (18). No analogous acceleration was observed, however, when a decinormal solution of hydrochloric acid in alcohol was used instead of alcohol as a solvent for nitrocamphor, although acids were known to have a marked influence in accelerating the mutarotation of the sugars. Later experiments (19) have shown that the velocity of mutarotation of an aqueous solution of glucose is a symmetrical function of the hydrogen-ion concentration, falling to a flat minimum at $pH = 5$, and rising steeply when pH is less than 2 or greater than 8. The acceleration therefore begins to be appreciable in acid solutions at concentrations above N/100 and in alkaline solutions at concentrations above N/1,000,000.

Since nitrocamphor is insoluble in water, and the values of pH in non-aqueous solutions are unknown, it is not practicable to plot a similar curve for the influence of hydrogen-ion concentration on the velocity of mutarotation of this compound. Experiments on the mutarotation of solutions of nitrocamphor in benzene (20) showed, however, that *acids* as well as bases can act as catalysts for the underlying prototropic change, although this effect was masked by the catalytic activity of the solvent when the first test was made in aqueous alcohol as described above. Experiments on the catalytic activity of acids are complicated by the fact that, even at ordinary temperatures, a further irreversible isomeric change of the Beckmann type takes place, which does not occur in the presence of alkalis.



Nitrocamphor ψ-Nitrocamphor Camphoryloxime

Again, when chloroform was used as a solvent, it was found that acids may retard and even arrest the mutarotation of nitrocamphor, by accelerating the oxidation of chloroform to carbonyl-chloride, which acts as an anticatalyst for the mutarotation (see below, p. 245). In spite, however, of the limitations to which experiments of this type are subject, it was shown clearly that acids as well as bases have a definite catalytic activity in promoting the mutarotation of nitrocamphor. In particular, it was found that N/10,000 trichloracetic acid produced about the same acceleration as N/100,000 piperidine.

The remarkable catalytic activity of *bases* in the mutarotation of nitrocamphor can be illustrated by the fact that the velocity of change was doubled (as contrasted with the velocity normally developed by casual impurities in the inert solvent) when the proportion of base was only one part in 10 million, or 1 decigram per ton of benzene. Piperidine in benzene was shown to be 100,000 times more active than aniline in the same solvent, and 100 times more active than sodium ethoxide in alcohol; but, since none of these effects can be attributed to hydroxyl ions, which were not present in any of the solutions, except perhaps as impurities, they cannot very well be expressed as a function of the alkalinity of the bases in water, or of the hydroxyl-ion concentration of their aqueous solutions.

Neutral *salts* also have a marked catalytic activity in the mutarotation of nitrocamphor. Thus the velocity of change of a solution in alcohol or in benzene was increased fourfold by shaking the solvent in the first case, and the solution in the second case, with solid potassium chloride. This result follows naturally from the fact that the salts of nitrocamphor are neutral compounds, which do not readily undergo hydrolysis, and are therefore derived from an acid of sufficient strength to compete with a mineral acid for possession of a base. The sugars, on the other hand, which have no marked acid or basic properties, scarcely respond at all when experiments on mutarotation are carried out in presence of neutral salts, such as sodium or potassium chloride, even at relatively high concentrations.

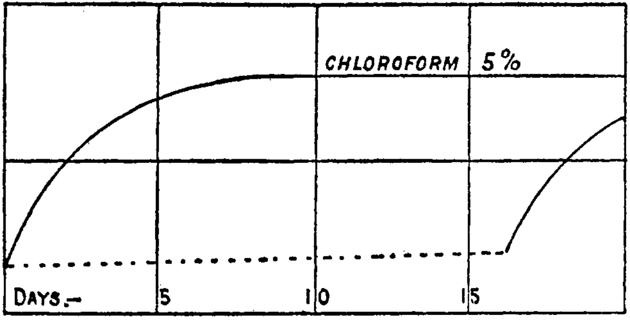


FIG. 1. CHANGE IN ROTATORY POWER OF NITROCAMPHOR IN SOLUTION IN CHLOROFORM

10. Arrest of mutarotation in inert solvents

Special interest attaches to those cases in which an isomerism, which is normally dynamic, can be rendered static by special methods of treatment, since it is very important to determine whether these facile change4 are or are not spontaneous. The first case of this kind to be recorded amongst prototropic compounds was that of nitrocamphor, where an arrest of mutarotation extending over a period of many days was observed in solutions of nitrocamphor in chloroform (21). Thus figure 1 shows that, whilst a 5 per cent solution which was transferred to a polarimeter tube of soft glass began to change immediately, and had reached a condition of equilibrium at the end of eight days, the remainder of the solution, which had been kept in a measuring-flask, had scarcely changed at all at the end of seventeen days, when it was transferred to the polarimeter tube for examination.

These abnormal solutions were probably contaminated with carbonyl chloride (formed as an oxidation product from chloroform according to the equation $2CHCl_3 + O_2 = 2COCl_2 + 2HCl$), since this compound acts as a powerful anticatalyst, especially by eliminating nitrogeneous bases in the form of carbamides. The deliberate addition of carbonyl chloride therefore made it possible at a later date to produce similar arrests of mutarotation in *benzene* and in *ether*, provided that silica vessels[6] were used to contain the solutions (22). The discovery that mutarotation could be arrested almost completely in ether was specially important, since the opinion had been held previously that whilst hydrocarbon solvents were inert, oxygenated solvents in general were active promoters of mutarotation. This early opinion was also disproved when it was found that the mutarotation of tetramethylglucose in dry *ethyl acetate* (fig. 2, a) could be arrested completely during a period of at least 10 hours before a change was slowly initiated (23).

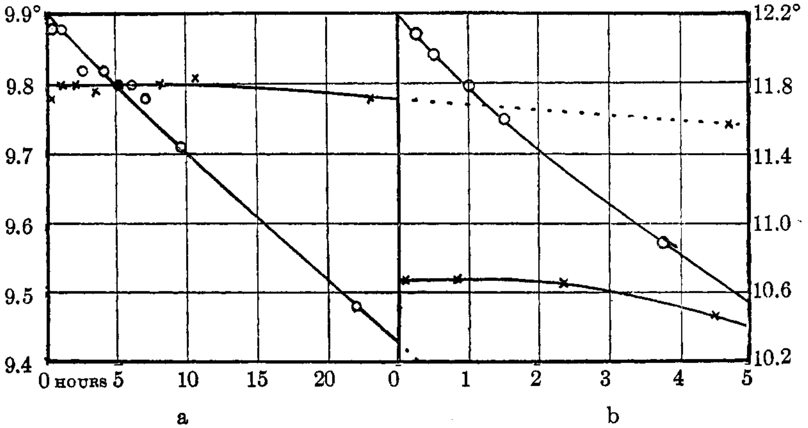


FIG. 2

a. Mutarotation of tetramethylglucose in "dry" and "wet" ethyl acetate. ×, dry. ○, wet.

b. Mutarotation of tetramethylglucose and glucose in "dry" pyridine. ○, glucose. ×, tetramethylglucose.

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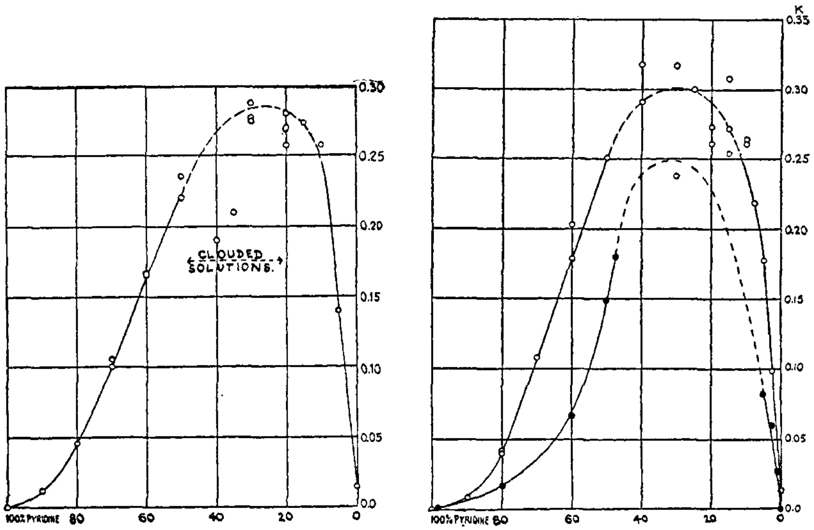
[6] Compare the later work of Kurt Meyer: *Ber.* **53**, 1410 (1920); **54**, 579 (1921) on the aseptic distillation of ethyl acetoacetate in vessels of alkali-free silica-glass.

Even more important was the discovery that the mutarotation of a sugar in *pyridine* can be arrested for two or three hours by moderate purification and drying (23), since the legend that pyridine was a catalytically-active solvent like water had been widely circulated and generally accepted. The complete arrest during a period of two or three hours of the mutarotation of tetramethylglucose in dry pyridine is shown in figure 2 b, which also illustrates the failure to produce a similar arrest in the mutarotation of glucose, the purification of which to the point of yielding metastable solutions, in any of the limited range of solvents in which it will dissolve, is a task of much greater difficulty than in the case of the methylated sugars.



a b

FIG. 3

a. Mutarotation of glucose in pyridine and water.
b. Mutarotation of tetramethylglucose (i) in pyridine and water ⊙, (ii) in pyridine and cresol ●.

A final stage in this development of the theory of mutarotation was reached when it was shown that *cresol,* like pyridine, is not an active catalyst when used alone, but that a mixture of cresol and pyridine, in virtue of its strongly developed amphoteric properties, is a far better catalyst than pure water (24). This is shown in figure 3 where curves are given showing the velocity of mutarotation of tetramethylglucose in mixtures of pyridine with cresol and with water, as well as for the mutarotation of glucose in aqueous pyridine.

11. Further experiments on the arrest of mutarotation

Recent experiments of the author, carried out with the collaboration of Mr. G. Owen, have been devoted to finding conditions under which these arrests of mutarotation, which were at first observed only accidentally, may be produced at will. This was done mainly with a view to determining the influence of small quantities of various catalysts *on solution which were sufficiently pure to inhibit the occurrence of isomeric change,* since under no other conditions would it be possible to guard against secondary effects produced by interaction of the added catalyst with unknown catalysts already present in the solution. The principal results of these experiments were as follows:

a. Purification of polarimeter tubes. The ordinary methods of cleaning a polarimeter tube, e.g., by washing with absolute alcohol and with water, soaking with chromic acid, and then washing repeatedly with water, leave it in a highly active condition, which gives rise to rapid mutarotation when a "clean" solution of tetraacetyl glucose in ethyl acetate is introduced. The best method of purifying the tube is to add fresh quantities of the same "clean" solution, without any intermediate washing, when slower and slower mutarotations are produced. These remarks apply only to silica polarimeter tubes which are clean enough to give quite low velocities of mutarotation; they do not necessarily apply to glass tubes, where the alkaline silicates may perhaps act like the alkaline phosphates or borates of a buffer solution to produce a steady concentration of alkali, and may thus give rise to more uniform velocities than those which are observed when using silica tubes.

b. Arrest of mutarotation in silica flasks. Whilst silica polarimeter tubes can never be relied upon to give an arrest of mutarotation, much more confidence can be placed in the behaviour of *silica flasks which have been ignited and allowed to cool in a desiccator containing phosphoric oxide.* By making use of this discovery it was possible to build up a technique for studying the behaviour of solutions exhibiting arrested mutarotation. This technique depends on making up a solution *in the silica flask,* and transferring samples to a polarimeter tube (1) immediately, and (2) at the end of twelve or twenty-four hours. The solutions in the tube usually exhibit a more or less rapid mutarotation; but when, as sometimes happens, the initial readings of the two samples are identical, it is clear that the solution in the flask is not undergoing isomeric change. It is then possible to add *to the solution in the flask* a trace of a catalyst, and thus to test the effect of the addition of the catalyst *to the uncontaminated solution* by taking out another sample at the end of a further period of twelve or twenty-four hours. In view of the remarkable effects which are produced by mixing together compounds of different types which possess catalytic properties, this condition appears to be essential if trustworthy conclusions are to be drawn from the experiments.

c. Influence of water. A noteworthy feature of these observations was the impotence of water as a catalyst when used in presence of a large excess of ethyl acetate. Thus, in one case, in which a complete arrest of mutarotation had been revealed by the examination of two samples taken from a silica flask at an interval of fourteen hours, the addition of a drop of water to the second sample in the tube (giving a water-concentration of 0.3 per cent) produced a mutarotation with a half-change period of about seventy days, as compared with seventy-five days for the original dry sample. The inability of water to promote mutarotation, when added to a hygroscopic medium which possesses no inherent catalytic properties, was in agreement both with our own theoretical views and with recent observations on the mutarotation of tetramethyl-glucose in aqueous acetone (25) which showed that mutarotation was almost completely inhibited in solutions containing less than *5 per cent* of water. It is indeed obvious that, in experiments of this kind, it is far more important to make use of clean apparatus than of perfectly dry solutions, and that the object to be attained is not so much "Bakerian dryness" as "Bakerian cleanness."

d. Influence of dilute acids and alkalis. In complete contrast to the impotence of pure water was the effect produced by the addition of a drop of decinormal hydrochloric acid to a solution, which was showing an almost complete arrest of mutarotation *in the polarimeter tube.* In this case, a half-change period, which had gradually increased to one hundred and twelve days, fell to six hours on the addition of 0.3 per cent of water containing 0.3 per cent of HCl. A final acid-concentration of only 0.001 per cent had therefore increased the velocity of change about 500-fold, although pure water in a duplicate experiment appeared to retard rather than to accelerate the action. In a precisely similar way the addition of a single drop of normal sodium hydroxide to a polarimeter-tube, containing a solution which was giving a half-change period of about one hundred days, again showed a 500-fold acceleration, the half-change period falling to about five hours. It is noteworthy that this addition of alkali "fouled" the polarimeter tube to such an extent that, when a further sample of the clean solution from the flask (which was still showing a half-change period of about sixty-four days) was poured into the tube, it exhibited an almost identical velocity of mutarotation, with a half-change period of about six hours.

D. CONCLUSIONS

12. "Tautomeric" changes not spontaneous

When Laar put forward his theory of "tautomerism," he supposed that the migration of a hydrogen atom was a form of perpetual motion, like the movement of a planet, and that the formulae which assigned certain fixed positions to the hydrogen atom might be compared with a record of the phases of the moon. This view became untenable, and the theory of tautomerism (but not the name) was generally abandoned, when in one case after another isomeric hydrides were separated as definite entities from the equilibrium-mixtures which are formed in the liquid state or in solution. Nevertheless, the assumption, first made by Butlerow, that prototropic change is spontaneous has persisted even to the present time, since the view has been widely expressed that "tautomerism" is an intramolecular change, in which the solvent does not intervene (26).

It cannot be stated too clearly, however, that this primitive view, although quite plausible when first advanced by Butlerow in 1877, has been experimentally untenable since 1899, when an arrest of prototropic change was first recorded. The fact that these changes are not spontaneous, but depend on a definite mechanism, in which the molecules or ions of the medium (as well as the molecules or ions of the prototropic compound) play an essential part, has been confirmed by many subsequent examples of the arrest of isomeric change under "aseptic" conditions. It may indeed now be accepted as a general proposition that, since prototropic change can be arrested by careful purification, just as other chemical changes can be stopped by intensive drying, a definite mechanism is needed in each case, and that unless this is provided the isomerism will remain static instead of becoming dynamic.

13. The mechanism of prototropic change

The simplest basis for such a mechanism is to suppose that the migration of a hydrogen atom in a prototropic compound is an ionic process, and therefore depends on making use of a medium which possesses a dielectric constant of sufficient magnitude to enable it to act as an *ionising solvent.* According to this view, prototropic change should be possible in any solvent in which an anhydrous acid develops an appreciable electrolytic conductivity. This supposition, although it accounts for the special readiness with which mutarotation takes place in aqueous solutions, was disproved when it was found that mutarotation could be arrested not only in chloroform and in benzene, but also in ether, ethyl acetate, acetone and pyridine. A more plausible explanation of the efficiency of water in promoting the mutarotation of the sugars was then found in its behaviour as an *amphoteric solvent.* This explanation had the advantage of assigning a normal rôle to acid and basic catalysts, since their efficiency could then be attributed to their characteristic behaviour as proton-donors and as proton-acceptors respectively. The conclusion that prototropic change depends on the transfer of a proton *to the medium,* and the recovery of a proton *from the medium,* was, however, finally vindicated, when it was shown that cresol and pyridine were impotent to promote the isomeric change of tetramethyl glucose, but that a mixture of the weak acid and base possessed a remarkably high catalytic activity.

14. Outstanding anomalies

The mechanism suggested above accounts for almost the whole range of observed facts, and there is therefore all the more interest in recording two anomalies which still remain unexplained. The first of these has reference to the fact that solutions of tetra-acetylglucose in ethyl acetate, in which mutarotation had been arrested by working under clean conditions, gave inflected mutarotation curves when a change of rotatory power was finally initiated by the addition of a drop of dilute acid or alkali. Curves of this type are often observed in solutions which undergo a progressive change as the result of a gradual absorption of impurities from the containing vessels, or the like; but it is altogether exceptional for this effect to occur when the solvent is already a complete catalyst. It is possible that, under the rather exceptional conditions of these experiments, successive stages of the process were disclosed, which are usually concealed beneath the apparently unimolecular character of the mutarotation curves.

A second anomaly is found in the fact, first revealed by Hudson, but fully confirmed by the subsequent work of Kuhn and of Euler, that mutarotation at the isoelectric point proceeds much faster than can be accounted for by allowing for the concentrations of hydrogen and hydroxyl ions in the solution. The ratio (about 10 to 1) between the observed and calculated velocities is far too great to be accounted for by any minor error, and could not possibly be corrected by any minor alteration such as the substitution of "activity" for "concentration." Allowance can be made for it, however, by introducing a term representing the concentration of neutral water molecules in the solution. In view of the fact that ether, which resembles neutral water in its oxonium reactions, etc., is not a catalytic solvent, it is difficult to see what rôle these neutral molecules can play in promoting mutarotation except by giving rise to hydrogen and hydroxyl ions. A complete solution of this problem may, however, be looked for in the development, on lines that have already been indicated (27) of an electrolytic theory of catalysis, based upon Armstrong's theory of chemical change.

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