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CONTENTS:

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THE REVIVAL OF ORGANIC CHEMISTRY.[*]

CUSTOM has placed upon the presidents of the Chemical Society the duty of delivering an annual address, and in pursuance of that duty I spoke to you last year upon the 'Revival of Inorganic Chemistry.'[†] I endeavored to show that this branch, so long overshadowed by organic chemistry, so long but little more than a collection of almost unconnected facts, subordinate to analytical and technical chemistry and to mineralogy, is gradually, and especially since the discovery of the Periodic Law, rising to the rank of an independent and important division of our science.

I have chosen for my present topic one which is complementary to the former, 'The Revival of Organic Chemistry.' I may perhaps appear to most of you almost facetious in speaking of the revival of a branch of chemistry which has been in rapid growth for so many decades, which never counted a greater number of adherents than to-day, and which, regarded from the systematic standpoint, is not only the most highly developed portion of chemistry, but also one of the most highly developed of all the sciences. Yet I believe that the use of the term *revival* is justifiable. I do not share the opinion which appears to be held by some inorganic and physical chem-

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[*] Annual Address of the President of the Chemical Society of Washington, October 11, 1900.

[†] SCIENCE, April 28, 1899.

ists, that organic chemistry is approaching the condition in which it will have ceased to afford a profitable field for research, and in which it must be turned over for exploitation to the technologist. I believe that never in its history has there been a time when more directions for truly original work were visible than to-day, and if I have urged the claims of inorganic chemistry to greater recognition, I do not believe that this should be accomplished by abandoning the investigation of carbon compounds, but rather by increasing the number of workers. To those trained in the older organic chemistry of twenty years ago, but who have not followed its recent development, it may indeed seem that formula worship is still supreme, and that further evolution, in a theoretical sense, has been arrested. It cannot be imagined, however, in these times of progress, when even analytical chemistry is beginning to lose its purely empirical nature, and to assume a scientific aspect, that the organic chemist will be content with indefinitely developing the ideas inherited from the past, without originating, or at least assimilating essentially new conceptions. Two courses are open to him if he would remain a scientist: the one, to admit that carbon chemistry has reached its limit of development, and to abandon it for other more profitable fields; the other, to seek new directions of work in this field, to devise new methods, suggest new hypotheses and apply principles originating in other provinces of science. My present object is to point out some of the newer lines of work which appear to me to be particularly important, some of which are already well known, while the significance of others, while doubtless apparent to some, does not yet seem to be generally recognized or insisted on.

Every chemical student is more or less familiar with the remarkable theoretical growth of carbon chemistry between 1830 and 1860, leading up to the valence hypothesis and the hypothesis of the linkage of the atoms, and culminating in the fully developed structural formula, representing schematically the relation of the atoms in organic molecules. This was followed by a period almost devoid of theoretical developments, but characterized by intense activity in devising synthetical methods and applying them to building up new or already known compounds, or in systematically decomposing complex bodies, with the sole object of establishing their structural formulas. The beautiful researches based on the benzene ring theory of Kekulé, the synthesis of alizarine by Graebe and Liebermann, and of indigo by Baeyer, brilliantly conceived and executed as they were, threw not a single further ray of light on the deeper problems of chemistry, and were of much less theoretical significance than the discovery, in 1830, of the transformation of ammonium cyanate into urea. The determination of the structural formula became the final end of nearly all organic chemical research, in so far as this was prompted by scientific rather than practical motives.

The structural formula once developed, the compound possessed little further interest, except in so far as its transformations could lead to the setting up of similar formulas for other bodies. When I was a student of organic chemistry, in the eighties, formula worship was rampant. Neither in America nor in Germany was I led to believe that organic chemistry could have any other aim and end than making new compounds and studying their constitution. A new compound! How the soul of the young investigator thrilled with joy when his substance showed a new percentage of carbon and hydrogen, a new melting or boiling point; this was something no god nor mortal had yet beheld. The constitutional formula was then deduced, if possible; if impossible, then at least one which it might have without violating the laws of valency, the substance was placed in a specimen tube, labeled with its formula and laid away. It was true that two Norwegians, Guldberg and Waage, had claimed to have discovered what they called the law of mass action, Wilhelmy and Menschutkin had studied the time required in certain reactions, a physicist named Hittorf had spent much time in studying the electrical conductivity of solutions, while van't Hoff, a chemist in a Dutch veterinary school, had suggested a theory intended to account for the differences between dextro- and lævo-tartaric acids and similar bodies, which was alluded to as a chemical curiosity, but none of these things were thought worthy of serious consideration by the organic chemist, who was blinded by the really beautiful system of carbon chemistry, and wrapped in dreams of structure. The physiological chemist likewise, failed to realize the fact that he must get beyond the question of constitution before he could accomplish any real progress in his science. I was urged by a well-known chemist with physiological proclivities to take up the study of the proteids. "What we want," said he, "is a sort of map or chart showing the constitution of each of these bodies." The synthesis of uric acid was hailed as a valuable contribution to physiological chemistry, although it did not establish its structure; was effected under conditions impossible in the organism and gave no clue whatsoever to its mode of formation in the body. The term 'formula artificer' (Formelkünstler) applied in a somewhat derogatory sense, fairly expressed, as it still does, the state of mind of those engaged in this kind of work. I have often wondered why chemists persist in speaking of *discovering*, rather than of *devising* a new compound. Organic chemistry might well have been defined as the art of devising new combinations of carbon atoms, for although using scientific methods, the compound maker, as far as his appreciation of his own work was concerned, was rather to be compared with a designer or architect than with his fellows in other branches of science.

Of course, it is far from my intention to belittle the preparation of new compounds or the study of structure. These are valuable pioneer work and necessary precedents to the solution of many problems of chemistry, but they should not be made the final aim of research, as the organic student has so often made them. The ease with which new carbon compounds are made is illustrated by the fact that while the first edition of Richter's *Tables*, which appeared in 1883, embraced 16,000 different organic substances, the new edition, just published, enumerates 75,000, and this number might easily be tripled or quadrupled without the application or discovery of a single new principle of chemistry. It is clear, then, that the honor of adding another to these 75,000 cannot be very great, unless the new body be one calculated to throw light on unsolved problems. The nature and limitations of the structural formula, too, are so well known, that mere variations on the theme cannot be of any great value.

The rapid development of formula worship, and by this term I mean, not the study of structure in itself, which is perfectly legitimate, but the making it the sole aim of research, was due partly to the ease with which the brilliant methods and conceptions of Frankland, of Kekulé and of Couper could be applied to nearly all classes of organic compounds and partly to the comparatively narrow training of chemists during this period. Science does not of necessity develop in a rational way; it grows along the lines of least resistance, whether or not these be those which a mature and broadly trained intellect would indicate as the best. The line of least resistance in organic chemistry was the synthetical direction, the direction requiring persevering application of a comparatively few methods and ideas, while progress in other directions was barred by the chemist's ignorance of subjects lying outside his special field. It has been but a few years that even the scientific chemist has been expected to know much more of physics than that required to comprehend his methods of molecular weight determination. The importance of physics in a chemical education was greatly underrated, and it is, therefore, not in the least surprising that the significance of such studies as those relating to mass action, reaction velocities, equilibrium, electrical conductivities, optical rotation and other provinces of modern physical chemistry should have been greatly underestimated or wholly ignored by the organic chemist, and that he should have become a man of one idea, unwilling even to take the time to open his eyes to the light which was beginning to be thrown on his field by those whose broader education enabled them to discern the future more clearly.

It is perhaps worth while to call attention here to the part which isomerism has played in the various steps forward which organic chemistry has taken. Before 1820, the different modifications of chromic oxide, of silica, of the stannic acids had been discovered, but attracted little attention. The correctness of the discovery of the isomerism of the silver salts of cyanic and fulminic acids by Liebig and Wöhler, in 1823, was even at first doubted. Once established, it become clear that the atoms composing the molecule could not be combined in an indifferent or chaotic fashion, but that, as suggested by Gay-Lussac, combination must take place in a definite and fixed manner, differing in the different isomers. It is to this conception that we owe the 'radical theory,' which assumed the presence in the molecule of groups of atoms having an independent existence and capable of being transferred without change from one compound to another, and, in short all the various theories of constitution which culminated in structural chemistry as represented by Kekulé. We shall presently see how a finer kind of isomerism led to the study of space chemisty, and still later, how isomerism lies at the foundation of the subject of tautomerism, which is of such importance at the present day.

The structural formula implies (if we may disregard the view of the few more cautious chemists who regard it as a reaction formula only) that the atoms are in each case linked together according to a definite plan, but it is purely diagrammatic, it says nothing about their relation in space; this may be fixed or nearly fixed, or it may vary as the Solar System varies, the plan remaining the same, but the relative positions of the component bodies changing entirely from instant to instant. Up to 1860 scarcely a chemist concerned himself in the least with the relative positions of the atoms or groups in space, and it was not till 1887 that the chemical mind became awakened to the importance of this question. A few earlier chemists, it is true, as Boyle, Wenzel, Wollaston, Gmelin, Laurent, had suggested the possibility of the existence of such definite relations, but the absence of any experimental basis for such speculations prevented their suggestions from having any positive results. It is about the year 1887, therefore, that I am inclined to place the beginning of the revival of organic chemistry.

The development of the conception of chemistry in space is inseparably bound up with the chemical and crystallographic study of tartaric and racemic acids, and with Biot's discovery of the rotation of the plane of polarization of light by certain dissolved organic compounds. The isomerism of tartaric and racemic acids was recognized by Gay-Lussac in 1826 and by Berzelius in 1830, but nothing in their observations indicated that this isomerism was in any way peculiar and of a finer kind than that existing in other cases. Still earlier, in 1815, Biot had found that tartaric acid and various other organic bodies, such as sugar, camphor, turpentine, possess the power of rotating the plane of polarization of light, and as this property is shown by them in the dissolved state, it was clear that it must be due, not to crystalline structure, but to intramolecular constitution. In 1841, de La Provostaye investigated the crystallography of tartaric and racemic acids and their salts without noticing any difference between the two series, while in 1844 Mitscherlich examined the double sodium ammonium salts of these acids crystallographically with the same result. Referring to the discovery of Biot that the tartrates are dextrorotary, the racemates indifferent, Mitscherlich says: "Nevertheless, the nature and number of the atoms, their arrangement and their distances apart are the same in both bodies."

In 1848, Louis Pasteur, who was then a chemical student just beginning independent work, turned his attention to the study of crystals as offering a possible assistance to him in his chemical researches. With no expectation of making a discovery, with a view to practice solely, he began by repeating de La Provostaye's work of seven years before, as far as it related to tartaric acid. He soon observed a fact which had escaped the former, this being that crystals of the tartrates possess certain hemihedral faces, and further that the hemihedrism is in the same sense in all the tartrates. Led by the observation of Hauy and Weiss, on the existence of right- and left-handed hemihedrism in quartz, of Biot, on the existence of dextro- and lævo-rotary quartz, and of Sir John Herschel, that the crystallographic difference of the two kinds of quartz is associated with a corresponding difference in the sense of their optical rotation, he undertook an investigation designed to ascertain whether in the various crystalline organic bodies possessing optical rotation in solution, this property is always accompanied by hemihedrism, and whether absence of the one implies corresponding absence of the other. He examined the crystals of the optically indifferent racemic acid and its salts; none of these showed hemihedrism. Mitscherlich had failed to observe the hemihedrism of the active sodium ammonium tartrate and found that its crystals differ in no wise from those of the corresponding inactive racemate. Herein was an apparent exception to the rule, and Pasteur, therefore, repeated Mitscherlich's work. He found the hemihedrism of the sodium ammonium tartrate which had escaped the eye of Mitscherlich, but he also found—and this is the observation which entitles him to be regarded as one of the founders of chemistry in space—that exceptionally the double racemate also showed hemihedral faces, but that while half of the crystals were hemihedral in a right-handed sense, the other half were so in the opposite sense.* Carefully separating the two kinds, dissolving them and placing the solutions in the polarimeter, he found, to his great surprise and delight, that the one solution was dextro-, the other lævo-rotatory. From the latter he prepared lævo-tartaric acid, the hitherto unknown isomer of common tartaric acid. Mixing the two acids in equal quantities, he regenerated the inactive racemic acid.

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* The inversion temperature of sodium ammonium racemate is 27° C. (van't Hoff and van Deventer, *Zeit. physik. Chem.* **1**, 173). Above this temperature the racemate is stable, below it, the mixed dextro- and lævo-sodium ammonium tartrates. Mitscherlich's failure to detect the facts afterwards observed by Pasteur may therefore have been due, not to erroneous observation, but to improperly selected temperatures.

This is an old story for us, but at that time it appeared highly improbable, and even Biot, the veteran discoverer of the optical rotation of dissolved organic substances, who had for twenty years vainly endeavored to convince chemists that in the study of this phenomenon was to be found one of the best means of investigating molecular structure, entertained strong doubts as to its accuracy. As an illustration of scientific skepticism, I may quote Pasteur's own words, relating to Biot's reception of his discovery:* "He (Biot) summoned me to his laboratory, in order to have me repeat the various experiments under his own eyes. He supplied me with racemic acid, which he himself had examined and had found to be optically inactive. I prepared in his presence the sodium-ammonium double salt, for which he wished to furnish even the soda and ammonia. The solution was set aside in his laboratory to evaporate slowly, and after 30–40 grams of crystals had formed, he again summoned me to the Collège de France to collect the dextro- and lævo-rotatory crystals, and separate them according to their crystallographic character, requiring me to repeat the assertion that those which I placed at his right hand were dextro-rotatory, and those at his left hand lævo-rotatory. When this was done, he said that he himself would carry out the rest. He carefully prepared the solutions and at the moment when he was about to observe them in the polarimeter he called me again into his room. He first brought into the apparatus the more interesting solution, that which should rotate towards the left. Without making the reading, merely by viewing the shades of color on the two halves of the field of vision, he recognized the presence of distinct lævo-rotation. Then the old man, visibly affected, grasped my hand and said, 'my dear child, I have loved science my whole life so much that I hear my heart beating for joy.' "

Pasteur was able to give but a vague, yet true explanation of his observations. He attributed this physical isomerism to a sort of asymmetry of the molecule, the two kinds being identical in every respect except that they cannot be made to coincide; they are like an object and its reflection in a mirror, the right and left hand, or a right- and left-handed screw. In his opinion, the asymmetry was caused by the action of forces peculiar to the organism.

Pasteur's discovery waited long before exercising a perceptible influence on the course of chemical research. Kekulé's *Lehrbuch*, published in 1866, describes the facts, but makes no mention of Pasteur's theoretical views. The investigations of Wislicenus, on the lactic acids, published in 1869, showed that four of these exist (β oxypropionic acid and two optically opposite forms of α oxypropionic acid with their racemic combination), while the structure theory indicates but two. Without giving a more concise explanation, he suggested that the difference of the acids is a geometrical one, and called this kind of isomerism *geometrical isomerism*. It is curious that at even this date Wislicenus makes no mention of Pasteur's discovery of the enantiomorphic tartaric acids or his theory of molecular asymmetry, although the facts were precisely analogous, and the explanation a more definite one than his own.

Pasteur's conception of molecular asymmetry, first stated, I believe, in 1860, had to wait until 1874 before assuming a form sufficiently definite to admit of application to the theory of structure. In this year there appeared independently and almost simultaneously two publications of essentially similar nature, the one by Le Bel in Paris, the other by van't Hoff, then professor in Utrecht. Le Bel acknowledged

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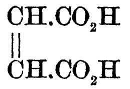
* Ostwald's Klassiker, No. 28, p. 14. This contains Pasteur's own account of his observations.

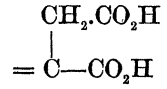
his indebtedness to Pasteur, while van't Hoff made no special mention of him and proceeded to develop his theory on *à priori* grounds, though he has elsewhere told us that his interest was aroused by Wislicenus' discovery of the physically isomeric lactic acids. Beginning with the assumption that the four valences of the carbon atom are directed towards the apices of a tetrahedron, van't Hoff showed that if any two of the four combined atoms or groups are identical (Caabc) but one form can result, while if they are all different (Cabcd) there must result two forms, identical in so far as their plane structural formulas are concerned, and identical in all chemical and physical respects, save that the one is to the other as an unsymmetrical object and its reflection in a mirror; they would constitute right- and left-handed figures, their influence on polarized light and on the form of the crystal would be the same, but in opposite senses, that is, they would be dextro- and lævo-rotatory, and if showing hemihedrism, this, too, would be opposite in the two forms. Proceeding to apply this hypothesis, he showed that every optically active organic compound, the constitution of which was then known, contains one or more such asymmetric carbon atoms, carbon atoms combined with four different atoms or groups; the dextro- and lævo-tartaric acids are identical when the ordinary formulas are considered, but different when the space relations are taken into account. It was further shown that two or more asymmetric carbon atoms in the same molecule might reinforce or neutralize each other with respect to rotatory power, in the latter case giving bodies like inactive tartaric acid, which differs from racemic acid in not being separable into optical antipodes.

Van't Hoff further applied his theory of the tetrahedral carbon atom to other obscure cases of isomerism, found only in bodies having doubly united carbon atoms, such as fumaric and maleic acids, which are not chemically identical, but the interpretation of which on the current views of structure had not been satisfactorily accomplished. Fittig regarded fumaric acid as



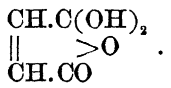
$$\begin{array}{l}\mathrm{CH.CO_2H}\\ \|\\ \mathrm{CH.CO_2H}\end{array}$$

and the isomeric maleic acid as



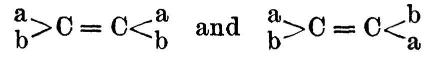
$$\begin{array}{l}\quad\mathrm{CH_2.CO_2H}\\ \quad|\\ =\mathrm{C{-}CO_2H}\end{array},$$

the latter formula, however, not being in harmony with the facts, while Anschütz held maleic acid to be



$$\begin{array}{l}\mathrm{CH.C(OH)_2}\\ \|\qquad >\mathrm{O}\\ \mathrm{CH.CO}\end{array}.$$

On van't Hoff's hypothesis, the doubly combined carbon atoms are incapable of free rotation, the combined groups or atoms being, therefore, compelled to retain their relative positions, thus giving stability to the two configurations



$${}^{a}_{b}\!>\!\mathrm{C}=\mathrm{C}\!<^{a}_{b} \quad \text{and} \quad {}^{a}_{b}\!>\!\mathrm{C}=\mathrm{C}\!<^{b}_{a}$$

We have thus two distinct types of geometrical isomerism; in the one, the type with asymmetric carbon atoms, the chemical properties are identical and likewise the physical, except in so far as they involve space relations, as optical rotation and hemihedrism; in the other, that of the doubly united carbon atoms, the chemical properties, while not absolutely identical, are so nearly so that they can be expressed by the same structural formula of the old style.

Van't Hoff and Le Bel's explanation of physical isomerism long attracted but little attention among chemists, partly because such cases were then comparatively rare, partly because of the inertia of the chemical mind, which preferred to seek an explanation in new forms of plane structural formulas, or which simply ignored the facts, much as the inorganic chemist long ignored the existence of double salts, which did not conform to his notions of what valency should do. The theory, however, at once found a warm advocate in Johannes Wislicenus, whose mind had been prepared by his investigation on the lactic acids, but in other quarters it met with open opposition. Among its opponents was the illustrious but pugnacious Kolbe, whose words * I cannot refrain from quoting, both because they are extremely characteristic of his style of criticism, and because they were directed towards a man who has since won the highest renown as a chemist, and towards a theory which has now earned an accepted place in science.

"In a recently published article under the above title,† I have denoted, as one of the causes of the present retrogression of chemical investigation in Germany, the lack of general, and at the same time fundamental chemical training, under which not a small number of our chemical professors labor, to the great disadvantage of science. The result is the prevalence of a vegetation of apparently learned and intellectual, but in reality trivial and soulless, natural philosophy, which, set aside fifty years ago by the exact investigation of nature, is again being hauled forth by pseudo-scientists from that rubbish room which contains the wanderings of the human mind, and which, like a wench dressed in the height of fashion and freshly painted, it is being attempted to smuggle into good society in which it does not belong.

"Let him to whom this fear seems overdrawn, read, if read he can, the recently published brochure, bristling with the play of fancy, of Messrs. van't Hoff and Herrmann, on the 'Position of the Atoms in Space.' I should ignore this, as I have many others, had not a reputable chemist* taken it under his protection and warmly recommended it as a valuable production.

"A certain Dr. J. H. van't Hoff, at the Veterinary School in Utrecht, has, as it appears, no taste for exact chemical research. He has considered it more convenient to mount his Pegasus (evidently borrowed from the Veterinary School), and to announce, in his 'Chimie dans l'espace,' how, from the chemical Parnassus, reached in his bold flight, the atoms of the universe are seen to be arranged. * * *

"To criticise this brochure even half-way is impossible, because the fancies contained in it are wholly without foundation in fact, and absolutely incomprehensible to the sober investigator. But to get an idea of what floated before the minds of the authors, it will suffice to read the two following sentences. The brochure begins with the words: 'Modern chemical theory has two weak points; it speaks neither of the relative positions of the atoms in the molecule, nor of the nature of their motions.' The second sentence reads: 'In the asymmetric carbon atom we have a medium which is characterized by the screw-like arrangement of its smallest parts, the atoms!' * * *

"It is characteristic of the present uncriticising and criticism hating age that two practically unknown chemists, the one in a veterinary school, the other in an agricultural institute, confidently pass judgment upon the highest problems of chemistry, which in all probability will never be solved, especially the spatial relations of the atoms, and undertake their solution with an assurance which sets the true investigator in positive amazement. * * *

"Wislicenus herewith announces that he has abandoned the ranks of exact investiga-

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* Zeichen der Zeit. *Journ. prakt. Chem.* N. F. **15.** 473.

† *Journ. prakt. Chem.* N. F. **14.** 268.

* Wislicenus.

tors, and has gone over to the camp of the natural philosophers of unhappy memory, which but a thin 'medium' separates from the spiritualists."

Upon this criticism van't Hoff remarks, in a later work,* "But ten years have passed—Kolbe is dead, and by a strange freak of fate it is Wislicenus who has succeeded him in the University of Leipzig," to which we may add, that after twenty-five years, the Utrecht horse doctor has become professor in the University of Berlin, and the chemical world has united in doing him honor upon the twenty-fifth anniversary of his doctorate.

Time is wanting to do more than allude to the interesting 'tension theory' of von Baeyer, dating 1885, which, by adopting van't Hoff's conception of the tetrahedral arrangement of the carbon valences, and assuming that these tend to maintain their relative positions with considerable force, like elastic springs, offered an explanation of the relative stability of the polymethylene rings and the instability of the polyacetylene compounds.

The first strong impulse to the study of the space relation of carbon compounds was given by Johannes Wislicenus in 1887, by his paper on 'The Spatial Arrangement of the Atoms in Organic Molecules, and its Determination in Geometrically Isomeric Unsaturated Compounds.'† In this paper the subject was treated essentially as it had been twelve years before by van't Hoff, but with important extensions, covering the lactones and anhydrides. After the appearance of this epoch-making work, stereochemistry was no longer a scientific curiosity; it at once became the fashion, and has so remained ever since. Many speculations have appeared, but few have obtained much foothold, and the stereochemistry of to-day, so far as it concerns carbon, is essentially that of van't Hoff, Le Bel and Wislicenus. The classical researches of von Baeyer on the hexahydrophthalic acids are based essentially on extensions of the theory of the geometrical isomerism of bodies of the ethylenic type and have contributed not a little to its confirmation. The preparation of stereoisomers of both types is now a matter of almost daily occurrence.

Unquestionably the greatest achievements of stereochemistry are to be found in Emil Fischer's magnificent researches on the sugars. If to explain old facts and to lead to the discovery of new ones be any test of the truth of an hypothesis, then the applicability of the theory of the asymmetric carbon atom to the carbohydrates affords a very strong presumption in its favor. The stereochemistry of the sugars might by itself form the subject of many lectures. Not only were the relations of the already known sugars satisfactorily explained, but the synthesis of whole new groups was effected, the configuration of each of which was determined.

Pasteur discovered the three chief methods which are still used for separating an optically inactive mixture into its active components, namely, (1) separating by selection the two kinds of hemihedral crystals corresponding to the dextro- and lævo-rotatory forms, (2) separation by means of alkaloid salts, the alkaloids being themselves optically active and forming with the two constituents of the racemic mixture two salts which are not enantiomorphic and therefore differing chemically and physically, one being less soluble than the other and (3) separating by means of fermentation, the fermenting organisms frequently showing a tendency to destroy one of the forms while leaving the other un-

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* Dix années dans l'histoire d'une théorie, p. 21.

† Ueber die raümliche Anordnung der Atome und ihre Bestimmung in geometrisch-isomeren ungesättigten Verbindungen. Abhand. d. K. Sächs. Gesellsch. d. Wiss. Bd. 24.

touched. The alkaloid and the fermentation methods are of the widest applicability, and the latter is especially important because of its bearing on vital phenomena. Pasteur showed that the micro-organism is able to attack one of the geometrically isomeric forms, while incapable of acting on the other. In his work on the sugars Fischer further demonstrated that this selective power is not to be ascribed to any peculiar vital property of the living cell, for the soluble ferments, the enzymes, have frequently the same selective power. This power he attributes to the existence of the proper molecular asymmetry in the enzyme, by virtue of which its molecule is able to come into proper relationship with the asymmetric molecule of the body to be fermented; with exactly the same constitution on the part of one of the reacting bodies, but with the opposite configuration, this relationship cannot be brought about and fermentation does not ensue; as Fischer expresses it, sugar and enzyme must be adapted to each other as lock and key. Lock and key may be made on the proper model, but only when the notches of the key are on the same side as the wards of the lock can they fit each other. From this it would follow that the form which is left unattacked during the fermentation with a particular enzyme should be decomposed by an enzyme having the same chemical formula but the opposite configuration.

In fact, the physiological significance of stereochemistry is so great that we do not yet begin to appreciate it. The carbohydrates all contain asymmetric carbon atoms, and the same is unquestionably true of the proteids, all of which are optically active; the enzymes, as bodies closely related to the proteids, probably possess molecular asymmetry. The different digestibility or assimilability of various carbo-hydrates and proteids may be partly due to the different space configuration of their molecules rather than to any specifically chemical cause. Fischer has suggested the possibility of synthesizing a sugar capable of assimilation by diabetics. The power of digesting cellulose and horny matter possessed by some animals may be due simply to the peculiar configuration of their digestive enzymes. The curious fact that dextro-asparagine is sweet, while lævo-asparagine is insipid, is doubtless due to the asymmetric structure of the active molecules of the taste buds. It is possible that a dextro-strychnine might be innocuous, a dextro-quinine a virulent poison.

It is well known that all asymmetric compounds produced by purely artificial methods consist of an optically inactive mixture of dextro- and lævo-rotatory forms in equal proportions; only nature is able to produce one form to the exclusion of the other; the chemist can do this only with the aid of a natural product such as an alkaloid or enzyme, itself active in one sense, or by intelligent selection, as where Pasteur separated the two tartrates. At present we can perceive no escape from the dilemma that in the synthesis of its optically active substances the organism either employs some ultra-chemical process, or produces them by chemical means through the agency of previously existing active substances. The latter alternation would lead us back to the existence of one-sided asymmetry in the very first organism of the series, the origin of which it is equally impossible to explain on chemical grounds. This interesting fact, pointed out by Japp* is regarded by him as indicating that something besides chemical and physical forces was concerned in the original production of life. The difficulty is a real one, and we still know of no better explanation than

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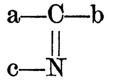
* Address before Section 'B,' British Association for the Advancement of Science. *Nature*, Vol. 58, p. 452.

is suggested by the words of Pasteur:* "Is it not necessary, and also sufficient to assume that at the moment when the vegetable organism originates, an asymmetric force is active? * * * Do there perhaps exist such asymmetric activities, subordinated to cosmic influences in light, heat, magnetism, electricity? Are they associated perhaps with the motion of the earth, with the electric currents by which the physicists explain the magnetic poles of the earth? We are to-day not in the position to express even the least opinion on the subject."

Before we assume the existence of a vital force or other mysterious agency, however, to explain the difficulty, let us not forget the confidence with which Berzelius asserted the hopelessness of the problem of producing organic compounds from purely inorganic material.

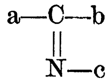
Speculation on the space relations of the atoms has not been slow in extending itself to other elements than carbon. More especially has nitrogen occupied the attention of stereochemists. Many attempts to prepare geometrically isomeric ammonium compounds have been made, by introducing the substituting groups in different orders, without positive results. Within a year, however, Pope and Peachey† have succeeded in decomposing inactive α-benzyl-phenyl-allyl-methyl-ammonium into its dextro- and lævo-rotatory constituents by means of dextro-camphor sulphonic acid, thereby affording a proof of the existence of stereoisomeric compounds of pentavalent nitrogen, a discovery which, if confirmed by the preparation of other similar compounds, is of the very highest importance. Still more recently, the same chemists have obtained optically active compounds of tetravalent sulphur and tin.‡

More fruitful has been the hypothesis of Hantzsch and Werner originally suggested by the existence of physically isomeric oximes, and now applied by them to the compounds containing the group—N = N—. According to this view the triad nitrogen atom may be regarded as occupying one apex of a tetrahedron, the combined groups occupying the others, or in other words, the three valences of the nitrogen do not act in the same plane. In the case where the nitrogen atom is doubly united to another nitrogen or a carbon atom, free rotation is prevented, as in the case of doubly united carbon atoms, and we may have stereoisomers of the types



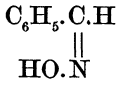
$$\begin{array}{c} a—C—b \\ \| \\ c—N \end{array}$$

and



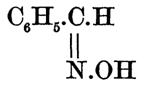
$$\begin{array}{c} a—C—b \\ \| \\ N—c \end{array}$$

Benzaldoxime, for instance, exists in the forms



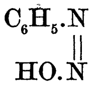
$$\begin{array}{c} C_6H_5.C.H \\ \| \\ HO.N \end{array}$$

and



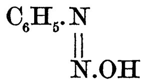
$$\begin{array}{c} C_6H_5.C.H \\ \| \\ N.OH \end{array}$$

and diazobenzolhydroxide as



$$\begin{array}{c} C_6H_5.N \\ \| \\ HO.N \end{array}$$

and

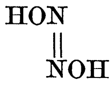


$$\begin{array}{c} C_6H_5.N \\ \| \\ N.OH \end{array}$$

while according to Hantzsch, the isomeric nitramide and hyponitrous acid are simply

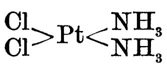
$$\begin{array}{c} HON \\ \| \\ HON \end{array}$$

and



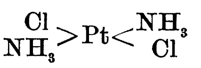
$$\begin{array}{c} HON \\ \| \\ NOH \end{array}$$

It is quite possible that the Hantzsch-Werner hypothesis may also find an application in the study of the labile compounds of the organism. Still more recently, Werner has considered as stereo-isomeric a number of metal-ammonias and their derivatives, notably the platinum compounds



$$\begin{matrix} Cl \\ Cl \end{matrix}>Pt<\begin{matrix} NH_3 \\ NH_3 \end{matrix}$$

and



$$\begin{matrix} Cl \\ NH_3 \end{matrix}>Pt<\begin{matrix} NH_3 \\ Cl \end{matrix}$$

platosemidiamine chloride. platosamine chloride.

I have mentioned the latter examples as illustrating the tendency to extend the

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[*] Ostwald's Klassiker, No. 28, p. 31.

[†] *Journ. Chem. Soc.*, **75**, 1127.

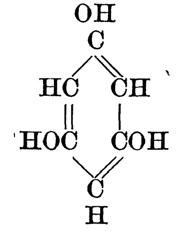
[‡] *Journ. Chem. Soc.* **77**, 1072; *Proceedings Chem. Soc.* **16**, 42, 116.

newer conceptions of the carbon atom to the atoms of other elements also. Whether we shall ever have a stereochemistry of all the elements is very questionable. As I shall point out presently, carbon compounds in general possess a kind of inertia, a tendency to retain their structure, the possibility of isomerism being due to this. At a higher level of temperature, ordinary structural isomers tend to assume the most stable form or system, while those isomers the existence of which depends on asymmetric carbon atoms tend to form a mixture composed of equal portions of both right- and left-handed forms; both dextro- and lævo-tartaric acids, for example, giving racemic acid on heating. That we do not find more cases of structural or of steric isomerism among inorganic bodies is perhaps due, not to their existence being inherently impossible, but to our working at too high a temperature, a temperature at which isomers are incapable of existence, lapsing at once into the most stable forms or into a mixture of structurally equivalent but geometrically opposite bodies, which, like the constituents of racemic acid, are identical in chemical and most physical properties, and which, existing in equal quantities, balance each other optically and crystallographically, like the two tartaric acids. The asymmetric tin atom shows great lability at ordinary temperatures. At a temperature much below zero, such steric and structural isomers may well exist independently. The investigation of this is but one of the many possibilities of low temperature work.

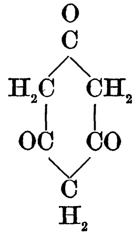
This brings us to a comparatively new and highly important branch of organic chemistry, the subject of *tautomerism*, and this, like stereochemistry, is an outgrowth of the subject of isomerism. Van't Hoff, in his remarkable, but little known book, 'Ansichten über die organische Chemie,' points out, as one of the reasons for the existence not only of the large number of carbon compounds, but also of isomers, the peculiar inertness of the union of carbon with itself and with other elements. Every one knows that in general the reactions of carbon compounds take place slowly, they form with difficulty and once formed are comparatively stable; there is a tendency to maintenance of the *status quo*. In the language of physical chemistry, we may say that carbon compounds usually tend to equilibrium with great slowness. They have a very small reaction velocity. By virtue of this property, the reason for which we do not know, the organic molecule, once formed, tends to maintain its individuality, hence the stability of isomers. Were it not for this, it would rapidly lapse to the system which is most stable, whether it be another simple body or a mixture. Just the opposite is characteristic of the inorganic molecule. We know a few inorganic isomers, it is true, but their occurrence is so rare as to excite comment. We are, for example, acquainted with three organic compounds $C_2H_5NO_2$, namely, ethyl nitrite $C_2H_5.ONO$, nitroethane $C_2H_5.NO_2$, and a less stable form of this, $CH_3.CH{=}NO.OH$, but we know but one nitrous acid and one series of metallic nitrites; we know but one sulphurous acid and one series of its metallic salts, while there are two series of organic derivatives, the sulphurous ethers and the sulphonates; but one hydrocyanic acid and one series of metallic cyanides, while there are two series of organic derivations, the nitriles and isonitriles; but one sulphocyanic acid with two series of organic derivatives, the sulphocyanates and the mustard oils. Such examples might be quoted indefinitely. Any one who has attempted to synthesize complex inorganic bodies by following the methods of organic chemistry must have been struck with the comparative rareness with which the desired results are obtained. In general, then, while organic isomers possess considerable stability, of the theoretically possible inorganic isomers expressed by any formula only one form is stable, and the others, if momentarily formed, tend to lapse spontaneously into this. As van't Hoff says, the carbon atom tends to confer on the molecule the power of storing up an enormous amount of energy, which power, for want of a better name, is termed the inertness of the carbon combination. It is this property, perhaps more than any other one fact, which distinguishes organic from inorganic compounds.

All organic isomers do not possess this power of maintaining their individuality to the same extent. We find every degree of transition from the stable to the labile, from those isomers which are not interconvertible at any temperature short of total decomposition, to those which change into each other upon the slightest provocation, such as slight elevation of temperature, fusion or solution, the presence of catalyzers or of bodies capable of reacting only with one form; from those whose individuality and stability are marked, to those where one form is stable, the other labile, and where the lability may vary to such an extent that in some cases the unstable form is easily obtained, in others only with the greatest difficulty, while in still others it is too unstable to exist at all under attainable conditions, and the isomerism disappears. It is the study of labile isomerism which, under the name of *tautomerism,* has attained such prominence in recent years. In the phenomena of labile isomerism, organic chemistry shows a distinct approximation to inorganic chemistry; the characteristic phenomena underlying tautomeric organic bodies and inorganic bodies is the same, namely, the tendency to pass easily from a labile to a stable form, in short, the absence, more or less marked, of the property which van't Hoff called inertness of union.

An extreme case of lability in one isomer is found in that of the hypothetical vinyl alcohol, $CH_2 = CHOH$. Reactions which theoretically should give this, in reality yield aldehyde, $CH_3.CHO$; the stability of the former is so slight that it passes at once, if formed, into the isomeric aldehyde. Baeyer obtained two ethyl-isatines, to which should correspond two isatines, while in reality but one exists. Allied to this is the behavior of phloroglucine, symmetrical trioxy-benzene, which, with acetyl chloride gives an acetate, indicating that its formula is

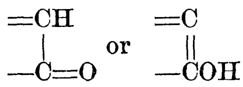


while with hydroxylamine it yields an oxime, which is explicable only on the assumption that it has the constitution



It is, therefore, impossible, by using the usual reactions for phenols and ketones, to ascertain to which of these groups phloroglucine belongs. Baeyer held that but one of the forms actually exists in the free state, the other, the pseudo-form, as he termed it, being too unstable for existence. Laar, on the contrary, held that in such cases both formulas are equally justifiable; that each molecule is constantly shifting back and forth between the two forms, each having but a momentary existence, and to such bodies he applied the term tautomeric.

The discussion on the nature of tautomeric bodies has been one of the hottest in the recent history of organic chemistry, and not altogether free from invective. Much of this could have been avoided had the organic chemist recognized that the problem is one in which the ordinary methods of organic chemistry find but little application, and then only with the greatest caution and judgment. The older methods are strictly applicable only to the more stable bodies. So impressed has he been with the inertness of the carbon union that he has failed to recognize that the laws of chemical equilibrium could have any place in organic chemistry. A certain compound may, for example, contain one of the two groups :



$$\begin{array}{c}=CH\\ |\\ -C{=}O\end{array} \quad \text{or} \quad \begin{array}{c}=C\\ \|\\ -COH\end{array}$$

The organic chemist assumed that it must be entirely the one or entirely the other, and was perplexed on finding that it reacted with a ketone reagent entirely in the former sense, and with a hydroxyl reagent entirely in the latter. To get around the difficulty, he was led to assume with Baeyer that only one of these actually exists in the free state, or with Laar, that each molecule is rapidly changing from the one form to the other and back again. The most elementary knowledge of reversible reactions would have taught him that the two forms must necessarily tend to a condition of equilibrium; that the final product must be a mixture of both forms, but that equilibrium might lie at a considerable distance from both extremes, or very near to one; that either form, if isolated, would tend with greater or less rapidity to the same condition; that if he removed one constituent by converting it into another compound, the equilibrium would be disturbed, and more of the other form would undergo transformation and be removed from the sphere of action until conversion is complete, and that, therefore, conclusions based on purely chemical evidence were to be accepted with a grain of salt unless the two forms, by virtue of their slow velocity of transformation, could be isolated and studied. The application of physico-chemical methods nowhere in organic chemistry finds better opportunity than in just this field. In some cases the laws of the so-called 'condensed systems,' with definite inversion temperatures, are doubtless applicable. Hantzsch's researches on the nitro-hydrocarbons afford a good illustration of the superiority of physico-chemical methods. Nitroethane $C_2H_5NO_2$ is a good example of this class. Its constitution was assumed by its discoverer, Victor Meyer, to be $CH_3.CH_2.NO_2$, and it forms salts with alkali metals, in which the metal has been variously supposed to be united to carbon $CH_3.CHM.NO_2$ or to oxygen $CH_3.CH{=}NO.OM$; in the latter case it was necessary to assume either that the originally proposed formula of nitroethane is wrong, or that in forming a salt it undergoes intramolecular rearrangement. Hantzsch now applied the method of electrical conductivity. The aqueous solution of nitroethane is practically a non-conductor, and hence contains no ions, which would make it decidedly not an acid. If this solution be mixed with the equivalent of caustic soda, it at first shows only the conductivity due to the alkali; gradually, however, this diminishes, indicating the slow formation of a salt, which, being the salt of a weak acid and therefore less dissociated than caustic soda, would conduct less. Were the nitroethane itself an acid, this effect should take place at once, as salts always form instantly or nearly so. If now just sufficient hydrochloric acid be added to convert the sodium nitroethane into nitroethane and sodium chloride, the solution at first shows a greater conductivity than is attributable to the sodium chloride alone; the nitroethane, therefore, takes part in it, and as ordinary nitroethane is non-conducting, a body of different constitution must be present, and this is regarded as the true acid $CH_3.CH{=}NO.OH$; this, however, gradually loses its conductivity, being transformed into common nitroethane. Nitroethane is, therefore, capable of existing in two forms, the ordinary form, the stable pseudo-acid $CH_3.CH_2.NO_2$, gradually metamorphosing under the action of an alkali into the true acid $CH_3.CH{=}NO.OH$, which, stable as a salt, is labile in the free condition, gradually passing back into the pseudo-acid. In this, as in many other cases studied by Hantzsch, we find an intimate relation between tautomeric metamorphosis and ionization. Brühl has also recently pointed out a relation between tautomeric change and the nature of the solvent in which it occurs, the change from the enol to the keto form being promoted by ionizing solvents like water and alcohol, while non-ionizing solvents prevent or hinder it.

Passing from isomers in which both forms are stable, through various degrees of tautomerism, to where one of them is too labile to exist at all, at least under ordinary conditions, we reach the state of affairs prevailing among inorganic bodies. The tautomeric organic bodies are an approximation to the inorganic ; their chemistry is an approximation to inorganic chemistry. Ostwald has recently suggested a division of chemical compounds into two great classes, the ionizing and non-ionizing.* These would, in general, correspond to inorganic and organic, but some of the inorganic bodies would be found in the non-ionizing groups, while besides the carboxylic acids, a few organic compounds will be found in the ionizing group. The tautomeric compounds would occupy the intermediate position. We learn from these considerations one reason why inorganic isomers are so seldom found. The labile tautomer the more readily transforms into the more stable form the higher the temperature. The reason that we do not have inorganic tautomers is simply because we are working at too high a range of temperature. Much below room temperature we shall probably find a field of inorganic tautomerism and isomerism as rich or richer than that presented by organic chemistry. There is no sharp line of demarcation between the two fields; the apparent difference results from the relatively greater inertness of the carbon union. If the methods of physical chemistry have hitherto found most application in inorganic chemistry, they are now being extended, in organic chemistry, first of all to those compounds which most closely resemble the inorganic, namely, the tautomers.

A word on the application of tautomerism in physiological chemistry. The organic constituents of protoplasm, in so far as they are essentially active, are, on Loew's theory, highly labile. The death of the protoplasm is at once accompanied by the transformation of its labile proteids into their stable forms. What it is that prevents this change taking place in life we do not know, yet it is evident that if we are to get light on the subject from the chemical side, it will not be so much by attempting to synthesize dead proteids, as by studying labile forms. I incline to the opinion, therefore, that the study of the phenomena of tautomerism is of the highest importance for physiological chemistry, and that physiological chemists will do well to turn their attention to this field.

It is usually assumed that no portion of organic chemistry is further removed from the inorganic than the study of the living cell. I am inclined to hold the opposite opinion. If, as I have suggested, the labile tautomeric compounds lie between the stable organic compounds on the one

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*Grundriss der allgemeinen Chemie, 3^{te} Aufl. S. 522.

hand and the stable inorganic on the other, then, too, the labile compounds of protoplasm occupy an intermediate position. The chemical phenomena of life, are as close to those of the inorganic as to those of the stable organic bodies. It is not so much by emphasizing the differences between carbon and the inorganic elements that we shall aid in the explanation of life as by looking for those features in which carbon approximates to the inorganic.

Hitherto the organic chemist has occupied himself mainly with the end-products of chemical reactions. With those important factors, the time and the yield, he has seldom concerned himself, further than to obtain the greatest possible yield in the shortest possible time, and he has reached this end by purely empirical processes. Now we know that most, if not all, reactions do not proceed to an end in the sense expressed by the chemical equation.* Every equation is true, not only when read from left to right but from right to left likewise ; there is always a state of equilibrium, lying between the two extremes, sometimes so far from each that the reaction is obviously incomplete, sometimes so near one extreme that for practical purposes it may be considered as coinciding with it, but in reality never absolutely does so. This state of equilibrium is influenced by the relative amounts or active masses of the reacting bodies, and is approached with a velocity varying from what is practically instantaneous to a slowness which can be measured only by ages. The ionized bodies reach equilibrium with exceeding rapidity, while undissociated substances, or those dissociating slowly, usually show a much smaller reaction velocity. The reactions of organic chemistry are to a great extent comparatively slow, and the equilibrium lies at a considerable distance from both extremes, hence the almost invariable wide deviation from the 'theoretical' yield of the desired products. It seems, therefore, that the study of reaction velocities and of the laws of equilibrium has a most important bearing on the work of the organic chemist, a study which he has been most tardy in taking up. The precious 'Ausgangsmaterial,' which he has spent months in preparing, is often wasted unnecessarily through ignorance of these laws, while in technical processes the case is no better ; this, too, quite apart from the contributions which could be made to physical chemistry by duly considering these points. As organic chemistry advances, relatively more and more attention will be devoted to the way in which the reaction takes place. In physiological chemistry especially is this important, because here it is not the final products themselves, as a rule, which are interesting, but the mode of their formation ; physiological chemistry is not a science of compounds, but a science of *processes* ; it is the most physico-chemical branch next to physical chemistry itself.

Most important for organic chemistry and its applications is the study of the influence which certain substances exert on the course of a reaction, without being themselves permanently changed. Such phenomena have long been known, and to them the name *catalytic* was applied by Berzelius. The most obvious characteristics of such reactions are that the foreign substance, or catalyzer, is able to exert an influence altogether out of proportion to its quantity and that it remains unaltered at the end of the process. Such catalytic reactions are well known both in inorganic and in organic chemistry. In the former I may cite the well-known influence of small quantities of platinum in decomposing hydrogen peroxide, and the influence of the oxides of nitrogen or of spongy platinum in the formation of sulphuric acid, in the latter, the inversion of cane sugar by

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* This of course does not apply to the so-called 'condensed systems.'

acids, and the phenomena of fermentation under the action of organized ferments or of enzymes. Various theories have been proposed to explain this phenomenon, but none of them seems to be universally applicable. Such theories as the temporary formation and splitting up of an additional product are not applicable in the case of the action of platinum on hydrogen peroxide. Moreover, we have not only positive or accelerating catalysis, but also negative or retarding catalysis, as in the preservation of hydrocyanic acid by traces of other acids, the retardation of the action of free oxygen on sodium sulphite by traces of alcohol, aldehyde and other organic substances, and the influence of palladium on sugar inversion. Such retarding actions can hardly be explained on any hypothesis yet offered. In recent years Ostwald has contributed greatly to the possible future solution of the problem by defining in what it consists. I have stated that every reaction proceeds to a state of equilibrium, with a certain definite reaction velocity; the element of time is, therefore, an important one in chemical changes. Ostwald has pointed out that the influence of the catalyzer is solely to modify the time factor. Reactions which may proceed ordinarily with a velocity so small as to be inappreciable in a lifetime, may be made by the presence of a catalyzer to take place in a few minutes or hours, and conversely, reactions ordinarily proceeding rapidly may be greatly retarded; but whichever occurs, the final state of equilibrium is the same, whether the catalyzer be present or not; it acts solely by modifying the reaction velocity. The knowledge of this important generalization is essential to any further progress. The importance for organic chemistry of a thorough study of catalysis can hardly be overestimated. I need only mention the important Friedel-Crafts reaction, in which anhydrous aluminium chloride is the catalyzer, and the reaction discovered by Beckmann. Probably a large portion of the chemical reactions known to us can be controlled by the use of a suitable catalyzer, being capable of acceleration or retardation at will, while many which do not occur with appreciable speed may be brought about in a limited time.

Especially important are the relations of catalysis to physiological chemistry. The unorganized ferments of the organism, the enzymes, are simply catalytic agents. Besides the well-known diastase, ptyalin, pepsin, and trypsin, there are many others, the importance of which is becoming more manifest every day. Since Buchner's discovery of zymase, the enzyme of the yeast cell, there seems to be a tendency to attribute nearly all the chemical processes of the organism, even oxidation, to enzymes. How far these views are correct is without the scope of the present subject, and I can allude to but a single recent discovery, the importance of which can hardly be overrated. A. C. Hill* has recently shown that the transformation of maltose into dextrose under the action of the enzyme maltase is in reality a reversible reaction. The equation is:

$$C_{12}H_{22}O_{11} + H_2O = 2C_6H_{12}O_6.$$

Before the reaction is complete, the action of the ferment ceases. If, on the contrary, we add the enzyme to a solution of dextrose, a portion of the latter is converted into maltose, the reaction being expressed by the above equation read from right to left. This is a striking confirmation of Ostwald's view that the catalyzer simply influences the rate, not the final condition, of the system. It has been suggested, and the view is a very plausible one, that in the living organism the very same enzymes which produce decompositions may under other conditions, in conformity with the law of

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* *Journ. Chem. Soc.* (London), 73. 634.

mass action, reverse the reactions and bring about the corresponding synthesis. Every one knows that the amount of glucose in the blood is practically constant. When, through the assimilation of carbo-hydrates the glucose in the blood of the portal vein rises above the normal, the liver cells convert it into glycogen and store it away. As soon as the glucose in the blood begins to fall below the normal, as in the condition of hunger, the glycogen begins to break up and pass into the circulation. The decomposition of the glycogen is presumably due to the action of some enzyme, and it is entirely possible that it is the same enzyme which produces the synthesis as well as the decomposition. If by any process we could remove the maltose from our dextrose-maltose solution as fast as it is found, the transformation would finally be complete. The glucose-glycogen cycle is doubtless equally subject to the law of mass action.

Not only is the subject of catalysis of immense importance in the study of the normal physiological processes. In another respect it has an equally important bearing. In recent years the toxines have assumed a prominent rôle in pathology. How is it that a chemically insignificant portion of a substance may work such enormous changes in the system? This can hardly be attributed to chemical action in the ordinary sense. Much more likely is it that the action of the toxine is catalytic, simply consisting in producing rapidly changes which without it would require time of almost indefinitely great duration. I have spoken of negative or retarding catalysis. The antitoxine is, perhaps, not to be regarded as chemically neutralizing the toxine, but rather as a retarding catalyzer, as one tending to retard the changes which the toxine would otherwise bring about. Not only the toxines and antitoxines, but many drugs which exercise an influence altogether out of proportion to their amount, may act as catalyzers rather than strictly as chemical reagents. In fact, it is not impossible to imagine that the scientific medicine of the future may be influenced largely by a better understanding of this remarkable phenomenon of catalysis.

I would call the attention of those interested in the subject of enzymes and toxines and antitoxines to the recent remarkable paper of Bredig and von Berneck on inorganic ferments,* which although essentially inorganic appears to be an important contribution to physiological chemistry. Hydrogen peroxide is a substance particularly susceptible to the action of catalyzers; its decomposition is expressed by the equation

$$2H_2O_2 = 2H_2O + O_2.$$

Among the substances which bring about this decomposition without themselves undergoing any perceptible change are platinum, gold, silver, and many other metals, the peroxides of manganese, lead and cobalt and certain enzymes. Schönbein† says, speaking of the enzymes: "It appears to me to be a highly remarkable fact that all these fermenting or catalytic substances also have the property of decomposing hydrogen peroxide after the manner of platinum, a coincidence in various activities which must give rise to the suspicion that all depend upon a common cause." And elsewhere:‡ "The results of my most recent investigations have only served to strengthen my conviction, long since expressed and often repeated, that the decomposition of hydrogen peroxide by platinum is the prototype of all fermentations." §

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* *Zeit. physik. Chemie*, 31. 258.

† *Journ. prakt. Chemie* [1], 39. 334.

‡ *Ibid* [1], 89. 335.

§ Whether or not the view of Loew (personally communicated) be true or not, that the action of most enzymes on hydrogen peroxide is due to contamination by a special enzyme *catalase*, does not affect the significance of Schönbein's statement.

This action of platinum depends on its fineness of subdivision, and the difficulty of obtaining it of uniform quality in this respect has hitherto prevented the extension of experiments to the quantitative stage. Recently, however, Bredig has succeeded in obtaining a colloidal solution of metallic platinum by volatilizing the metal in an electric arc under water.* In this form the metal exposes an enormous surface, and is capable of being measured volumetrically, and the introduction of quantitative experiments is now possible. As little as one gram-atom † of colloidal platinum diffused through seventy million liters of water shows a perceptible action on more than a million times the quantity of hydrogen peroxide. What I wish to point out as especially interesting in the work of Bredig and von Berneck is this: they find that relatively minute portions of certain substances are able to inhibit the action of the platinum, and that these are substances which exert a markedly poisonous effect on the living cell and on enzymes. 1/345,000 gram molecule per liter of hydrogen sulphide already exerts a strongly restraining action, 1/1000 gram molecule of hydrocyanic acid per liter stops it entirely, and much less is able to retard it greatly. Carbon disulphide and mercuric chloride show a similar behavior. All of these substances are powerful poisons, and Bredig uses the very expressive word 'poisoning' with reference to their restraining action on the platinum; the platinum is 'poisoned' by hydrocyanic acid. Here we have a complete parallel with what is observed in the organism, and the parallel suggests a similar cause. The platinum acts towards hydrogen peroxide as a toxine, and the hydrocyanic acid as an antitoxine; or conversely, the metal may be compared with a natural ferment, the acid to a toxine which inhibits its action. It is not impossible that such studies, conducted with purely inorganic bodies, may help to throw definite light on the nature of immunity. At least we may hope that the study of catalysis, using simple substances under conditions admitting of exact measurement, will help to solve some of the deepest problems of physiology and dispel the ignorance which hides itself under the name of *vitalism*.

Time is wanting to consider at any length the newer relations of organic chemistry to the theory of valency, especially interesting among which is the attempt of Werner to show that the supposed constant tetravalency of carbon is simply a particular phase of a general law of combination which does not come under the current valence doctrine. I may mention also that Nef regards many peculiar reactions as due to the existence of a bivalent condition of carbon, which we have hitherto recognized only in carbon monoxide. So important, indeed, is bivalent carbon, according to this savant, that he expresses the conviction "that in the chemistry of methylene is to be found a future exact scientific physiology and medicine and perhaps an explanation of the vital processes."* If this be true, physiological chemists cannot be too prompt in abandoning all other investigations for the study of bivalent carbon.

I have alluded to but a few features of the more recent progress of organic chemistry, and pointed out some of its newer tendencies. Slow as this revival is, there can be no question that the trend is away from a too narrow contemplation of the formula as a final end of study, and towards the deeper consideration of nature as the manifestation of energy. There can be no question that the continuity of all classes of chemical phenomena will be more and more recognized. Within a few years we have seen a new kind of chemistry come

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* *Zeit. Physik. Chemie.*, 31. 271.

† 193 grams.

* *Liebig's Annalen*, 298. 374.

into the field of view, narrowly called physical chemistry, but more properly designated as *general* chemistry, because its principles do not lie apart, but are the substratum of all chemical phenomena, and it is by the reaction of this on the special provinces that their true progress will be maintained. Who shall share the honor of contributing to this progress? Who shall remain behind pondering over antiquated problems? Let me recall to your minds the tenacity with which Priestley held to the doctrine of phlogiston, the persistence with which Berzelius fought the theory of substitution, the satire of Liebig on the discovery of the yeast plant, and the sneers with which Kolbe greeted the first announcement of the laws of stereochemistry. There are not wanting to-day those who take a similar position towards the newer principles and theories of general chemistry. Some of us are comparatively young, and in sympathy with the spirit of the time, but if the genius of Berzelius and Kolbe did not prevent their finally calling on the stream of progress to stop, how much more likely are we, as we grow older, to be found in a similar position if we once begin to yield to the spirit of indifference to that which does not most intimately concern us. As the truly scientific man is not he who limits his interest to a single province, but rather he who attempts to gain a rational comprehension of nature as a whole, so he only is truly a chemist in the highest sense of the word who is in sympathy with all branches of chemical investigation and with all progress, and who does not merely admit, with benevolent ignorance, but actually feels and sees that physical, inorganic, organic and physiological chemistry are not separate, but continuous with each other and with all nature. It is not enough that we occupy ourselves assiduously with researches in our chosen but often narrow field, if by much peering through the microscope of science we become myopic towards nature in general. We must, to use Kolbe's expression, frequently mount our Pegasus and soar to the heights of the scientific Parnassus. It is not the men who spend their lives in studying single groups of compounds or single phenomena, with interest in nought else, but those like van't Hoff, Ostwald, Fischer, and Hantzsch, who keep their minds open to light from all sources not the conservatives, but the radicals, who are lifting organic chemistry above the old fashioned and still fashionable structurism, and bringing about what I have called its *revival*.

H. N. Stokes.

THE WAIKURU, SERI AND YUMA LANGUAGES.

The area of the tribes of the Yuman family was visited and crossed in the earliest epoch of American exploration. These Indians became known through their large numbers and the fine exterior of their bodies, but chiefly through their spirit of opposition to the white man's progress. Scientific exploration of their country, settlements and languages began about 1850 on the Colorado and Gila Rivers. The area inhabited by them soon appeared to be largely in excess of what it had been supposed to be; for from San Luis Rey, on the Pacific Ocean, their territorial boundary extended south of the Shoshonean family to the Tonto Basin, included the Maricopas on the Gila River down to the Cocopa country, and thence again ran to the ocean.

Jesuit missionaries began working in the peninsula of California about 1697, but never met with cordial receptivity among the natives. At the southern extremity dwelt the Pericú Indians; they lived, says Venegas, from Cape San Lucas northward, beyond the harbor of La Paz; for Padre Miguel del Barco, who wrote in 1783, says