TIGHT BINGING
BOOK

MODERN THEORIES
OF
ORGANIC CHEMISTRY

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BY

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PREFACE

PROFESSOR G. N. LEWIS'S conception of the sharing of one or more electron pairs by two atoms gave a new and illuminating picture of the bonds which link carbon atoms into chains and rings, and set organic chemists the task of interpreting the reactions of carbon compounds of various types in terms of the electronic structures of the molecules. The problem was attacked ten to fifteen years ago, mainly by Professors Lapworth, Robinson, and Ingold. Considerations of the chemical evidence in the light of the electronic theory of valence led to results of great value, and it now became possible to express many of the earlier ideas in more definite and elegant language. Then followed the very fruitful alliance of organic chemistry with physics and mathematics, and a much clearer view of the principles underlying the behaviour of organic compounds has been opened up by the aid of modern physical methods of investigation, and of Planck's Quantum Theory and Schrödinger's Wave Mechanics. Some idea of the progress which the past fifteen years have witnessed may be obtained by comparing the conceptions set out in Henrich's excellent treatise dealing with Theories of Organic Chemistry, English translation dated 1922, with papers upon similar topics published in 1937.

In this volume an attempt is made to present the modern viewpoint in a concise and simple form, and to show how the new conceptions have followed logically from the earlier views. A brief and very elementary account of the physical foundations of the subject is followed by the development of the main theme of the book, viz. the application of the electronic theory to the reactions of organic compounds, and by a description of some of the better known phenomena (such as addition and substitution reactions, tautomeric changes, molecular rearrangements, and the stability of free radicals) in terms of modern ideas. An account of some of the recent developments in stereochemistry is also included.

Every effort has been made to avoid cumbersome detail, and to arrange and present the material in such a manner that it may be easily understood and assimilated by students reading for initial degrees and by those whose interests lie mainly in other fields of chemistry. The book has been based, in fact, upon lecture courses given to undergraduates over a number of years. It is inevitable that much matter of importance should be omitted from a brief and elementary survey of this type; a complete account of all aspects of theoretical organic chemistry would occupy many volumes of this size. The object of the present work is to give a general picture of the field rather than a detailed account of any particular section. The references to treatises and scientific journals (which do not claim, of course, to constitute a complete bibliography) will assist those who so desire to make a further and more comprehensive study of any sections in which they may be particularly interested. The references to journals are given in the form employed in the British Chemical Abstracts.

The many books and original memoirs which I have consulted during the preparation of the manuscript are referred to in their appropriate places. It is fitting, however, that special mention should be made of two of these which I have found more than usually helpful and illuminating; these are Professor Sidgwick's *Electronic Theory of Valency* (1927) and Professor Ingold's 'Principles of an Electronic Theory of Organic Reactions' published in *Chemical Reviews*, 1934.

I wish to take this opportunity of acknowledging my indebtedness to the late Professor Kennedy Orton; if any merit be found in this work, it must be ascribed first and foremost to his inspiring influence in early days. Then, I owe a great debt to Professor Ingold, who has read almost the whole manuscript; his helpful advice and suggestions have been of the utmost value. My thanks are also due to Professor Sidgwick and Professor Hinshelwood for their kind interest and assistance. Dr. E. D. Hughes, of University College, London, and my colleagues Dr. Dippy and Dr. Evans of the Cardiff Technical College have read the work in manuscript, and their suggestions, both those actually relating to the present work and those made during frequent discussions over a period of some years, have always proved helpful and stimulating. Professor Sugden and Professor Wardlaw have also given me assistance in portions of the work where their advice is of particular value.

I am also indebted to the Chemical Society, the Society of Chemical Industry, and the authors from whose papers several diagrams have been reproduced, for permission to include these illustrations.

Finally, it is a pleasure to express my appreciation of the efficient and considerate manner in which the officers of the Oxford University Press have carried out their share of the task, and to record my debt to my wife, whose encouragement and help in matters non-chemical have been no less valuable than the assistance of a more definite character which I have received from fellow chemists.

H. B. W.

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I

THEORIES OF CHEMICAL COMBINATION

THE ultimate particles of matter were described by Sir Isaac Newton as being 'solid, massy, hard, impenetrable, . . . incomparably harder than any porous body composed of them, even so very hard as never to wear or break in pieces', and John Dalton's famous contribution to science in 1803 consisted in the application of this ultimate particle or atom to the explanation of chemical processes. With the work of these great pioneers as its foundation, there has developed the conception of an atom of complex design, with electrons governed by quantum laws and a nucleus which is itself composite—in striking contrast with the Newtonian miniature cannon-ball. Our present views of molecular structure are equally distant from those of Lavoisier, who regarded inorganic and organic compounds as the oxides of simple and compound radicals respectively, and the long, long trail of investigation and progress, of experiment and theory, which has led from the old to the new, forms one of the most intriguing chapters in the history of science.

In the opening years of the nineteenth century the electrolytic decomposition of water (Nicholson and Carlisle, 1801), of aqueous solutions of salts (Berzelius and Hisinger, 1803), and of fused alkalis (Davy, 1807) was achieved, and upon these new discoveries Berzelius based his Dualistic Theory of Combination (1812). This hypothesis, which actually represented a development of the views of Davy, ascribed the union of atoms to opposite electrochemical characters, and it was not incompatible either with Lavoisier's original conceptions or with the Radical Theory as extended through the researches of Gay-Lussac, Liebig, Wöhler, Bunsen, and others. In the meantime, the barrier between organic and inorganic chemistry had been broken down by Wöhler's synthesis of urea (1828), and, commencing with Liebig's demonstration of the identity in composition of cyanic and fulminic acids, a number of examples of isomerism had been discovered. Thus far, however, there was no experimental evidence which was definitely contrary to a dualistic view.

But in 1839 Dumas found that three *electronegative* chlorine atoms could replace three *electropositive* hydrogens of acetic acid without change in the fundamental nature of the compound; the 'type' was unaltered. This discovery was the main cause contributing to the overthrow of dualism and the replacement of the conceptions of Berzelius by a unitary theory, the chief exponents of which were Dumas, Laurent, and Gerhardt, and which was elaborated in 1853 as Gerhardt's Theory of Types.

At the same time, the idea of valency or saturation-capacity was developing. Williamson (who is famous chiefly for his researches on the ethers) pointed out, in 1851, that different groups might replace different numbers of hydrogen atoms, and in the following year this conception was extended to atoms by Frankland, as the result of his study of the organo-metallic compounds. The suggestions thus made by Williamson and Frankland led to the Structural Theory of Kekulé and Couper, and ultimately to the modern representation of organic compounds with chains and rings of carbon atoms. So successful was the Structural Theory that there was a strong tendency for the electrochemical views of Berzelius to be completely forgotten; the forces binding atoms together were now regarded, indeed, as non-electrical in nature. The contrast between the two theories arose, of course, from the fact that Kekulé dealt with organic compounds while Berzelius had built up his views in relation to acids, bases, and salts. In spite, however, of the dominating influence of the Structural Theory, electrochemical ideas persisted in the minds of a minority of scientists, and a connexion between valency and electrical charges was postulated by Helmholtz in his well-known Faraday Lecture of 1881,[1] and rendered still more probable by the success of the Ionic Dissociation Theory of Arrhenius (1887).

Five years later, in an endeavour to represent the so-called 'molecular compounds' or 'compounds of higher order' which defied all known rules of valency, Werner postulated yet another type of linkage.[2] He spoke of atoms or groups as being 'co-ordinated' with a central atom, their number bearing no relationship to the periodic group of the element which, as Mendeléeff had pointed out, normally governs the valency; the 'co-ordination number' of an atom was quite distinct from its 'valency' as usually defined. Chemistry was

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[1] *J.C.S.* 1881, **39**, 302. In the same lecture Helmholtz pointed out how Faraday's Laws indicated that electricity, like matter, is discontinuous ('atomic') in nature.

[2] See Werner, *New Ideas on Inorganic Chemistry* (Longmans, 1911). Confirmation of Werner's theory, by the preparation of the stereoisomerides which it predicted, was obtained in 1911 (see Chapter XII).

thus left with the electrochemical, structural, and co-ordination theories, each satisfactory in its own sphere, but none capable of embracing the whole of the facts.

Now came four discoveries of the first importance, each of which was destined to play a leading part in the development of the theory of atomic and molecular structure. They were: the discovery of the inert gases by Rayleigh and Ramsay (1894), of X-rays by Röntgen (1895), of radioactivity by Becquerel (1896), and of the electron by Sir J. J. Thomson (1897). It soon became evident that the electron is a constituent of every atom,[3] and it was natural that attempts should be made to visualize valency and chemical combination in terms of this unit of negative electricity. Among the earlier electronic theories of valency were those of Sir J. J. Thomson,[4] Falk and Nelson,[5] and Fry;[6] the clear definition of chemical combination in electronic terms did not emerge, however, until 1916.

The necessity of accounting for the mass and the electrical neutrality of the atom, together with the results of Geiger and Marsden's experiments upon the scattering of α-particles, led Sir Ernest (now Lord) Rutherford to formulate his Nuclear Atom model (1911) in which a positively charged nucleus, responsible for practically the whole of the mass of the atom, was surrounded by a distribution of electrons, and Bohr's application of the Quantum Theory to this atom model in 1913 enabled him to make his distinguished contribution to the interpretation of line spectra. The work of Moseley (1913–14) upon the X-ray spectra of the elements made clear the fundamental character of the atomic number (the integer which denotes the position of the element in the natural sequence, i.e. the periodic table), and this was identified with the number of units in the positive nuclear charge,[7] and therefore, since the atom is electrically neutral, with the number of extranuclear electrons.

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[3] This conclusion was based mainly upon observations of the liberation of electrons (always identical in charge and mass) by the passage of electric discharges through gases at low pressures, by the raising of a metal to a sufficiently high temperature (thermions), by the action of ultra-violet and even visible light upon metals and to a lesser extent non-metals (photoelectric effect), and in radioactive disintegrations (β-rays). It was confirmed by the quantitative study of the Zeeman effect (the splitting of spectral lines by a magnetic field, Zeeman, 1896).

[4] *Electricity and Matter*, 1907.

[5] *J. Amer. Chem. Soc.* 1910, **32**, 1637; 1913, **35**, 1810; 1915, **37**, 1732.

[6] See Fry, *The Electronic Conception of Valence* (Longmans, 1921).

[7] The actual demonstration was given by Chadwick, *Phil. Mag.* 1920, **40**, 734.

The early calculations of Sir J. J. Thomson had indicated that these electrons must be arranged in layers or groups; in Bohr's theory they occupy different 'energy levels' denoted by quantum numbers. On the basis of the physical properties and the periodicity of the elements, Bohr has worked out the probable groupings of electrons in the various atoms,[8] and his scheme is in agreement with that of Bury which was based on chemical properties.[9] As the atomic number increases from unity upwards, a quantum group of two electrons (in helium) and then two quantum groups of eight (in neon and argon) are completed. In the transitional elements of the long periods, the last group but one expands to eighteen, and then at the end of these periods an outermost group of eight is again formed. In the elements of the rare earths the last group but two increases to thirty-two electrons. The following structures exemplify the general principles upon which the electronic arrangements are based.

Number of electrons in Quantum Groups

Quantum number	*1*	*2*	*3*	*4*	*5*	*6*
H	1					
He	2					
Li	2	1				
C	2	4				
F	2	7				
Ne	2	8				
Na	2	8	1			
Cl	2	8	7			
A	2	8	8			
K	2	8	8	1		
Ca	2	8	8	2		
Sc	2	8	9	2		
Zn	2	8	18	2		
Kr	2	8	18	8		
Xe . . .	2	8	18	18	8	
Ba	2	8	18	18	8	2
La	2	8	18	18	9	2
Ce	2	8	18	19	9	2
Lu	2	8	18	32	9	2
Hg	2	8	18	32	18	2
Rn	2	8	18	32	18	8

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[8] *Theory of Spectra and Atomic Constitution* (Cambridge, 1922).

[9] *J. Amer. Chem. Soc.* 1921, **43**, 1602.

Eight electrons are thus assigned to the outermost group in all the inert gases except helium, which has two, and an electronic group in an uncombined atom exceeds eight only when it is not the outermost.[10] The number of electrons occupying the outside group of each atom (excluding the transitional elements) is shown below:

Number of electrons in Outermost Group

Number of Electrons .	*1*	*2*		*3*	*4*	*5*	*6*	*7*	*8*
Hydrogen Period . .	H	He							
First Short Period . .	Li	Be		B	C	N	O	F	Ne
Second Short Period . .	Na	Mg		Al	Si	P	S	Cl	A
First Long Period . .	K	Ca	Transitional Elements	Ga	Ge	As	Se	Br	Kr
Second Long Period . .	Rb	Sr		In	Sn	Sb	Te	I	Xe
Third Long Period . .	Cs	Ba		Tl	Pb	Bi	Po	..	Rn
Last Period . . .	..	Ra							

The chemical properties of the element are determined mainly by these electrons in the outermost group, which are therefore termed 'valence electrons'. Periodicity is clearly due to a recurrence of the same number in this group. In the transitional elements the last group but one is in process of expansion to eighteen, and under suitable conditions the electrons of this group may function as valence electrons in addition to those of the outside group. The frequent variations in valency shown by these elements are thus accounted for.

The complete inactivity of the rare gases indicates extreme stability of their atoms, and it is logical, therefore, to ascribe chemical combination to the tendency of other atoms to take up the inert gas configuration, with its outermost group of eight electrons. This may be achieved by the complete transference of one or more electrons from one atom to another, a process which, in the early electronic theories referred to above, was assumed to occur in the formation of *all* linkages. In 1916 Kossel showed how this conception of complete electronic transference provides a satisfactory picture of the ions which are characteristic of electrolytes.[11] It obviously does not explain the binding of atoms in the molecules of non-ionizable substances, and the further problem presented by these compounds found a solution in G. N. Lewis's postulate of the sharing of a pair

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[10] Langmuir, (*J. Amer. Chem. Soc.* 1919, **41**, 868) had previously suggested arrangements in which the outermost electronic groups of the inert gases had 2, 8, 8, 18, 18, and 32 electrons respectively.

[11] *Ann. Physik*, 1916, **49**, 229.

of electrons by two atoms.[12] The two types of linking are designated '*electrovalent*' and '*covalent*' respectively, these terms being due to Langmuir,[13] and the distinction between them has been emphasized by the results of determinations of the crystal structures of electrolytes and non-electrolytes.[14]

The incorporation within the electronic theory of Werner's concept of co-ordination is based on the suggestion, made by G. N. Lewis, that an atom having one or more unshared pairs may contribute *both* electrons to its bond with another atom, provided that the latter is able to accommodate a further pair in its valence group. This view is applicable to the ammonium and borofluoride ions, the metallic ammines, and a vast number of other compounds, and the type of linkage here postulated has been discussed fully by Sidgwick[15] who terms it the '*co-ordinate*' bond. Important information regarding the presence of co-ordinate bonds in certain compounds has been obtained by the application of Sugden's Parachor.[16] In comparisons of molecular volumes it had been customary to employ values obtained either at a fixed temperature (Traube) or at the boiling-points of the liquids concerned (Kopp). Since boiling-points are approximately corresponding temperatures (equal fractions of the critical temperature), Kopp's values were long regarded as comparable, but Sugden points out that the most important factor to be considered is the internal pressure, which is of great magnitude, and is measurable with a good degree of approximation by the surface tension to which it gives rise. From MacLeod's equation for the effect of temperature upon surface tension,[17] viz. $\gamma^{\frac{1}{4}}/(D-d) = \text{const.}$ (where γ is surface tension and D and d the densities of liquid and vapour respectively, d being negligible at ordinary temperatures in comparison with D), Sugden deduces the expression $\gamma^{\frac{1}{4}}M/D = P$, where M is the molecular weight, and the constant P is termed the Parachor. The values of P for different liquids provide a measure of the relative molecular volumes under such conditions that the surface tension (and therefore the internal pressure) has a uniform

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[12] *J. Amer. Chem. Soc.* 1916, **38**, 762; *Valence and the Structure of Atoms and Molecules* (Chemical Catalog Co., New York, 1923).

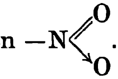
[13] Ref. 10. The characteristic properties of electrovalent and covalent compounds are discussed fully by Sidgwick, ref. 15.

[14] Sir W. H. and W. L. Bragg, *The Crystalline State*, G. Bell & Sons, 1933.

[15] *The Electronic Theory of Valency* (Clarendon Press, 1927).

[16] Sugden, *The Parachor and Valency* (G. Routledge & Sons, 1930). *J.C.S.* 1924, **125**, 1177; 1925, **127**, 1525.

[17] *Trans. Faraday Soc.* 1923, **19**, 38.

value, i.e. the conditions which are regarded as comparable. For a given compound, P has proved to be the sum of a series of terms, each referring to a particular atom or linkage, and a consideration of some 200 liquids enabled Sugden to compute atomic and constitutive parachors. A striking result which emerged from this work was the discovery that linkages conventionally written as 'double bonds' are of two types; the $C{=}C$, $C{=}N$, $C{=}O$, $C{=}S$, and $N{=}O$ bonds lead to an increase of 23·2 units in the parachor, while the 'double' bonds between oxygen and phosphorus or sulphur in derivatives of phosphoric, sulphurous, and sulphuric acids decrease its value by a small amount averaging 1·6 units. Linkages of the former type are identified with four-electron or non-polar double bonds. and those of the latter type are interpreted as co-ordinate bonds (they have been referred to by Sugden as 'semipolar double bonds' and by Lowry as 'mixed double bonds'[18]). Examination of a number of compounds containing the nitro-group led to the conclusion that one of the oxygens is linked by a four-electron bond and the other by a co-ordinate bond, and the group is therefore written  $-\mathrm{N}\begin{smallmatrix}/\!\!/\mathrm{O}\\ \searrow\mathrm{O}\end{smallmatrix}$.[19] Such a formula is in harmony with the fact that nitrogen never forms more than four covalent linkages, the fifth valency of 'pentavalent' nitrogen always being an electrovalency. Stereochemical evidence further indicates the presence of co-ordinate bonds in compounds such as amine oxides, sulphinic acids, and sulphoxides.[20]

In all the compounds referred to above the number of co-ordinate bonds is just that required to preserve the octet (group of eight valence electrons) of the central atom; for this and other reasons Sugden has suggested that the octet is the maximum valence group, and that, where more than four atoms are covalently linked to a central atom, bonds of one electron are present. Much evidence has been put forward by Sidgwick, however, in favour of the view that the valence group may expand beyond eight. His Covalency Rule[21] limits the covalency of an element in accordance with the *period* in which it stands in the Periodic Table, the following covalency maxima being postulated: H, 4 electrons;[22] elements of first short period (Li to F), 8 electrons; elements of second short period (Na to Cl)

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[18] *J.C.S.* 1923, **123**, 822.

[19] See further Chap. V, p. 60.

[20] See Chap. XII.

[21] Ref. 15. *Ann. Reports*, 1933, **30**, 110.

[22] On 'two-covalent' hydrogen, see p. 202.

and first long period (K to Br), 12 electrons; elements of higher atomic number, 16 electrons.

The above summary will serve to indicate how the electrochemical, structural, and co-ordination theories of chemical combination have been included in one comprehensive electronic theory of valency. Nothing has been said as yet, however, regarding the physical interpretation of the electrovalent and covalent bonds. It is evident that the force acting between the ions of an electrolyte is the attraction of opposite charges; the bond is of an electrostatic character. The manner in which atoms are bound by electron sharing, however, presents a far more complex problem, which is now being approached from the standpoint of the new Quantum or Wave Mechanics. Moreover, the recent development of physical methods of investigation has yielded much information regarding important details such as the lengths of covalent bonds (interatomic distances), the proportions in which the electrons are shared, the angles between linkages, and the strengths of the bonds, and much of this work is dependent upon the Quantum Theory. This chapter will therefore be concluded with a short account of the conceptions underlying the Quantum Theory and the new wave-mechanical treatment of atomic problems.

Applications of the Quantum Theory.[23] In 1900 Planck found that the experimental facts concerning thermal radiation, which could not be harmonized with the laws of classical mechanics, received a satisfactory interpretation on the basis of the postulate that the emission of energy occurred in definite small elements or 'quanta', the magnitude of which was given by the product of the frequency and a constant h; $E = h\nu$. This discovery marks the origin of the view that energy, like matter and electricity, is discontinuous or 'atomic' in nature. The quantity h is now known as Planck's Constant, and is a universal constant like the velocity of light or the charge on the electron. Five years later, Einstein applied Planck's theory to the interpretation of the photoelectric effect, i.e. the emission of electrons by a large number of metals and some gases under

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[23] For a clear account of the Quantum Theory the reader is referred to Castelfranchi's *Recent Advances in Atomic Physics*, vol. ii (Churchill, 1932). A simple account of its applications to Chemistry may be found in *Quantum Chemistry* by Haas (Constable & Co., 1930). The essentials of the wave-mechanical treatment of chemical problems are dealt with admirably in summaries by Hinshelwood, *Ann Reports*, 1930, **27**, 12, and *Kinetics of Chemical Change in Gaseous Systems*, 3rd edition (Clarendon Press, 1933). References to the original literature are given in these works, and are not repeated here.

the influence of X-rays, ultra-violet light, and even visible light. He was able to interpret the observed facts by postulating light quanta or photons, the magnitude of which depended solely upon the colour (frequency). In Einstein's hands, too, the quantum theory proved capable of yielding a law which correctly represented the experimental observations (Nernst and others) of the variation of specific heats with temperature, this law being perfected by Debye in 1912. The value of the Quantum Theory had thus been demonstrated in three directions when, in 1913, Bohr applied it to the Rutherford Atom and achieved remarkable success in the interpretation of the line spectrum of hydrogen. Classical mechanics and electrodynamics could not account for the stability of the atom as represented by the nuclear model. If the electrons were assumed to be at rest, some wholly unknown law of force was necessary;[24] if they circulated round the nucleus, energy would be radiated (since their velocities would continually change in direction), and the atom would thus suffer spontaneous destruction. Bohr now postulated that, while the electron actually circulates in an orbit in accordance with the inverse square law, only certain so-called 'stationary' orbits are possible, these being defined by the condition that the electron must possess a whole number of quanta of energy, i.e. $E = nh\nu$. He made the further assumption that no energy is radiated while the electron remains in one of these orbits. The whole number n was termed the 'quantum number' of the orbit, and Bohr thus introduced the conception of different states of the atom associated with different amounts of energy, the energy levels being defined by the quantum numbers. It may here be pointed out that, although the modern quantum theory has relinquished the conception of precise orbits, the energy levels retain their significance. Bohr's final postulate was that, under the influences which give rise to the emission of radiation, the electron is drawn out into a higher energy level, and its return (by a 'quantum jump') to the lower level gives rise to radiation of frequency $\nu = (E - E')/h$ where E and E' represent its energies in the two levels. On the basis of these postulates he calculated the frequencies of the lines in the hydrogen spectrum (circular orbits being assumed) as

$$\nu = \frac{2\pi^2 me^4}{h^3}(1/n_1^2 - 1/n_2^2) = R(1/n_1^2 - 1/n_2^2)$$

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[24] Such a law was postulated by Sir J. J. Thomson, *Phil. Mag.* 1921, **41**, 510.

(where m and e represent respectively the mass and charge of the electron, h is Planck's constant, and n_1 and n_2 are quantum numbers). This expression is identical with the Balmer formula for the line spectrum of hydrogen in the visible, ultra-violet, and infra-red regions, and the term R, calculated from the known values of the constants involved, was in quite good agreement with the experimentally determined value of the Rydberg Constant. Still better agreement was obtained when allowance was made for the motion of the nucleus, and the 'fine structure' of the lines was accounted for by Sommerfeld's postulate (1918) of elliptical in addition to circular orbits. The Bohr-Sommerfeld theory was thus remarkably successful in interpreting the line spectrum of hydrogen, and also that of ionized helium (spark spectrum). The spectra of other elements resemble that of hydrogen sufficiently closely to indicate that an interpretation might be found on similar lines, but the general problem of determining the orbits of more than one electron remained insoluble. Even the helium atom (with two electrons) and the simplest of all molecules, that of hydrogen, could not be dealt with by Bohr's method, the usefulness of which was thus very limited. Moreover, the selection of the stationary states was purely arbitrary, and the absence of any radiation when the electron circulated in one of these orbits found no explanation. The Bohr-Sommerfeld theory was clearly not altogether satisfactory.

From 1924 onwards a new line of attack upon the problems of atomic and molecular structure has been developed; it is the counterpart of a dual procedure employed of late years in the study of optical problems. The long struggle between the corpuscular and the undulatory theories of light is famous in the history of physics; in the first half of the nineteenth century the latter, as expounded by Fresnel and Young, gained a complete triumph over the Newtonian conception. In 1905, however, Einstein postulated light quanta in order to interpret the photoelectric effect; both this effect and its converse (the production of radiation when electrons impinge upon matter as in X-ray tubes) proceed as if the radiation were composed of small discrete units. Simultaneously with the photoelectric effect there occurs the Compton Effect, first observed in 1923; a portion of the incident radiation is scattered with a reduced frequency, and this is ascribed to the collision of a quantum with an electron, to which the energy is partially transferred with the production of a quantum of lower energy, and therefore lower frequency since $E = h\nu$. It is necessary, indeed, to postulate the existence of light quanta which obey the laws of collision between elastic bodies. Allied to the Compton Effect is the phenomenon observed by Sir C. V. Raman in 1928;[25] a quantum here encounters a molecule, atom, or ion, the energy level of which is raised with a corresponding reduction in the energy (and hence frequency) of the quantum itself.

Einstein's postulate of light quanta has thus been verified in several ways, with the result that of recent years a partial return to the corpuscular conception of light has taken place. Although, however, properties characteristic of matter can be ascribed to light, the undulatory theory still retains its value, and is necessary for the understanding of phenomena such as interference, diffraction, polarization, reflection, and refraction. The two points of view can be harmonized by assuming that the square of the amplitude of vibration (which, on the undulatory theory, is a measure of the intensity) gives the probability that a quantum is situated at a given spot. Either approach may be used, according to the requirements of the problem under consideration.

In 1924 de Broglie suggested the reversal of the process which had proved so successful in optics, by extending to matter the undulatory characters of light, and this procedure has received justification in observations of the diffraction of electrons, similar to that of X-rays, by metals and other substances. de Broglie's suggestion was followed by the development of Schrödinger's equation in 1926.[26] It has the form of the general equation for a three-dimensional vibrating system; the vibrating quantity is written ψ, and its frequency is E/h. The new viewpoint does not remove the significance of the electron and the atom as definite individual particles, but the *behaviour* of electronic systems is described in terms of a wave function. Otherwise expressed, the laws which govern atomic phenomena can be represented by differential equations of the same form as those which are normally applicable to wave motion, and in place of the orbits of the Bohr theory we are provided with the conception

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[25] See Chap. II.

[26] In 1925 Heisenberg developed a new quantum mechanics, in which he relinquished any mechanical model, and employed only quantities which are observable experimentally. Heisenberg's mechanics leads to the same results as Schrödinger's, though by a rather different route.

of the electrons moving in a manner defined by such an equation. The wave-mechanical view of matter is completely analogous to the method employed in treating optical problems; it provides a quantity the square of which represents the probability that the electron is situated at a given point.

Schrödinger's equation is expressed in terms of energy, and, in accordance with a general characteristic of differential equations of this type, there are characteristic values (eigenvalues) of the energy for which, and for which alone, the equation has solutions which are finite, continuous, and single-valued. These eigenvalues actually represent the energy levels of the Bohr theory. Bohr's arbitrary selection of the stationary states thus becomes a deduction from the wave equation, the energy states of the atom being determined by the eigenvalues.

In chemistry the main importance of the new developments lies in the phenomenon of quantum-mechanical resonance, which could not have been predicted otherwise. This has led to an interpretation, first given by Heitler and London, of the forces involved in chemical combination. The energy states of each of two isolated hydrogen atoms are determined by the solutions of the appropriate wave equation, and it is therefore to be expected that when the atoms interact a phenomenon analogous to resonance will occur. This is best understood by reference to the mechanical illustration of two equal pendulums connected at the point of suspension (e.g. suspended from the same flexible string).[27] The motion of each is modified by the other, and if their phases are the same or exactly opposed they will oscillate with a joint frequency which is either greater or less than the independent frequency of either. Similarly, two isolated hydrogen atoms have each a wave function of frequency E/h, but when they interact the combined wave equation has two solutions, the energies corresponding to which are in one case greater and in the other less than the sum of the individual energies of the two isolated atoms. The solution giving the minimum value of the energy represents chemical combination, and the values thus calculated wave-mechanically for the energy of dissociation of the hydrogen molecule and the separation of the nuclei are in agreement with those from spectroscopic data.

The final step in the Heitler-London theory is the application of

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[27] Hinshelwood, ref. 23.

Pauli's Exclusion Principle. Analysis of the spectra of atoms having more than one electron shows that the lines can be classified in series. Four such series can be distinguished, and are designated principal, sharp, diffuse, and fundamental. The lines of a given series have definite characteristics, and a physical agency such as a magnetic field affects all the lines of one series in a similar manner. Further, the terms representing the energy levels of the alkali metals (which, like hydrogen, consist of a core with one valence electron), when represented by the expression R/n^2, give values of n which are not integral, and this is interpreted by supposing that the term is actually composite and should be written $R/(n+\alpha)^2$, where α is called the 'quantum defect' and has a constant value throughout one series. The inference is drawn that the electrons can exist in states not accounted for by one quantum number alone, and we thus arrive at the conception of a subdivision of the principal energy levels into a number of subordinate levels. In addition to the *principal* quantum number n, therefore, a second or *azimuthal* quantum number is necessary; this is written l, and is assigned values from 0 to $n-1$. It is conventional to refer to electrons in energy states denoted by the azimuthal quantum numbers 0, 1, 2, and 3 as s, p, d, and f electrons respectively, the titles being derived from the initial letters of the spectral series to which they give rise (for example, a transition from an s state to a p state gives a line in the sharp series, and so on). The limit of $n-1$ for the azimuthal quantum number restricts the 1-quantum group ($n = 1$) to s electrons, the 2-quantum group ($n = 2$) to s and p electrons, and the 3-quantum group ($n = 3$) to s, p, and d electrons. The possible states of the electron, as indicated by the multiplicity of line spectra, are not yet provided for, however, and two further quantum numbers are necessary. One is the *magnetic* quantum number, having values from $-l$ to $+l$, and the other is the *spin* quantum number. This last describes the direction of spin of the electron, and hence must have two equal and opposite values, which are written $\pm\frac{1}{2}$. A complete description of every electron in the atom is possible in terms of these four numbers. The Pauli Principle states that, in a single atom, no two electrons can exist in exactly the same quantum state, i.e. they cannot coincide in all four numbers, and the number of electrons in a group of given principal quantum number, as calculated from this principle, agrees with that required for the interpretation of the periodic system as suggested by Bohr. In the case of the hydrogen molecule, both electrons belong to each atom, and they must therefore differ in at least one of the quantum numbers. Since they are identical energetically, Heitler and London conclude that they differ in the spin number, and they thus visualize the formation of the covalent bond as the pairing of electrons with opposite directions of spin.

The Heitler-London treatment of the hydrogen molecule has been extended to less simple cases by Pauling, Slater, and others, and this mathematical approach to the problem of molecular structure is termed the 'Method of Localized Pairs'. Meanwhile, from 1929 onwards, Hund, Lennard-Jones, and Mulliken have attacked the problem somewhat differently, by the 'Method of Molecular Orbitals'. The molecule is treated as a whole; the definite partnership between a given electron and a given nucleus is largely abandoned, and the electrons are regarded as wandering from nucleus to nucleus, their movements being described with reference to *molecular orbitals.* Some, however, are still considered to be localized to a greater or lesser extent, and these are assigned to *atomic orbitals.* Both the electron pair method and the molecular orbital method are approximations, and the exact truth probably lies intermediate between them.[28] The latter cannot be described as a wave-mechanical theory of valency, however, and the conception of the two-electron bond, as originally put forward by G. N. Lewis, still provides the most useful picture of the molecule for the purpose of interpreting chemical phenomena.

It will be appropriate to conclude this chapter with the following quotation, which expresses admirably the relationship of the new mechanics to theoretical organic chemistry:

> 'The success with which organic chemistry has solved its problems by the aid of its own conceptions about the nature of chemical bonds has, during the last few years, stimulated theoretical physicists to attempt the translation of these conceptions into the language of quantum mechanics. It is as well to realize at the outset that even the simplest problems of organic chemistry are much too complicated for anything like a complete and fundamental treatment not based upon drastic simplification and not introducing a considerable amount of assumption. The theoretical investi-

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[28] For a concise treatment of both methods, and references to relevant literature, see Penney, *The Quantum Theory of Valency* (Methuen & Co., 1935).

gation, therefore, can hardly be expected to predict new phenomena in organic chemistry. Nevertheless, it is satisfactory that the known phenomena can be described in terms acceptable to physicists, and that the rules can be formulated in ways which at least are not inconsistent with quantum-mechanical principles.'[29]

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[29] Hinshelwood, *Ann. Reports*, 1932, **29**, 20.

II

THE NEW PHYSICAL METHODS OF INVESTIGATION

THE recent advances in theoretical organic chemistry have been greatly assisted, and to a large extent, indeed, made possible, by the development of a number of purely physical methods of investigation. The knowledge thus gained regarding the dimensions and other properties of the bonds by which atoms are linked has been applied to the solution of many problems relating to structure, reactivity, and stereochemical configuration. A brief account of some of these new physical methods is given in this chapter.

1. *X-Ray Methods*[1]

X-rays were discovered by Röntgen in 1895, and examination of their behaviour showed that, while in many respects they resembled visible light, there were nevertheless marked differences between the two types of radiation. In particular, X-rays were not diffracted by the ordinary gratings; this was due to the fact that their wave-length (of the order 10^{-7} to 10^{-9} cm. as compared with 10^{-5} cm. for visible light) was much shorter than the distances between the lines of any grating that could be constructed. In 1912, however, Laue suggested that a crystal might be employed for the purpose, and the correctness of this suggestion was demonstrated experimentally by Friedrich and Knipping. The distances between the parallel planes of which the crystal is composed are of the same order of magnitude as the wave-length of X-rays, and this made possible their diffraction. Friedrich and Knipping passed a beam of the radiation through a crystal of zinc blende in a direction parallel to one of the axes of symmetry, and a photographic plate exposed to the emergent beam bore a symmetrical distribution of spots. They had thus obtained an X-ray spectrum for the first time, since each spot represented a ray of a particular wave-length. The classic investigations of Sir W. H. Bragg and his son, W. L. Bragg, followed. In their X-ray spectrometer the crystal was used as a *reflection* grating, and the resulting spectra

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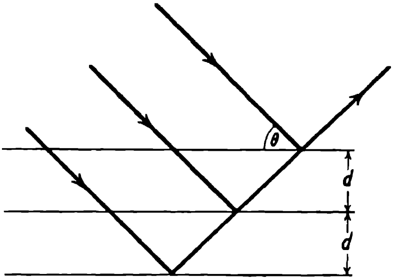
[1] See Sir W. H. and W. L. Bragg, *The Crystalline State* (G. Bell & Sons, 1933). Recent work is summarized in the 'Crystallography' section of the *Annual Reports*, 1933, 1935, and 1936.

were much easier to interpret than those of the 'Laue photographs'. When a beam of monochromatic X-radiation of wave-length λ impinges on a crystal at an angle of incidence θ, some of the rays are reflected from the surface, and others from the planes in the interior. The resultant beam is the sum of all these. The figure below illustrates the routes of rays which leave the crystal along the same path, and it is evident that such rays will either reinforce or destroy one another. From the geometry of the figure it can be shown very simply that reinforcement will occur if the angle of incidence is given by the expression $n\lambda = 2d \sin\theta$, where d is the distance between successive planes of the crystal, and n is a whole number. The reflected beam is of appreciable intensity only for these particular values of θ, and therefore, by measuring the angles of incidence at which such a beam is obtained, a relationship between λ and d is found. These angles were determined by passing the reflected beam into an ionization chamber (containing an easily ionizable gas such as sulphur dioxide) and observing an electroscope into which the ions of one sign were driven by an electric field.



The structures of a large number of crystals have been elucidated in this way, and interatomic distances calculated. A similar procedure (in which, however, the spectra were photographed) was employed by Moseley in his determination of atomic numbers from the wavelengths of the characteristic X-rays of various elements.[2] These rays are produced when the element (or a compound containing it) is subjected to bombardment by fast-moving electrons (cathode rays); by using a crystal for which the constant d was known Moseley was able to measure their wave-lengths, which were found to bear a simple relation to the atomic numbers. The application of Moseley's

[2] *Phil. Mag.* 1913, **26**, 1024; 1914, **27**, 703.

method of X-ray analysis has resulted in the discovery of at least four of the six elements which were then missing.

The original Bragg method required fairly large, well-formed crystals, but it has since been extended by Debye and others in such a way as to make it applicable to crystalline powders, and even to liquids and gases; interatomic distances can thus be determined with considerable accuracy for a wide range of substances. An analogous method, which is likely to increase in importance, involves the study of electron diffraction in gases.[3]

From the chemical point of view, the most significant results of the earlier X-ray work were the following: (1) the observed contrast between salts where only the individual ions were detected and covalent compounds in which the whole molecules were discernible; (2) the confirmation of the tetrahedral arrangement of the valencies of carbon from the structure of diamond; and (3) the demonstration of the actual existence of a hexagon of carbon atoms in aromatic compounds. More recent applications to the problems of organic chemistry include Mrs. Lonsdale's demonstration of the uniplanar (flat) character of the aromatic nucleus in hexamethyl- and hexachloro-benzenes,[4] and numerous instances of the use of X-ray methods in the determination of chemical structure, as exemplified by Bernal's contribution to the problem of the ring system of the sterols and allied compounds (cholane group).[5] The configurations of the valencies of a number of elements other than carbon have also been determined by X-ray examination (see Chap. XII).

2. *Visible and Infra-red Spectra*[6]

The study of absorption spectra in the visible and infra-red regions has become, of recent years, a valuable source of information. Apart from variations in kinetic energy of translation, the only energy changes which an *atom* can undergo are due to the movement of one or more electrons into other levels. The energy is purely *electronic*,

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[3] See Glasstone, *Recent Advances in General Chemistry* (Churchill, 1936), Chap. V.

[4] *Proc. Roy. Soc.* 1929, **123**, A, 494; 1931, **133**, A, 536.

[5] See *Ann. Reports*, 1933, **30**, 423, and references there cited.

[6] For a fuller account see Glasstone, *Recent Advances in Physical Chemistry*, 3rd edition (Churchill, 1936); also, Barratt, *Ann. Reports*, 1926, **23**, 304. The results of spectroscopic measurements are discussed by Sidgwick in *The Covalent Link in Chemistry* (Cornell University Press, New York, 1933); see also Sidgwick and Bowen, *Ann. Reports*, 1931, **28**, 367. References to original papers and larger treatises may be found in the above.

and the spectra to which the transitions give rise consist of series of lines (which, however, have a fine structure owing to the subsidiary levels, see Chap. I). The case of a molecule is more complex, however. Electronic transitions can occur here also, and the frequency of the resulting radiation is governed by the expression $h\nu = E_e - E'_e$, the quantum being of such magnitude that the spectrum is in the visible or ultra-violet region. Changes in *electronic* energy, however, are always accompanied by changes in *vibrational* and *rotational* energy. Taking the simplest case, namely, that of a diatomic molecule, there are variations both in the amplitude of oscillation of the nuclei in the line joining their centres, and in the frequency of rotation of the whole molecule about an axis perpendicular to this line; these changes are, of course, responsible for the well-known difference in the ratio of the specific heats of monatomic and diatomic gases. The total energy of the molecule, excluding kinetic energy, is therefore given by the expression

$$E = E_e + E_v + E_r,$$

and the complete energy change involved when an electronic transition occurs is

$$h\nu = (E_e - E'_e) + (E_v - E'_v) + (E_r - E'_r).$$

The vibrational quanta are smaller (by a factor of 0·1 to 0·01) than electronic quanta, and rotational quanta are much smaller still (about 0·01 of vibrational). The spectra produced by changes in the electronic energy levels are therefore series of bands, each band consisting of lines so closely spaced as to appear continuous except when observed with an instrument of high resolving power. Each line in the band represents a change in vibrational energy, and has a fine structure due to rotational changes.

The energy levels of a molecule are shown diagrammatically in Fig. 1. The lines in I represent different electronic states; for each of these there are a number of vibrational levels shown by the thinner lines in II; the dotted lines in III represent the rotational states associated with each vibrational level. The general form of an electronic band spectrum will be clear from an inspection of Fig. 2, in which the bands due to electronic transitions are seen to consist of lines indicating changes in vibrational energy, each line having a fine structure on account of accompanying rotational changes.[7]

[7] Diagrams of this type are given by Allmand, *The Nature of Simple Molecules and of Elementary Processes* (Institute of Chemistry, 1932).

Studies of electronic band spectra have led to the discovery of isotopes of oxygen, carbon, and nitrogen, which are present in proportions too small for detection by the mass spectrograph, and also to the observation of two forms of the hydrogen molecule, called *ortho-* and *para-*hydrogen, in which the nuclei have respectively the same and opposite directions of spin. Owing to the complexity of electronic band spectra, however, and the consequent difficulty of interpretation, the examination of vibration-rotation spectra is usually preferred. The vibrational quantum is of such small magnitude that these spectra, which arise from changes in vibrational energy with accompanying rotational changes, are in the near infra-red. The energy change is now

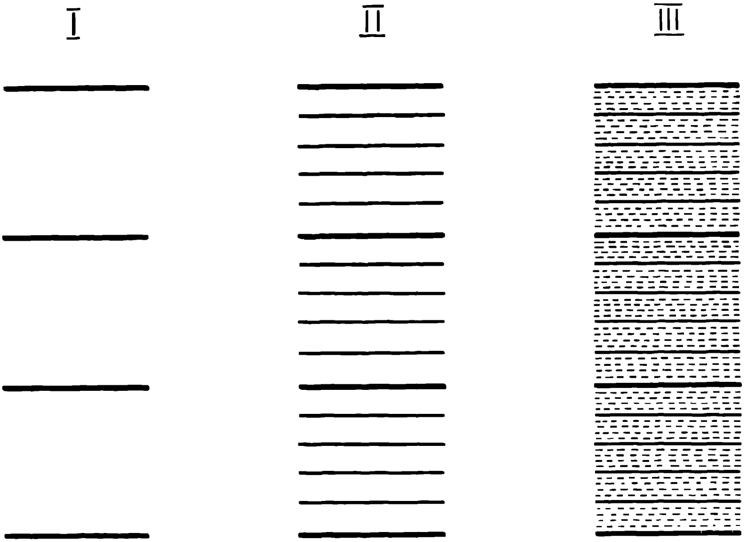

Fig. 1.

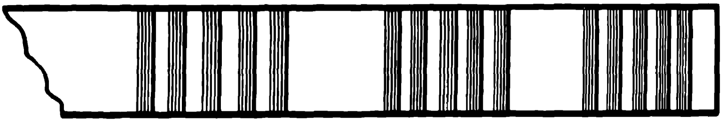

Fig. 2.

$$h\nu = (E_v - E'_v) + (E_r - E'_r),$$

and, in a diatomic molecule, for each vibrational change the spectrum consists of two series of lines (P and R branches), one on either side of a central line (Q branch, not observed) having the fundamental frequency of vibration of the molecule. The moment of inertia of the molecule, and hence the distance apart of the nuclei, can thus be determined. The same quantities have also been found, in some cases, from pure rotation spectra in the far infra-red. These are the least complicated of all molecular spectra, and for a diatomic molecule the moment of inertia I is got from the simple formula

$$\nu = nh/4\pi^2 I,$$

where n is an integer and h is Planck's constant; the internuclear distance r then follows from the well-known expression $I = \frac{m_1 m_2}{m_1+m_2} r^2$, where m_1 and m_2 are the masses of the atoms. The observation of pure rotation spectra is very difficult on the experimental side, however, and a balance between difficulties of experiment and interpretation is found in the vibration-rotation spectra for which, to a good degree of approximation, $\nu = \omega_0 + nh/4\pi^2 I$, where ω_0 is the fundamental vibrational frequency of the molecule. It is evident that, as the number of atoms in a molecule increases above two, there is a corresponding increase in the complexity of the spectra of all types.

Even greater importance attaches to the study of the effect first observed by Sir C. V. Raman in 1928, though predicted by Smekal at an earlier date.[8] When a beam of monochromatic light falls on a transparent substance—solid, liquid, or gas—the greater part undergoes no change of frequency, but at the same time a small proportion appears with a modified (usually smaller) frequency. The incident light quantum changes (as a rule raises) the energy level of a molecule, atom, or ion which it encounters, with a corresponding change in its own energy content and therefore frequency,[9] i.e.

$$\underset{\text{(normal)}}{\text{Molecule}}+\text{Radiation} \rightleftarrows \underset{\text{(excited)}}{\text{Molecule}}+\underset{\substack{\text{(degraded}\\ \text{frequency)}}}{\text{Radiation}}$$

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[8] Raman and Krishnan, *Nature*, 1928, **121**, 501; *Indian J. Physics*, 1928, **2**, 399. See also Kohlrausch, *Der Smekal-Raman Effekt* (Springer, Berlin, 1931). Useful summaries are as follows; Raman, *Trans. Faraday Soc.* 1929, **25**, 781; Hunter, *Ann. Reports*, 1929, **26**, 16; Woodward, ibid. 1934, **31**, 21. For a collection of Raman spectra data see *Chem. Reviews*, 1933, **13**, 345; 1936, **18**, 1.

[9] Comparison with the photoelectric and Compton effects is instructive. In the former the quantum is *completely* absorbed and ejects an electron from an atom with considerable velocity; in the latter the quantum gives up a portion of its energy to an *electron* and appears with a degraded frequency (see Chap. I, p. 10).

The difference between the frequencies of the initial and scattered radiation is called the Raman Frequency, and is governed *solely* by the nature of the molecule. As a rule the energy transferred is utilized completely in raising the vibrational level, and hence the Raman spectrum is not complicated by rotational changes; the Raman effect, indeed, makes possible the observation of the '*Q* branch' of the vibration-rotation spectrum without the experimental difficulties of working in the infra-red. Rotational changes, which sometimes occur, are indicated by lines of frequency very near to that of the exciting radiation.

Raman spectra have been employed in qualitative and even quantitative analysis, and in investigations of the degree of ionization of electrolytes. In the case of molecules of organic compounds, particular lines have been identified with definite linkages, and the natural vibrational frequencies of bonds such as C—H, C=C, C=O, C≡C, and C≡N are thus calculated; in general, those of the two-, four-, and six-electron bonds are of the order of 3,000, 1,600, and 2,000 cm.^{-1} respectively, and observations of Raman spectra have thus given information regarding the multiplicity of certain linkages.[10] Moreover, since the vibrational frequency is dependent upon the masses of the atoms concerned and upon the force constant of the linkage (the force which comes into play when the nuclei are displaced unit distance from their normal positions), the latter can be determined. Its significance lies in the fact that it is a measure of the strength of the bond.

The replacement of an element by its isotope leaves the force constant of the linkage practically unchanged, and the effect of such substitution upon the vibrational frequencies is therefore due to the change in the atomic mass. It is thus possible to calculate numerical relationships between the frequencies of vibration in the two molecules and to compare them with those observed. This method has recently been employed by Ingold and his collaborators[11] in a series of investigations upon the structure of benzene, in which its infra-red and Raman spectra have been compared with those of hexadeuterobenzene, C_6D_6 (where D represents deuterium, the heavy isotope of hydrogen).

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[10] An example is given in Chap. VII.

[11] *J.C.S.* 1936, 912, and following papers.

3. *Dipole Moments*[12]

In Sugden's formula for the nitro-group[13] the co-ordinate bond is obviously dipolar, the nitrogen atom being charged positively and one of the oxygens negatively; this is, indeed, a general property of co-ordinate bonds formed between neutral atoms or molecules, since one atom gives and the other accepts a share in an electron pair.[14] Dipolar character is not peculiar to co-ordinate bonds, however. Thus, the chemical behaviour of the carbonyl group indicates that the carbon and the oxygen are positive and negative respectively; for example, in an addition reaction such as cyanohydrin formation, hydrogen always attaches itself to oxygen and the anionic portion of the addendum unites with carbon. Chemical evidence would thus lead to the representation $\rangle\overset{\delta+}{C}=\overset{\delta-}{O}$, where $\delta+$ and $\delta-$ denote fractional positive and negative charges respectively.

The unequal sharing of the electron pair forming a covalent bond was postulated by G. N. Lewis: 'the pair of electrons which constitutes the bond may lie between two atomic centres in such a position that there is no electric polarization, or it may be shifted toward one or the other atom in order to give to that atom a negative, and consequently to the other atom a positive charge'.[15] If the latter be the case, the bond is an electrical dipole,[16] equivalent to a rod with equal and opposite charges at the ends, and having a moment given by the product of either charge and the distance between them.

Since all molecules contain both positively and negatively charged particles (nuclei and electrons), there will of necessity be an 'electrical centre' (analogous to centre of gravity) of the positive charges and

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[12] For comprehensive accounts of this subject, see Debye, *Polar Molecules* (Chemical Catalog Co., New York, 1929); Smyth, *Dielectric Constant and Molecular Structure* (American Chemical Society Monograph Series, New York, 1931). Summaries may be found as follows: Sidgwick, ref. 6; Glasstone, ref. 6; Smyth, *Chem. Reviews*, 1929, 6, 549; Williams, ibid., p. 589. A list of dipole moments, with full references, is given in *Trans. Faraday Soc.*, Sept. 1934, appendix.

[13] See Chap. I, p. 7.

[14] A similar remark does not apply, for obvious reasons, to a bond formed by co-ordination of an ion with a neutral molecule as in the ammonium and borofluoride ions. See Sidgwick, *The Electronic Theory of Valency* (Oxford University Press, 1927), p. 69.

[15] *Valence and the Structure of Atoms and Molecules* (Chemical Catalog Co., New York, 1923), p. 83.

[16] This must not be confused with the 'electrovalent' bond. See Sidgwick, *Covalent Link*, p. 126 (footnote).

a similar centre of the negative electricity, and if these do not coincide the molecule *as a whole* will be an electrical dipole. The electrical moment will be zero only (*a*) if every pair of electrons is shared equally by the atoms concerned,[17] or (*b*) if the molecule is perfectly symmetrical, like methane, so that the moments cancel. In actual fact, the only completely non-polar bonds are those between like atoms, as in the molecules H_2, N_2, or O_2, and hence the existence of a molecular electric moment is the rule and not the exception.

Measurement of Dipole Moments. The conception of 'polar molecules' was first arrived at on purely physical grounds. Apart from any permanent *polarization* of the type described above, all molecules have a definite *polarizability*. Thus, if the space between two charged plates be filled with any medium, the electric field induces a displacement of the positive and negative electrical centres of the molecules of the medium; they become *temporarily* dipolar, the positive ends being towards the negative pole and vice versa. The electrical field is thus opposed, and the ratio of its strength in a vacuum to its strength under these conditions is the dielectric constant (ϵ) of the medium. The 'molecular polarizability' (α) is then given, according to the well-known Clausius-Mosotti Law, by the expression

$$\frac{\epsilon-1}{\epsilon+2}\frac{M}{d} = \frac{4\pi N}{3}\alpha,$$

where M and d are respectively the molecular weight and density of the substance, and N is the Avogadro Number (number of molecules per gram-molecule). This equation contains no temperature term, and yet the dielectric constants of a number of compounds were found to vary with temperature; for these compounds, too, Maxwell's Law equating the dielectric constant with the square of the refractive index ($\epsilon = n^2$) was invalid. Accordingly, Debye suggested in 1912[18] that the molecules of these substances are permanently dipolar. The dipoles are normally oriented at random, but in an electric field they tend to aline themselves with their ends towards the oppositely charged pole. Thus, the permanent polarization is superimposed upon the induced polarization, $P = P_I + P_\mu$. The term P_I in this expression is that given by the Clausius-Mosotti equation, and since

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[17] This is really a simplified statement of the necessary conditions. The *unshared* electrons must also be arranged symmetrically with respect to their nuclei; compare Sidgwick, op. cit., p. 143 (footnote).

[18] *Physikal. Z.* 1912, **13**, 97.

the orientation of the dipoles will be opposed by thermal agitation the second term P_μ is dependent upon temperature. Debye thus arrived at a mathematical relationship of the form $P = A+B/T$, the complete expression being

$$\frac{\epsilon-1}{\epsilon+2}\frac{M}{d} = \frac{4\pi N}{3}\left(\alpha+\frac{\mu^2}{3kT}\right),$$

where μ is the dipole moment of the molecules, T is absolute temperature, and k is the gas constant per molecule ($k = R/N$).

The dipole moments of a large number of molecules have now been determined. The most accurate method depends upon the effect of temperature upon the dielectric constant of the substance in the vapour state. In Debye's equation $P = A+B/T$, the relationship between P and $1/T$ is linear; if the substance is non-polar, $B = 0$ and the line is parallel to the $1/T$ axis, while for a polar molecule its slope gives the value of $4\pi N\mu^2/9k$. The method is also applicable to dilute solutions in non-polar solvents. In this case the solvent will undergo induced polarization, and the observed effect P_{12} is $P_{12} = f_1 P_1+f_2 P_2$, where f_1 and f_2 are the proportions ($f_1+f_2 = 1$) of molecules of solvent and solute, which would individually give the polarizations P_1 and P_2 respectively. The interactions between dipoles at relatively short distances render the method inapplicable to concentrated solutions or pure liquids, and in the calculation of μ the values of P are extrapolated to infinite dilution.

The wide temperature range necessary makes this method difficult from the experimental standpoint, however, and an alternative procedure, the optical method, has been employed more frequently. Using Maxwell's relation $\epsilon = n^2$, the Clausius-Mosotti equation can be written

$$\frac{n^2-1}{n^2+2}\frac{M}{d} = \frac{4\pi N}{3}\alpha$$

(compare the Lorenz-Lorentz expression for molecular refraction). The refractive index is determined for visible light, i.e. for vibrations of relatively high frequency, and the polar molecules will not, under these conditions, have time to orient themselves between one wave and the next. The difference between the total polarization P (obtained from the dielectric constant) and the induced polarization P_I (from the refractive index) should therefore give the permanent polarization P_μ. An error arises, however, from the fact that the induced polarization itself is in reality the sum of two terms. In the determination of the dielectric constant, the electrical field displaces the electrons towards the positive pole, giving the electron polarization P_E, but at the same time the nuclei suffer a small displacement leading to the atom polarization P_A, i.e. $P_I = P_E + P_A$. Like the orientation of the permanent dipoles, the atom polarization does not occur under the agency of visible light, and hence the difference between the values obtained by dielectric constant and refractive index observations actually gives $P_\mu + P_A$. The atom polarization is relatively small, and is often neglected without very serious inaccuracy; a correction made on the assumption that P_A is 5 per cent. of P_E appears to be satisfactory, however, and Groves and Sugden have recently calculated the dipole moments of a number of vapours on this basis.[19]

The values of dipole moments are all of the order 10^{-18} e.s.u.; this would be anticipated, since the unit electronic charge is $4{\cdot}77 \times 10^{-10}$ e.s.u., and molecular distances are of the order 10^{-8} cm. 1×10^{-18} e.s.u. is spoken of as 1 Debye unit, and written D.[20]

Many of the available dipole moment values have been obtained by measurements in solution, and they vary somewhat with the nature of the solvent.[21] The true value of the moment must be regarded as that given by the vapour, and accurate data referring to the vapour phase are accumulating. Values determined in the same solvent are no doubt comparable, however, and are used in the sequel in cases where the moment of the vapour is not available (and sometimes, indeed, cannot be found owing to decomposition).

Sign of Dipole Moments. The methods outlined above provide values for the *magnitudes* of dipole moments, but give no information with regard to their *sign*; they do not indicate which atom forms the positive end and which the negative end of the dipole, i.e. no distinction is drawn between $\overset{+}{X}\text{—}\overset{-}{Y}$ and $\overset{-}{X}\text{—}\overset{+}{Y}$. An ingenious method of ascertaining this further fact for the bond linking a substituent to nuclear carbon in an aromatic compound was suggested by Sir J. J.

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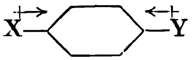
[19] *J.C.S.* 1935, 971; 1937, 158.

[20] An approximate method for determining dipole moments, which is sometimes applicable where the others fail, is an adaptation of the Stern and Gerlach process for the determination of magnetic moments (see p. 86). A fine beam of molecules emerging through a slit from a tiny oven is passed, under high vacuum, through a highly inhomogeneous electric field and received on a brass plate cooled by liquid air. The moment of the molecule is indicated by the broadening of the trace produced on the plate. A useful summary of this method is given in Dole, *Experimental and Theoretical Electrochemistry* (McGraw-Hill Book Co., New York, 1935), p. 195.

[21] See Glasstone, *Annual Reports*, 1936, **33**, 117; ref. 6, p. 144.

Thomson[22] and worked out by J. W. Williams.[23] The absence of a resultant dipole moment in unsubstituted benzene is accounted for by the symmetrical character of the aromatic nucleus. Since moments are directed magnitudes, the value for a disubstituted derivative C_6H_4XY should be the vector sum of the individual moments of the C—X and C—Y bonds (making the assumption which, however, is only approximately true, that the value for any particular bond is unaffected by other bonds in the molecule). If the nucleus is flat,[24] the moments of the bonds linking the carbon atoms to two groups in *p*-positions will be in a straight line, and hence the resultant is in this case the arithmetic sum or difference of the two bond moments. When the directions of the moments with respect to the ring are the same, as in[25]



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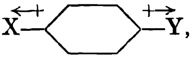
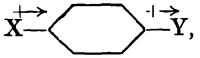


they will oppose, and the resultant will be approximately the difference of those produced by each group when present alone (i.e. of C_6H_5X and C_6H_5Y); when the directions are opposite, however, as in



they will reinforce, and the observed moment of C_6H_4XY will be the sum of those of C_6H_5X and C_6H_5Y. In accordance with this view, it is found that *p*-dialkyl-, *p*-dihalogeno-, and *p*-dinitro-benzenes have dipole moments which are indistinguishable from zero, and the same remark applies to the symmetrical trialkyl- and trihalogeno-benzenes (and probably to *s*-trinitrobenzene); the flat configuration of the nucleus is thus confirmed.

Among derivatives with two *different* substituents in *p*-positions, the observed values for *p*-nitrotoluene and *p*-nitrochlorobenzene show that the former is very nearly the *sum* of the moments of toluene and nitrobenzene, while the latter is approximately the *difference* of those of chlorobenzene and nitrobenzene. Examples of

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[22] *Phil. Mag.* 1923, **46**, 497.

[23] *Physikal. Z.* 1928, **29**, 174.

[24] Compare p. 18.

[25] The arrow indicates the direction in which the electrons are displaced from a perfectly symmetrical position with respect to the two nuclei; the head of the arrow therefore points towards the negative end of the dipole, and the tail denotes its positive end. This notation is used by Sidgwick.

this kind make it possible to divide the bonds into two classes; C—NO_2 and C—Halogen fall into one, and C—Alkyl into the other, and the direction of the dipole is different in the two classes. It remains to determine which class has the positive end of the dipole on carbon, and vice versa, and this can be done from other considerations. The clearest indication is perhaps given by the known structure of the nitro-group, from which it is obvious that the direction of the C—NO_2 dipole is away from the ring, $\overset{+\!\!\longrightarrow}{\mathrm{C{—}NO_2}}$. Hence, for the other groups the directions are $\overset{+\!\!\longrightarrow}{\mathrm{C{—}}}$Halogen and $\overset{\longleftarrow\!\!+}{\mathrm{C{—}A}}$lkyl. It is conventional to denote moments having the direction $\overset{\longleftarrow\!\!+}{\mathrm{C{—}X}}$ (e.g. C—Alkyl) by a positive sign and those having the reverse direction, $\overset{+\!\!\longrightarrow}{\mathrm{C{—}Y}}$ (e.g. C—NO_2, C—Hal.), by a negative sign. Thus the dipole moment of toluene is $+0{\cdot}41$ D, while those of nitrobenzene and chlorobenzene are $-3{\cdot}97$ D and $-1{\cdot}56$ D respectively.

Dipole Moments of Aliphatic Compounds. The symmetrical hydrocarbons methane, ethylene, and acetylene have zero moment. The same applies, indeed, to all the paraffins; it has been demonstrated for the straight chain members up to *n*-dodecane, and for all the nine isomeric heptanes. It is no doubt correct to assume that the C—C bond is non-polar, but this does not necessarily apply to the C—H bond;[26] methane is completely non-polar on account of symmetry. Since, however, any paraffin can be derived from methane by successive replacements of H by CH_3, it is evident that such replacements do not endow the molecule with a permanently polar character. Members of other homologous series also have moments which show hardly any perceptible difference; the moments of primary alcohols with carbon atoms numbering from one to twelve are all between 1·6 D and 1·7 D, and those of secondary and tertiary alcohols differ but little from this value; ketones from acetone to methyl nonyl ketone all have moments of approximately 2·8 D, and nitroparaffins up to C_4 give a practically constant value. The moments of homologous alkyl chlorides reach a limiting value at C_3, but bromides and iodides (especially the latter) have moments which increase beyond this point.[27] The moments of homologous

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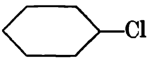
[26] Sidgwick accepts 0·2 D as the most probable moment for this bond. The reader is referred to his very clear discussion of this and other bond moments in *The Covalent Link*, pp. 141–53.

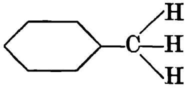
[27] Groves and Sugden, ref. 19; Cowley and Partington, *J.C.S.* 1933, 1252; 1935, 604.

series are discussed further in Chapter V. Carbon tetrachloride, being symmetrical, has zero moment, and a fall in moment from methyl chloride to chloroform is due to the directions of the C—Cl bonds.

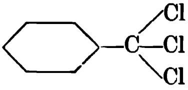
Dipole Moments of Aromatic Compounds. The resultant moment of benzene, like that of methane, is zero owing to the symmetry of the molecule. Similarly, a number of *p*-disubstituted and *s*-trisubstituted benzene derivatives have zero moment, while the corresponding monosubstituted compounds are definitely polar:



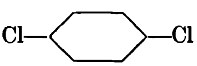
$\mu = 1\cdot56$



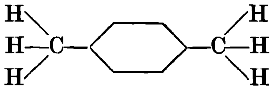
$\mu = 0\cdot41$



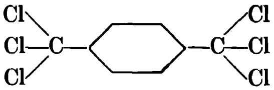
$\mu = 2\cdot07$



$\mu = 0$

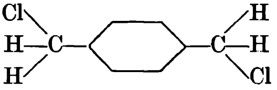


$\mu = 0$

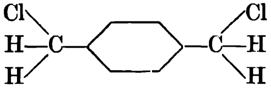


$\mu = 0$

Other compounds having two identical substituents in *p*-positions have quite large moments, however. One of these is *p*-xylylene dichloride, $C_6H_4(CH_2Cl)_2$, for which $\mu = 2\cdot2$ D. The free rotation of the $—CH_2Cl$ groups about the bonds linking them to the nucleus makes possible any structural configuration between the extremes I and II, and of all these only that represented by I is non-polar.

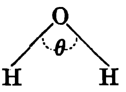


I.

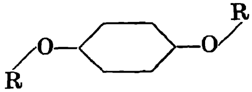


II.

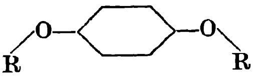
It is important to realize that, in contrast with a case of this kind, all the possible configurations of *p*-xylene or $p\text{-}Cl_3C\cdot C_6H_4\cdot CCl_3$ (above) are identical and non-polar. A relatively high resultant moment is also found in *p*-disubstituted compounds where oxygen is linked to the nucleus, as illustrated by the dialkyl ethers and diacetate of hydroquinone, where μ is of the order 2 D. This is due to the arrangement of the valencies of oxygen. The value of 1·84 D for the moment of water indicates a 'triangular' structure,



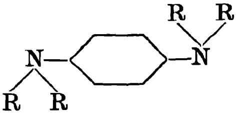
since a linear molecule, H—O—H, would be non-polar. The most probable value for the angle θ between the oxygen valencies, as determined by spectroscopic measurements, is 105°–110°.[28] The hydroquinone derivatives referred to above could take up any configuration between III and IV (below), III alone being non-polar. Dialkylterephthalates ($\mu = 2{\cdot}2$) and *p*-phthalaldehyde $C_6H_4(CHO)_2$ ($\mu = 2{\cdot}35$) are similarly capable of an infinite number of configurations of which only one extreme is non-polar. Fairly large moments have also been observed in *p*-phenylenediamine (1·5) and its tetramethyl derivative (1·2), where trivalent nitrogen is linked to the nucleus. Ammonia itself has a definite moment ($\mu = 1{\cdot}5$), in harmony with a multiplanar configuration of the atoms (a tetrahedron with nitrogen at the apex), and the results of infra-red spectroscopy again indicate a valency angle not far from 110°.[29] The extreme positions for *p*-phenylenediamine may be written as in V and VI, and of all the possible structures only V is non-polar.



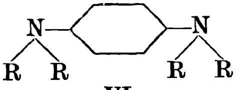
III.



IV.



V.



VI.

In all these compounds the *average* configuration will be intermediate between the two extremes, and it is therefore to be expected that the measured moment should be considerable, but less than that calculated for the most polar form. This is in harmony with observation. A resultant moment for *p*-dinitrobenzene would be anticipated on these grounds, and its absence indicates a symmetrical structure for the nitro-group (compare, for example, *p*-$Cl_3C{\cdot}C_6H_4{\cdot}CCl_3$ above); this is discussed in Chapter V.

Another matter of considerable importance is the difference between the dipole moments of corresponding aliphatic and aromatic compounds, which is illustrated in the table below. The values are from the list in *Trans. Faraday Soc.*, Sept. 1934, Appendix, or from those recorded in the papers of Groves and Sugden and of Cowley

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[28] Mecke (*Trans. Faraday Soc.* 1934, **30**, 90) gives 105° 6′.

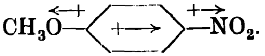
[29] Dennison and Uhlenbeck, *Phys. Rev.* 1932, **41**, 313.

and Partington (refs. 19 and 27). Values for the vapour and for benzene solution are given where available.

Dipole Moments of Aliphatic and Aromatic Compounds

	Solution	*Vapour*		*Solution*	*Vapour*
CH_4	..	0	C_6H_6	0	0
$CH_3{\cdot}CH_3$	..	0	$C_6H_5{\cdot}CH_3$	0·41	0·37
$CH_3{\cdot}OH$	1·68	1·69	$C_6H_5{\cdot}OH$	1·61	..
$CH_3{\cdot}O{\cdot}CH_3$	..	1·31	$C_6H_5{\cdot}O{\cdot}CH_3$	1·16	..
$CH_3{\cdot}F$	..	1·81	$C_6H_5{\cdot}F$	1·45	1·57
$CH_3{\cdot}Cl$	..	1·87	$C_6H_5{\cdot}Cl$	1·56	1·73
$CH_3{\cdot}Br$	..	1·80	$C_6H_5{\cdot}Br$	1·53	1·71
$CH_3{\cdot}I$	1·60	1·64	$C_6H_5{\cdot}I$	1·30	..
$CH_3{\cdot}CHO$	..	2·70	$C_6H_5{\cdot}CHO$	2·75	..
$CH_3{\cdot}CO{\cdot}CH_3$	2·76	2·85	$C_6H_5{\cdot}CO{\cdot}CH_3$	2·93	3·00
$CH_3{\cdot}COOC_2H_5$	1·85	1·76	$C_6H_5{\cdot}COOC_2H_5$	1·92	1·95
$CH_3{\cdot}CN$	3·44	3·94	$C_6H_5{\cdot}CN$	3·90	4·37
$CH_3{\cdot}NO_2$	3·02	3·54	$C_6H_5{\cdot}NO_2$	3·97	4·24
$CH_3{\cdot}NH_2$	..	1·23	$C_6H_5{\cdot}NH_2$	1·52	..

Bennett and Glasstone have carried out an analysis of the dipole moments of some *p*-substituted derivatives of phenol, anisole, and aniline.[30] Their comparison of the experimentally determined values with those calculated, by vector addition, from the moments of the appropriate monosubstituted benzenes indicates that there is an additional moment operating across the nucleus, away from —OH, —OCH_3 or —NH_2, e.g.



The following figures, extracted from Bennett and Glasstone's paper, illustrate their observations.

X	*Moment of* X⬡OCH_3		*Moment of* X⬡NH_2	
	$\mu_{calc.}$	$\mu_{obs.}$	$\mu_{calc.}$	$\mu_{obs.}$
F	1·34	2·09	2·36	2·75
Cl	1·42	2·24	2·46	2·90
Br	1·40	2·27	2·42	2·87
I	1·27	2·12	2·23	2·82
NO_2	3·47	4·74	4·66	6·20

It may be concluded, both from the different values of the moments for analogous aliphatic and aromatic compounds, and from Bennett and Glasstone's calculations, that when a group is in aromatic

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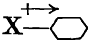
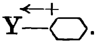
[30] *Proc. Roy. Soc.* 1934, **145**, A, 71. In the calculated values quoted, the valency angles of oxygen and nitrogen are assumed to be 109·5°, but the actual value taken does not affect the conclusions reached.

combination displacements of the electrons of the benzene nucleus occur; the resultant moment of the molecule is not accounted for completely by the polar character of the bond linking the group to nuclear carbon as in  or . This observation is not surprising in view of the polarizability of the nucleus. The matter will be considered further in subsequent chapters.

III

APPLICATIONS OF THE ELECTRONIC THEORY IN ORGANIC CHEMISTRY. STRENGTHS OF ACIDS AND BASES. THE INDUCTIVE EFFECT

IN 1839 Dumas made the important observation that the substitution of three chlorine atoms in acetic acid led to no change in the fundamental *type* of the compound, and this discovery had a profound influence upon the development of theoretical chemistry.[1] Nevertheless, the replacement of hydrogen by another atom or group frequently results in a very considerable modification of reactivity and chemical characters, and many striking observations of the influence of substituent groups have been recorded. Notable examples are found in the formation of salts by the nitroparaffins, and the exceptional reactivity of certain substituents in the benzene nucleus when one or more nitro-groups are also present. The carbonyl, carbethoxyl, and cyano groups also confer unusual properties upon compounds containing them, as is indicated by the extraordinary mobility of the hydrogen atom of a methylene group situated between two of these (e.g. formation of metallic derivatives and general reactivity exhibited by β-diketones and by acetoacetic, cyanoacetic and malonic esters). On the basis of such observations, these groups were designated 'negative'. Of great significance, also, was the discovery of the 'directive influences' of groups in aromatic substitution.[2] It thus became evident that the properties of a bond linking two atoms may be strongly influenced by the nature of other atoms or groups present in the molecule.

A further line of facts was forthcoming from the study of the relative strengths of organic acids and bases, and Ostwald's determination of the dissociation constants of a large number of carboxylic acids[3] provided numerical data upon which comparisons of the characters of substituents could be based. In general, a 'negative' group increased acidity and lowered basicity. Subsequent investigations of substitution reactions, tautomeric changes and other chemical phenomena have thrown further light upon the problem of group influences, while the conception of the dipole moment has

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[1] See Chap. I.

[2] See Chap. IV.

[3] *Z. physikal. Chem.* 1889, **3**, 418.

made available an additional and powerful method of attack by means of purely physical measurements.[4] In this and succeeding chapters, observations of this type will be considered in the light of the electronic theory of valency.

Strengths of Organic Acids. The Ionic Theory of Arrhenius appeared in 1887. Strengths of acids had previously been compared by methods involving competition for a limited quantity of a base (Thomsen, 1853; Ostwald, 1878), the catalysed hydrolysis of acetamide, methyl acetate, or cane sugar, or the electrical conductivity at a given concentration (Ostwald). Arrhenius postulated an equilibrium between ions and undissociated molecules, the degree of ionization (α) at any particular concentration (c) being given by the ratio of the equivalent conductivity (Λ) to the conductivity at infinite dilution (Λ_0), and the application of the law of mass action to this equilibrium led to the Ostwald expression (dilution law) for the dissociation constant, viz. $K = \alpha^2 c/(1-\alpha)$, or $K = \Lambda^2 c/\Lambda_0(\Lambda_0-\Lambda)$. Ostwald determined the dissociation constants of more than two hundred organic acids (all weak electrolytes), values of Λ being derived from the results of conductivity measurements at concentrations ranging from N/4 to N/2048, and Λ_0 being found by an independent measurement on the sodium salt.[5] Ostwald's data have been supplemented by the results of numerous subsequent investigations in which his procedure was employed;[6] these values are now referred to as 'classical' constants, K_{class}.

The failure of the dilution law when applied to strong electrolytes led to various empirical modifications, and ultimately to the theory of Debye and Hückel[7] and its extension by Onsager.[8] This modern view assumes complete dissociation of strong electrolytes, and visualizes the effects upon the measured conductivity of the interionic attractive forces, the frictional resistance of the medium, and the Brownian movement of the ions. The same factors must be considered in weak electrolytes; variations in concentration affect not only the *number* of ions but also, to some extent, their *velocities*, and the values of Λ_0 must be corrected accordingly. Dissociation

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[4] See preceding chapter.

[5] For an account of the theory and technique of conductivity measurements, see Davies, *The Conductivity of Solutions*, 2nd edition (Chapman and Hall, 1933).

[6] e.g. Kendall, *J.C.S.* 1912, **101**, 1275; H. C. Jones *et al.*, *Amer. Chem. J.* 1913, **50**, 1 and references there cited; Walden, *Z. physikal. Chem.* 1892, **10**, 638.

[7] *Physikal. Z.* 1923, **24**, 185, 305.

[8] *Trans. Faraday Soc.* 1927, **23**, 341.

constants are therefore calculated by the use of the Debye-Hückel-Onsager equation, and the 'true' or 'thermodynamic' constant, K_{therm}, is thus obtained. At the same time, vast improvements in experimental technique have endowed modern determinations with an accuracy not obtainable in Ostwald's day.

From the standpoint of the organic chemist, the main interest lies in the *relative* values of the dissociation constants of different acids. As a rule, the same general features are observed in the older and the modern data, but for matters of detail, where small differences are considered, it is necessary to rely exclusively upon the accurate values found in recent years. It is still more important to select *comparable* values. Temperature has a definite, though not large effect upon the dissociation constant;[9] changes of medium naturally exert a very great influence, but as a rule the *order* of strengths is the same in different solvents.[10] The influence of temperature and medium upon dissociation constants calls for further investigation, but there is little reason to doubt that a true comparison of acid strengths can be made by the use of values referring to a single temperature and medium.

A number of accurate values for isolated acids have been obtained during the past few years by the conductometric method.[11] Dissociation constants have also been calculated from the pH values of solutions as determined by electromotive force measurements,[12] and in certain cases by a refinement of the old catalytic method;[13] where comparison is possible, these show good agreement with the values from the more usual conductivity determinations.[14] The thermodynamic dissociation constants of a series of monocarboxylic acids have recently been determined by Dippy and his co-workers[15] by an expeditious conductometric method; while their procedure does

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[9] See for example, Jones *et al.*, ref. 6; Harned *et al.*, ref. 12.

[10] See, for example, Wooten and Hammett, *J. Amer. Chem. Soc.* 1935, **57**, 2294; Bennett, Brooks, and Glasstone, *J.C.S.* 1935, 1821. But compare Wynne-Jones, *Proc. Roy. Soc.* 1933, **140**, **A**, 440.

[11] MacInnes and Shedlovsky, *J. Amer. Chem. Soc.* 1931, **53**, 2419. Saxton *et al.*, ibid. 1933, **55**, 3638; 1934, **56**, 1918; Brockman and Kilpatrick, ibid. 1934, **56**, 1483; Jeffery and Vogel, *J.C.S.* 1932, 2829; 1934, 166; Ives *et al.*, ibid. 1933, 561, 731.

[12] Harned *et al.*, *J. Amer. Chem. Soc.* 1930, **52**, 5079; 1932, **54**, 1350; 1933, **55**, 652, 2379; 1934, **56**, 1042, 2039; Branch and Yabroff, ibid. 1934, **56**, 2568.

[13] Grove, ibid. 1930, **52**, 1404; Deyrup, ibid. 1934, **56**, 60.

[14] For example, $10^5 K$ for acetic acid in water at 25° is found to be 1·747 by conductivity determinations (MacInnes and Shedlovsky, ref. 11), and 1·754 by E.M.F. measurements (Harned and Ehlers, *J. Amer. Chem. Soc.* 1932, **54**, 1350).

[15] *J.C.S.* 1934, 161, 1888; 1935, 343; 1936, 644; 1937, 1008.

not give the extreme accuracy of 'precision' measurements, the values are doubtless correct within the limit of ±1 per cent., and they form an important contribution to theoretical organic chemistry.

The values of the dissociation constants of a number of carboxylic acids, all in water at 25°, are collected in Tables I and II. Table I contains 'classical' constants for a series of substituted acetic acids (mainly Ostwald's values), and Table II records thermodynamic constants for benzoic and phenylacetic acids[16] (Dippy *et al.*). In

TABLE I

Classical Dissociation Constants of substituted Acetic Acids, $X\cdot CH_2\cdot COOH$

X	10^5K	X	10^5K
CH_3	1·34	I	75
H	1·82	Br	138
C_6H_5	5·60	Cl	155
OCH_3	33·50	F	217

Dichloroacetic, 5,140
Trichloroacetic, 121,000

TABLE II

Thermodynamic Dissociation Constants of substituted Aromatic Acids

X	10^5K	
	Benzoic acids $X\cdot C_6H_4\cdot COOH$	*Phenylacetic acids* $X\cdot C_6H_4\cdot CH_2\cdot COOH$
p-OCH_3	3·38	4·36
p-CH_3	4·24	4·27
m-CH_3	5·35	..
H	6·27	4·88
m-OCH_3	8·17	..
p-F	7·22	5·68
p-Cl	10·55	6·45
p-Br	10·7	6·49
p-I	..	6·64
m-F	13·65	..
m-Cl	14·8	7·24
m-Br	15·4	..
m-I	14·1	6·93
m-NO_2	32·1	10·8
p-NO_2	37·6	14·1

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[16] When calculated from the same conductivity data, the classical constant is a little higher than the thermodynamic constant. Thus, the experimental figures of Dippy and Williams (*J.C.S.* 1934, 1888) for acetic acid give $10^5K_{\text{class}} = 1\cdot 81$, and $10^5K_{\text{therm}} = 1\cdot 76$, while for benzoic acid the values are 6·46 and 6·27.

Table III are listed the thermodynamic dissociation constants of some phenylboric acids in 25 per cent. alcohol at 25° (Branch and collaborators[17]).

TABLE III

Thermodynamic Dissociation Constants of substituted Phenylboric Acids, $X \cdot C_6H_4 \cdot B(OH)_2$

X	$10^{10}K$	X	$10^{10}K$
p-OC_2H_5	0·608	p-Br	7·26
p-CH_3	1·00	m-F	11·0
m-CH_3	1·40	m-Cl	13·5
H	1·97	m-Br	14·6
m-OC_2H_5	3·05	m-NO_2	69·0
p-F	3·66	p-NO_2	98·0
p-Cl	6·30		

The values recorded in Tables I to III show that the introduction of a substituent may either increase or decrease the strength of the acid. The magnitude of the influence is dependent, moreover, both upon the nature of the substituent and upon its position. Thus, the dissociation constants of isomeric acids have different values.[18] In a saturated aliphatic acid, the influence of the substituent decreases as its distance from the carboxyl group becomes greater, the fall from the α- to the β-substituted acid being far more pronounced than the subsequent differences; this is illustrated by the following values for chlorinated acids.

TABLE IV

Classical Dissociation Constants of Chloro-Aliphatic Acids

Acid	10^5K
Monochloroacetic	155·0
β-Chloropropionic	8·5
γ-Chlorobutyric	c. 3·0
δ-Chlorovaleric	c. 2·0

Strengths of Bases and Phenols. The strengths of organic bases have been investigated in various ways, the processes employed including the determination of the hydrolysis of their salts by partition,[19] catalytic,[20] conductometric,[21] and solubility methods,[22]

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[17] *J. Amer. Chem. Soc.* 1934, **56**, 937, 1850, 1865.

[18] Only m- and p-substituted aromatic acids are here referred to; the discussion of o-substituted acids is postponed until Chap. XII.

[19] Farmer and Warth, *J.C.S.* 1904, **85**, 1713; Flürscheim, ibid. 1909, **95**, 718; 1910, **97**, 84. Moore and Winmill, ibid. 1912, **101**, 1635. Williams and Soper, ibid. 1930, 2469.

[20] Walker, *Z. physikal. Chem.* 1889, **4**, 319; *J.C.S.* 1895, **67**, 576.

[21] Walker, ref. 20; Bredig, *Z. physikal. Chem.* 1894, **13**, 288. Moore and Winmill, ref. 19.

[22] Löwenherz, *Z. physikal. Chem.* 1898, **25**, 385.

electrometric titration,[23] and colorimetric and ultra-violet spectroscopic observations.[24] The measurements are, of course, not of equal value, but the results in general are completely comparable with those already recorded for acids, the strengths being in the reverse order. The relatively scanty data concerning the strengths of phenols[25] are also in general agreement with those referring to acids.

Theoretical Considerations. The wide variations in the dissociation constants of a series of carboxylic acids in a solvent S must be ascribed to the influence of the group R upon the equilibrium[26]

$$\mathrm{R{\cdot}COOH+S \rightleftarrows R{\cdot}COO^{\ominus}+SH^{\oplus}},$$

which becomes, when the solvent is water,

$$\mathrm{R{\cdot}COOH+H_2O \rightleftarrows R{\cdot}COO^{\ominus}+H_3O^{\oplus}}.$$

Those substituents which strengthen the acid favour the right-hand side of the equilibrium, and vice versa. The group may either facilitate or impede the removal of hydrogen ion; at the same time it may operate either against or in favour of recombination.

Flürscheim[27] suggested that there is associated with each group a 'polar factor', which has more recently been defined as 'that effect which, when the substituent occurs at the α-, β-, γ-, or more remote positions in a saturated aliphatic acid, leads consistently to a rise or consistently to a fall in the ionization constant of the acid, and diminishes as the distance from the substituent increases'.[28] The 'polar factor' is equivalent to the conception of 'positivity' or 'negativity', which Derick, on the basis of the equation $A = RT \log K$ for the change in free energy of ionization, proposed to express quantitatively by a logarithmic function of the dissociation constant of the appropriate substituted monocarboxylic acid.[29] Derick also pointed out that the effect may be transmitted to the carboxyl group

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[23] Brönsted and Duus, ibid. 1925, **117**, 299; Hall and Sprinkle, *J. Amer. Chem. Soc.* 1932, **54**, 3469; Bennett, Brooks, and Glasstone, ref. 10.

[24] Hammett *et al.*, *J. Amer. Chem. Soc.* 1932, **54**, 2721; 1934, **56**, 2010; 1935, **57**, 2103.

[25] e.g. Bader, *Z. physikal. Chem.* 1890, **6**, 289; Walker, ibid. 1900, **32**, 137; Hantzsch and Farmer, *Ber.* 1899, **32**, 3066; Walker and Cormack, *J.C.S.* 1900, **77**, 18; Boyd, ibid. 1915, **107**, 1538.

[26] The solvation of the hydrogen ion in solution, postulated by Fitzgerald and Lapworth (*J.C.S.* 1908, **93**, 2163, 2187), is now well established; see Taylor, *A Treatise on Physical Chemistry*, 2nd edition (Macmillan, 1931), vol. i.

[27] *J.C.S.* 1909, **95**, 718.

[28] Cocker, Lapworth, and Walton, ibid. 1930, 443.

[29] *J. Amer. Chem. Soc.* 1911, **33**, 1152.

either through the intervening atoms in the molecule or directly through the medium.

The polar factor associated with a substituent will, of course, modify the strength of a base in the reverse direction. The equilibrium here is

$$B+S \rightleftarrows BH^{\oplus}+(S-H)^{\ominus}$$

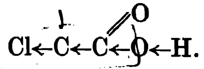
or, for water as solvent,

$$B+H\cdot OH \rightleftarrows BH^{\oplus}+OH^{\ominus},$$

and influences which facilitate the removal of hydrogen ion from an acid will oppose the co-ordination of proton with the base, and vice versa.

The electronic interpretation of the polar factor was given by G. N. Lewis, in terms of his conception of the unequal sharing of the electron-pair forming a covalent bond.[30] The application to the influence of a substituent is as follows (quoting his own words):

> 'Let us consider once for all that by a negative element or radical we mean one which tends to draw toward itself the electron pairs which constitute the outer shells of all neighbouring atoms, and that an electropositive group is one that attracts to a less extent, or repels, these electrons. . . . As a familiar example we may consider acetic acid in which one hydrogen is replaced by chlorine, $H_2ClCCOOH$. The electrons, being drawn towards the chlorine, permit the pair of electrons joining the methyl and carboxyl groups to approach nearer to the methyl carbon. This pair of electrons, exercising therefore a smaller repulsion upon the other electrons of the hydroxyl oxygen, permit these also to shift in the same direction. In other words, all the electrons move towards the left, producing a greater separation of the electrons from the hydrogen of the hydroxyl, and thus a stronger acid. This simple explanation is applicable to a vast number of individual cases. It need only be borne in mind that although the effect of such a displacement of electrons at one end of a chain proceeds throughout the whole chain, it becomes less marked the greater the distance and the more rigid the constraints which hold the electrons in the intervening atoms.'[31]

These displacements are commonly represented  $Cl\leftarrow C\leftarrow \overset{O}{\overset{\nearrow\!\!\!\nearrow}{C}}\leftarrow O\leftarrow H$. Regarding the transmission of the effect, Lewis writes:

> 'It is not at all certain that the whole effect is produced through the carbon chain. If we knew how to construct thoroughly satisfactory spatial

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[30] See preceding chapter, p. 23.

[31] *J. Amer. Chem. Soc.* 1916, **38**, 781; *Valence and the Structure of Atoms and Molecules* (Chemical Catalog. Co., New York, 1923), p. 84.

models of our molecules, we might see how in certain cases there might be some more immediate steric effect which would exaggerate the effect produced through the chain. But that the latter effect, passing through the molecule atom by atom, is a real one we have no reason to doubt.'[32]

On this view, which is now accepted universally, increased acidity arises from the electron-attractive nature of the substituent, while an enhanced basic (or decreased acidic) character is to be ascribed to electron-repulsion, the effect being transmitted both through the intervening bonds and through the medium. The term 'Inductive Effect', due to Ingold,[33] is now employed in place of Flürscheim's expression 'Polar Factor'. Hydrogen is the natural standard of reference, and a group which, relatively to hydrogen, repels electrons, is spoken of as having a +I effect, while the influence of a group which is relatively electron-attractive is designated —I.[34] It has been suggested that those portions of the effect which are transmitted through the chain and through space respectively might be distinguished by the terms 'inductive' and 'direct';[35] since, however, there is no means of separating them quantitatively, the term 'Inductive Effect' is invariably used to denote the sum of the two.

The values of the dissociation constants of the substituted acetic acids recorded in Table I indicate that methyl is electron-repulsive (+I) in character while the remaining groups are electron-attractive (—I) in the following order:

$$\text{Decreasing electron attraction} \longrightarrow$$

$$\underbrace{F > Cl > Br > I > OCH_3 > C_6H_5}_{-I} > H > \underbrace{CH_3}_{+I}.$$

It is evident that the same property of a group, viz. its electron-attractive or -repulsive character, is under observation whether the

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[32] *Valence*, p. 139.

[33] *Ann. Reports*, 1926, **23**, 140. Compare *Rec. trav. chim.* 1929, **48**, 797; *Chem. Reviews*, 1934, **15**, 225. The term 'general polar effect' has also been used frequently (e.g., Allan, Oxford, Robinson and Smith, *J.C.S.* 1926, 401).

[34] Robinson [*J.* 1932, 1445; *Outline of an Electrochemical Theory of the Course of Organic Reactions* (Institute of Chemistry, 1932), p. 34] has suggested that these signs should be reversed, in accordance with the charge conferred by the group upon adjacent atoms. The original signs are more commonly used, however, and will be employed throughout this book. Their correspondence with the signs normally written for dipole moments (preceding chapter, p. 28) is convenient.

[35] Ingold and Vass, *J.C.S.* 1928, 417.

physical constant measured be the dipole moment of a substituted hydrocarbon or the dissociation constant of a carboxylic acid. Among aliphatic compounds, indeed, where the group is attached to a saturated carbon atom, either set of data may be taken as a measure of Inductive Effects.[36] It is thus to be expected that some quantitative relationship should exist between dissociation constants and dipole moments, and such a relationship has actually been observed.[37] By plotting the logarithms of the dissociation constants of a series of substituted acetic acids, $X \cdot CH_2 \cdot COOH$, against the dipole moments of the corresponding substituted methanes, $X \cdot CH_3$, a smooth curve is obtained, as shown in Fig. 3. This curve can be represented by the equation $\log K = \log K_0 - C(\mu + a\mu^2)$, where K_0 is the dissociation constant of the unsubstituted acid ($X = H$) and C and a are constants for the series. The only data available for testing the expression are Ostwald's classical constants, but the inaccuracies are unimportant in view of the wide range covered. This relationship recalls Derick's expression for the 'negativity' of a substituent as a logarithmic function of the dissociation constant of the appropriate acid;[38] it is actually a connexion between dipole moments and changes in free energy of ionization.

An inspection of Tables II and III shows that while, in the aromatic acids, the *general* sequence is in agreement with that observed in aliphatic acids and in dipole moments, viz. $NO_2 > Hal > H > CH_3$, the order differs in some details. Certain peculiarities appear when the substituent is attached to the benzene nucleus, the most obvious of which are the following:

1. Whereas methoxyl increases the dissociation constant of acetic acid, and also of benzoic acid when it is in the *m*-position, *p*-methoxyl has the reverse effect; it weakens both benzoic and phenylacetic acids. *p*-Ethoxyl has the same influence upon the strength of phenylboric acid and, indeed, the peculiarity is general for —OR groups.

2. The nitro-benzoic and -phenylacetic acids are much stronger than the corresponding unsubstituted acids; the effect of *p*-NO_2, however, is more powerful than that of *m*-NO_2, in spite of the greater distance of the substituent from the carboxyl group.

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[36] The case of alkyl groups, which give no moment when linked to saturated carbon in hydrocarbons, is discussed in Chap. V, p. 70. It may be pointed out here, however, that it is quite correct to designate their effect on the dissociation constants of carboxylic acids as +I.

[37] Nathan and Watson, *J.C.S.* 1933, 893.

[38] See p. 38.

3. Halogens cause an increase of strength in both aliphatic and aromatic acids, and in the latter their effect is greater in the *m*-position than in the *p*-position, as would be expected. The order of strengths of the halogenoaromatic acids *among themselves* is not, however, that found in the halogenoacetic acids, viz. F > Cl > Br > I; in the *p*-halogenoaromatic acids this order is completely inverted, while there is a partial inversion in the *m*-substituted acids (the strengths of which do not, however, differ very greatly). Similar irregularities are observed in the strengths of the halogen-substituted anilines and phenols recently determined by Bennett, Brooks, and Glasstone,[39] and recorded in Table V.

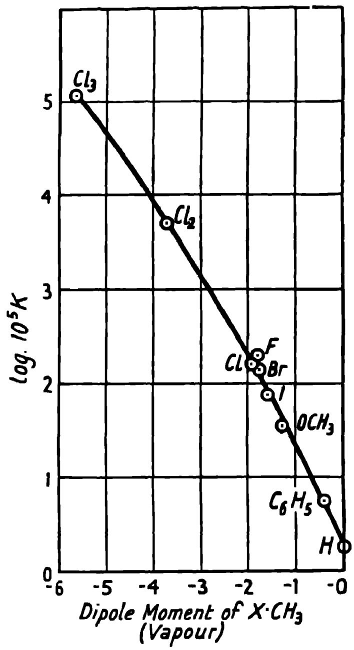

Fig. 3.

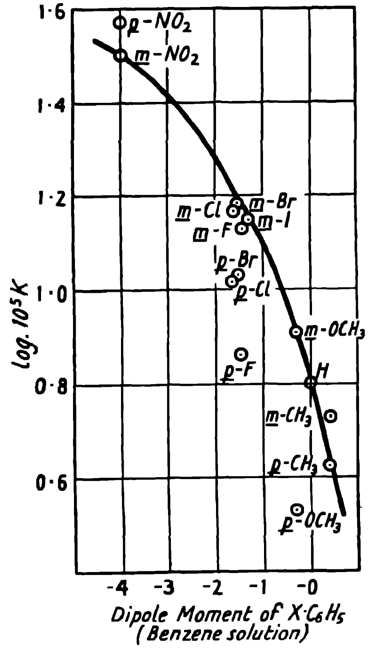

Fig. 4.

Relationship of Dissociation Constants of Acids to Dipole Moments of Substituted Hydrocarbons.

Fig. 3. Acetic Acids, $X \cdot CH_2 \cdot COOH$.
(Nathan and Watson, *J.C.S.* 1933, 894)

Fig. 4. Benzoic Acids, $X \cdot C_6H_4 \cdot COOH$.
(Dippy and Watson, *J.C.S.* 1936, 438)

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[39] Ref. 10.

TABLE V

Strengths of Anilines and Phenols in 30 per cent. alcohol at 25°

X	$10^{12}K_b$		$10^{10}K_a$	
	p-$X\cdot C_6H_4\cdot NH_2$	m-$X\cdot C_6H_4\cdot NH_2$	p-$X\cdot C_6H_4\cdot OH$	m-$X\cdot C_6H_4\cdot OH$
H . .	126		0·32	
F . .	120	10·5	0·26	1·51
Cl . .	28·8	8·51	1·32	4·90
Br . .	21·9	7·94	1·55	4·37
I . .	15·1	7·59	2·19	3·89

These peculiarities lead to the conclusion that, while the relative strengths of the saturated aliphatic acids are governed by the Inductive Effects of the substituent groups and may be regarded as a measure of the magnitudes of these effects, an additional factor operates when the substituent is attached to the aromatic nucleus. The influence of an atom or group cannot therefore be expressed completely in terms of its Inductive Effect. The existence of such an additional factor is indicated also, as already pointed out,[40] by the different dipole moments of aromatic and aliphatic compounds. If, however, the effects observed in the dissociation constants of aromatic acids were identical in nature and magnitude with those influencing the dipole moments of benzene derivatives, the dissociation constants of a series of *m*- or *p*-substituted benzoic acids, $X\cdot C_6H_4\cdot COOH$, should be connected with the dipole moments of the corresponding substituted benzenes, $X\cdot C_6H_5$, by a relationship similar to that illustrated in Fig. 3. The values of $\log K$ for the *m*-substituted acids would be expected to give a smooth curve when plotted against the dipole moments, and a similar curve should be obtained for the *p*-substituted acids. This is not the case, however, as is shown in Fig. 4.[41] *m*-Substituted acids do not show serious divergence from the relationship, but there is no simple connexion between dipole moments and dissociation constants of *p*-substituted acids. These observations might be due to either or both of the following causes:

(*a*) The permanent displacements of the nuclear electrons indicated in the dipole moments of benzene derivatives may vary in magnitude from compound to compound, such variations having an appreciable

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[40] Chap. II, p. 31.

[41] Dippy and Watson, *Chem. and Ind.* 1935, **54**, 735; *J.C.S.* 1936, 436. Since the resultant moment due to $—OCH_3$ does not operate in the plane of the nucleus, the 'effective moment' is taken as $\mu \cos 105°$ (see p. 29).

influence upon the carboxyl group only when the substituent is in the *p*-position. Thus, for example, the nitro-group in *p*-nitrobenzoic acid may cause a greater displacement of the nuclear electrons than the same group in nitrobenzene does. Bennett and Glasstone's analysis of the dipole moments of *p*-disubstituted benzenes[42] indicates that the permanent electronic displacements are actually subject to variations of this type.

(*b*) The equilibrium $R \cdot COOH + H_2O \rightleftarrows R \cdot COO^{\ominus} + H_3O^{\oplus}$ may be susceptible to influences which are not present in the isolated molecule. The electrolytic dissociation of an acid is dependent upon the attack of a reagent (solvent molecule), and an additional factor may intervene at the moment of reaction (the same applies, of course, to the reassociation of the ions); such a factor may be described as 'time-variable' (as opposed to 'permanent'). This effect also must be supposed to operate from the *p*-position, but only feebly, if at all, from the *m*-position.

The conclusions drawn from an inspection of the values of dipole moments of aromatic compounds and of the dissociation constants of simple aromatic acids may therefore be summarized as follows. The former indicate that when a group is attached to the benzene nucleus some permanent factor operates in addition to the inductive effect. In the latter there is the manifestation of a further complicating feature. Either the permanent factor indicated by dipole moment values is variable in magnitude (the variations being notable in *p*-substituted acids), or a time-variable factor (dependent upon the attack of a chemical reagent) operates in these acids, or both of these complications contribute to the total effect. The possibility of at least *three* polar influences is thus presented, viz. a permanent displacement of electrons which is common to aliphatic and aromatic compounds (inductive effect), and two additional effects, one permanent and one time-variable, which are operative only when the group is linked to a suitable system (e.g. the aromatic nucleus). Further evidence leading to the same conclusion will be considered in the following chapter, and a general discussion of these effects will be given in Chapter V.

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[42] See p. 31.

IV

APPLICATIONS OF THE ELECTRONIC THEORY IN ORGANIC CHEMISTRY. SUBSTITUTION REACTIONS

THE term 'substitution', when used in its widest sense, refers to all processes which lead to the replacement of *any* atom or group by *any other*, as represented by the substitution of Z for X in the reactions

$$RX+YZ = RZ+XY$$

$$RX+Z = RZ+X.$$

The familiar replacement of hydrogen,

$$RH+YZ = RZ+HY$$

(as in

$$CH_4+Cl_2 = CH_3Cl+HCl, \quad \text{or} \quad C_6H_6+NO_2OH = C_6H_5NO_2+H_2O),$$

first investigated by Dumas over a century ago, is in reality a particular example of the more general phenomenon. It will be convenient, however, to adhere for the present to long-established convention, and to use the word 'substitution' to denote this special case. The contrast between the substitution reactions of the paraffins and the addition processes to which the olefins are susceptible forms the main justification for classifying these hydrocarbons as saturated and unsaturated respectively, while the predominance of substitution in aromatic compounds has played a leading part in connexion with the problem of the structure of benzene. Since observations of nuclear substitutions in benzene derivatives form one of the foundation stones of the modern electronic theory of the reactions of organic compounds, a survey of the main features of these processes will first be given, and processes of replacement in their wider aspect will be considered later.

Aromatic Substitution. Kekulé's ring formula for benzene was published in 1865.[1] It has been confirmed of recent years by X-ray evidence, and, in fact, the Kekulé model of a nucleus with alternate single and double bonds still remains the most convenient representation of aromatic compounds.[2] By 1874 the problem of the orientation

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[1] For an excellent account of the early work on the benzene problem see Lachman, *The Spirit of Organic Chemistry* (New York, 1899), chap. iii.

[2] See Chap. V.

of benzene derivatives was solved, largely through the work of Körner. Then, at an early date, it became evident that the introduction of a further group into a nucleus already containing one or more substituents did not lead to the production of all the possible isomerides in equal quantities. The main factor determining the position of substitution was the nature of the group or groups already present; thus, hydroxyl, alkoxyl, amino, dialkylamino, halogens, and alkyl groups directed the entering group mainly or entirely to the positions *ortho* and *para* to themselves, while the nitro, carbonyl, carboxyl, and sulphonic acid groups caused the new substituent to take up principally the *meta*-position. Attempts to express these facts in a generalized form led to various orientation rules, of which the best known were those of Körner (1874), Hübner (1875), Nölting (1876), Armstrong (1887), Crum Brown and Gibson (1897), and Vorländer (1902). In these generalizations a connexion was sought between orientation and other characters of the directing group X, such as its acidic nature (Körner, Hübner, Nölting), the valencies of its atoms (Armstrong), its relationship with the compounds XH or XOH as indicated by the capacity for direct oxidation possessed by XH (Crum Brown and Gibson), and its saturated or unsaturated nature (Vorländer). None of these rules, however, embraced the whole of the experimental observations.

In 1895 Holleman proceeded to a systematic and quantitative study of the problem of aromatic substitution.[3] He devised improved methods of separating and estimating the isomerides, and was able to show that, when a second group enters a nucleus already containing one substituent, all three derivatives are usually formed, though in very unequal proportions. Pure *op*- or pure *m*-substitution is rare, if it ever occurs, but the entering group takes up *principally* the *m*- or the *o*- and *p*-positions with respect to the substituent already present. The entry of the second substituent, in fact, takes place by three simultaneous reactions. They have widely differing velocities, however, and one or more may sometimes be so slow as to give hardly perceptible amounts of the corresponding isomerides. Thus, only the *m*-derivative has been detected in the products of substitution of phenyltrimethylammonium salts and other 'onium'

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[3] *Die direkte Einführung von Substituenten in den Benzolkern* (Leipzig, 1910). The most widely applicable method of determining the proportions of isomerides consists in the study of fusion curves.

compounds where the directive group is associated with an integral positive charge;[4] substitution in phenols and phenolic ethers has usually been regarded as occurring exclusively at the *o*- and *p*-positions,[5] but small quantities of *m*-isomerides have more recently been detected in the nitration products.[6] It is probably correct to state that, in certain limiting cases, the quantities of one or more isomerides are too small for experimental detection, while there are other instances where the very small proportions of certain isomerides render their detection difficult though not impossible.

Holleman further showed that, while other factors such as the nature of the attacking reagent, temperature, and catalysts affect the proportions of the isomerides, sometimes to a very appreciable extent, the directive influence of the substituent is of prime importance; a given group directs either *op* or *m*, independently of external conditions. This is known as the Law of Conservation of Substitution Type. Certain apparent exceptions admit of a simple explanation; perhaps the most obvious is the production of nearly 50 per cent. of *m*-derivative when aniline is nitrated in presence of concentrated sulphuric acid,[7] a result which is due to salt-formation with the consequent change of the directing group from $-NH_2$ to $-NH_3^{\oplus}$. The considerable variations in the relative quantities of the *o*- and *p*-isomerides which frequently accompany a change in the substituting reagent are, of course, 'within the type', whatever be their explanation. It must be pointed out, however, that there is really no sharp boundary line between *op*- and *m*-directive groups, but a gradual transition. This is illustrated by the steady variation in the percentage of *m*-isomeride in the products of nitration of the side-chain chlorinated derivatives of toluene ($C_6H_5\cdot CH_3$, 4 per cent.; $C_6H_5\cdot CH_2Cl$, 12 per cent.; $C_6H_5\cdot CHCl_2$, 33 per cent.; $C_6H_5\cdot CCl_3$, 48 per cent.[8]) The *relative* directive powers of different groups were deduced by Holleman from determinations of the proportions of the isomerides formed when a third substituent enters a nucleus already containing the two groups to be compared. Thus, in the nitration of *p*-chlorotoluene the isomeride having the nitro-group *ortho* to chlorine

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[4] For references see Ingold, *Ann. Reports*, 1926, **23**, 130.

[5] Holleman, op. cit. (ref. 3), p. 155.

[6] Arnall, *J.C.S.* 1924, **125**, 811. Griffiths, Walkey, and Watson, ibid. 1934, 631.

[7] Holleman, Hartogs, and van der Linden, *Ber.* 1911, **44**, 704.

[8] Flürscheim and Holmes, *J.C.S.* 1928, 1611. Compare Holleman, Vermeulen, and de Mooy, *Rec. trav. chim.* 1914, **33**, 1.

was in excess of that with this group *ortho* to methyl, and he concluded that the directive influence of chlorine was the greater. By experiments of this type he arrived at the following sequences:

op-directive influence $OH > NH_2 >$ Halogen $> CH_3$

m-directive influence $COOH > SO_3H > NO_2$.

Holleman pointed out the very important fact that *op*-substitution is normally far more rapid than *m*-substitution. This is obvious, indeed, in elementary laboratory work; for example, the practically instantaneous bromination of aniline and phenol to give the *s*-tribromo-derivatives offers a sharp contrast with the slow *m*-nitration of nitrobenzene. It is a matter of common experience that the last-named compound is nitrated far less readily than benzene itself, whereas Ingold and Shaw have shown that the nitration of toluene is about fourteen times faster than that of benzene under similar conditions.[9] In naphthalene and anthraquinone, moreover, the presence of an *op*-directive group normally leads to further substitution in the same nucleus, while a *m*-directive group causes substitution to occur in the other ring. The inevitable conclusion is that, in general, *op*-substitution is associated with activation, and *m*-substitution with deactivation of the benzene nucleus. The significance of this was appreciated by Holleman. Kekulé regarded substitution as preceded by addition of the reagent molecule, and this view has persisted; Holleman suggested that *op*-directive influence arises from the facilitation of addition at the 1.2 and 1.4 positions (Kekulé's benzene formula), while *m*-substitution is the result of the retardation of this addition.[10]

The modern view also relates *op*- and *m*-directive influences with selective activation and deactivation respectively of the *o*- and *p*-positions.[11] The most powerful of all directive groups are those carrying an integral charge; thus a positively charged group [e.g. $—\overset{\oplus}{N}(CH_3)_3$] directs exclusively *meta*, so far as can be ascertained, while

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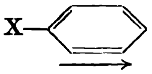
[9] *J.C.S.* 1927, 2918. The figure was arrived at on the basis of experiments in which benzene and toluene (both in excess) were nitrated together, and the percentage of nitrobenzene in the product determined from the density. The result obtained was 7 mols of nitrobenzene per cent. Combining this with the proportions of the isomeric nitrotoluenes known to be produced (59 per cent. *o*, 4 per cent. *m*, 37 per cent. *p*, Holleman *et al.*, ref. 8), calculation showed that the reactivity of the *o*- and *p*-carbon atoms is increased about thirty-fold, and that of the *m*-carbon atom about two-fold.

[10] *Chem. Reviews*, 1924, **1**, 187.

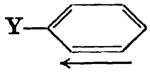
[11] Ingold, *Ann. Reports*, 1926, **23**, 134; *Rec. trav. chim.* 1929, **48**, 805.

negatively charged oxygen has a much greater influence than hydroxyl or alkoxyl, as shown by the fact that the phenoxide ion is halogenated far more readily than undissociated phenol or a phenolic ether.[12] These facts connect *op*-substitution and nuclear activation with a *repulsion* of electrons by the directing group, and *m*-substitution and nuclear deactivation with *attraction* of electrons. A superficial consideration of the process of substitution would, indeed, lead to a similar conclusion. Considering, as an example, nuclear chlorination, $RH+Cl\cdot Cl = RCl+HCl$, it is evident that the chlorine atom which forms chloride ion must retain the covalent pair of the chlorine molecule, and the atom which enters the nucleus will therefore seek a point where there are electrons available for the completion of its octet. Thus, the chlorine molecule is an electron-seeking or 'electrophilic' reagent,[13] and the same applies to the other common substituting agents such as nitric or sulphuric acids. The reactive points of the aromatic nucleus will therefore be those of high electron availability, and such points are provided by an electron-repulsive group. The conclusion is thus reached that *op*-substitution is the result of the accession of electrons to the nuclear carbon atoms situated *o* and *p* with respect to an electron-repulsive group, while *m*-substitution takes place when an electron-attractive group withdraws electrons from the nucleus as a whole, but especially from the *o*- and *p*-positions.[14]

op-substitution.



m-substitution.



Clearly, if the influence of a substituent were due solely to its inductive effect, all those groups which increase the strength of a saturated aliphatic acid would lead to *m*-substitution; the *op*-directive influence of groups such as hydroxyl and halogens thus confirms the conclusion, already reached on different grounds,[15] that these groups give rise to electronic displacements which are distinct from their inductive effects. The case of halogens is particularly complex. In accordance with its electron-attractive character,

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[12] Soper and Smith, *J.C.S.* 1926, 1582; 1927, 2757.

[13] Ingold, *J.C.S.* 1933, 1120.

[14] The reason for the *selective* activation or deactivation of the *o*- and *p*-positions will appear in Chap. V.

[15] See Chap. III, p. 43.

chlorine deactivates the nucleus, since substitution in chlorobenzene is slower than in benzene, and a chlorine atom in one ring of naphthalene causes a second substituent to enter the other ring. Yet its directive influence is *op*. These peculiarities are discussed in the following chapter.

Substituent groups in a saturated side-chain (e.g. X in $C_6H_5 \cdot CH_2X$) exert influences in accordance with their inductive effects. This is illustrated by the increasing percentage of *m*-derivative present in the products of nitration in the following instances:[11]

$C_6H_5 \cdot CH_3$	$C_6H_5 \cdot CH_2Br$	$C_6H_5 \cdot CH_2Cl$	$C_6H_5 \cdot CH_2F$	$C_6H_5 \cdot CH_2 \cdot NO_2$
4 per cent.	7 per cent.	12 per cent.	18 per cent.	48 per cent.

(compare also the chlorinated derivatives of toluene referred to on p. 47). The falling off of the effect with increasing distance of the group from the nucleus is exemplified in the following series of figures for the percentage of *m*-derivative formed on nitration;[11]

$C_6H_5 \cdot \overset{+}{N}(CH_3)_3$	$C_6H_5 \cdot CH_2 \cdot \overset{+}{N}(CH_3)_3$	$C_6H_5 \cdot CH_2 \cdot CH_2 \cdot \overset{+}{N}(CH_3)_3$	$C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot \overset{+}{N}(CH_3)_3$
100 per cent.	88 per cent.	19 per cent.	5 per cent.

$C_6H_5 \cdot NO_2$	$C_6H_5 \cdot CH_2 \cdot NO_2$	$C_6H_5 \cdot CH_2 \cdot CH_2 \cdot NO_2$
93 per cent.	48 per cent.	13 per cent.

Before concluding this survey of the facts relating to aromatic substitution, a brief reference must be made to two recent generalizations or orientation rules which appear to be of general application. Hammick and Illingworth[16] have pointed out that, in a benzene derivative C_6H_5XY, when Y is in a higher periodic group than X, or, if in the same group, is of lower atomic weight, XY is *m*-directive; in all other cases, including that where the substituent is a single atom, *op*-direction results. The rule appears to hold generally, with the reservation that an integral charge residing on XY will always take control, a positive charge directing *m*, and a negative charge *op*. The other observation is due to Sutton, who has detected a relationship between the directive influence of a group X and the sign of the difference between the moments of Aryl X and Alphyl X.[17] If, using the conventional positive and negative signs for the

[16] *J.C.S.* 1930, 2358.

[17] *Proc. Roy. Soc.* 1931, **133 A**, 668.

moments, the difference ($\mu_{\text{Aryl X}}-\mu_{\text{Alphyl X}}$) is positive, then X is *op*-directive; if it is negative, X is *m*-directive. In order to make the moments comparable, Sutton uses, when values are available, those of aliphatic compounds where the group X is linked to tertiary carbon;[18] the possibilities of induced polarization in bonds adjacent to C—X are then as nearly as possible equal. The following table illustrates Sutton's relationship; all the values recorded are for solutions in benzene.

Group X	$\mu_{\text{Aryl X}}$	$\mu_{\text{Alphyl X}}$	*Difference*	*Directive influence*
CH_3	+0·41	0	+0·41	*op*
Cl	−1·56	−2·15	+0·59	*op*
Br	−1·53	−2·21	+0·68	*op*
I	−1·30	−2·13	+0·83	*op*
CH_2Cl	−1·82	−2·14	+0·32	*op*
CN	−3·90	−3·46	−0·44	*m*
NO_2	−3·97	−3·29	−0·68	*m*

Groves and Sugden have more recently drawn up a similar table employing values measured in the vapour state; for $\mu_{\text{Alphyl X}}$ they use the limiting values to which the moments of the homologous series *n*-Alphyl X tend. Their table is as follows:[19]

Group	$\mu_{\text{Aryl X}}$	$\mu_{\text{Alphyl X}}$	*Difference*	*Directive influence*
F	−1·57	−1·92	+0·35	*op*
Cl	−1·73	−2·04	+0·31	*op*
Br	−1·71	−2·08	+0·37	*op*
CN	−4·37	−4·07	−0·30	*m*
NO_2	−4·24	−4·03	−0·21	*m*
$CO\cdot CH_3$ . . .	−3·00	−2·80	−0·20	*m*

The vapour values confirm Sutton's generalization, although the differences are smaller than for the moments found in solution.

The permanent electron displacements set up when a group is attached to the aromatic nucleus are thus in the direction necessary for its observed directive influence, being away from the group when substitution is *op*, and towards the group when substitution is *m*. It must not, however, be assumed that these permanent effects are

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[18] For example, Alphyl Cl is *tert*-butyl chloride. This accounts for the fact that the moments of the alphyl compounds in the above table are not identical with those given in Chap. II, p. 31.

[19] *J.C.S.* 1935, 973.

solely responsible for the directive influences, since time-variable effects may operate, and the group will behave in accordance with the sum of the variable and permanent factors.[20]

Side-Chain Reactions. Reference has already been made[21] to the 'electrophilic' character of the common reagents which bring about the replacement of nuclear hydrogen by another atom or group. They attack those points of the molecule where electrons are available, and substitution is therefore, in general, accelerated by *op*-directive groups, which give rise to such points. Olivier was the first to direct attention to the existence of a 'correspondence' between the effects of groups upon nuclear substitution of hydrogen and upon certain reactions in a side-chain.[22] He studied the hydrolysis of a series of substituted benzyl chlorides in aqueous alcohol (solution originally neutral and becoming acid),[23]

$$X{\cdot}C_6H_4{\cdot}CH_2Cl+H{\cdot}OH = X{\cdot}C_6H_4{\cdot}CH_2OH+HCl.$$

The order of decreasing reactivity when X varied was as follows: $CH_3 > H > Hal > NO_2$; i.e. groups which increase the speed of nuclear substitution of hydrogen also increase that of the replacement of chlorine in the side-chain, and vice versa. A number of other side-chain processes are accelerated by electron-repulsive groups and retarded by electron-attractive groups in the nucleus, and all of these are referred to as reactions of 'Type A'.[24] They obviously include processes in which an electrophilic reagent brings about the substitution of hydrogen as in side-chain chlorination, and the formation of quaternary ammonium salts from dialkylanilines where the controlling factor is the electron-availability of the nitrogen atom.[25]

There exists also a large class of side-chain reactions, termed 'Type B', in which substituents have the reverse effect; the general order of velocities is indicated by the sequence

$$NO_2 > Hal > H > CH_3.$$

These include various *alkaline* hydrolyses, in which the controlling

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[20] Compare Chap. III, p. 44. Also following chapter.

[21] p. 49.

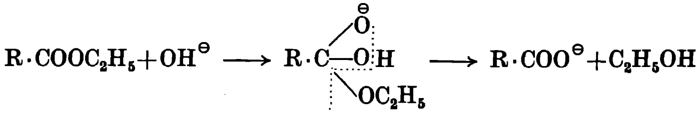
[22] *Rec. trav. chim.* 1923, **42**, 775.

[23] Bennett and B. Jones (*J.C.S.* 1935, 1815) have more recently studied the same reaction, with similar results.

[24] Ingold and Rothstein, *J.C.S.* 1928, 1217. See list of reactions given by Williams, *J.C.S.* 1930, 40.

[25] See W. C. Davies and Lewis, *J.C.S.* 1934, 1599.

step is the attack of the hydroxyl ion; e.g. the hydrolysis of benzoic, phenylacetic, and cinnamic esters[26] which may be formulated



$$R\cdot COOC_2H_5 + OH^{\ominus} \longrightarrow R\cdot C(O^{\ominus})(OH)(OC_2H_5) \longrightarrow R\cdot COO^{\ominus} + C_2H_5OH.$$

Hydroxyl, in common with other anions, has its full quota of electrons, and hence seeks a point of attack where there is a *deficiency* of electrons; it is positive-centre-seeking or 'nucleophilic'.[27] Alkaline hydrolyses are therefore favoured by electron-attractive substituents, which tend to draw electrons away from the side-chain. The alkaline hydrolysis of benzyl chlorides is a reaction of 'Type B'.[28] Their hydrolysis in acid solution is of 'Type A' (see preceding page) because it is not a straightforward bimolecular reaction; its speed is governed mainly by the ease of removal of the chloride ion. This is considered more fully in the following section.

Mechanism of Substitution. It is evident from the foregoing that substituting reagents and substitution processes (the word 'substitution' now being used in its widest sense) are divisible into two classes, which Ingold has described as 'electrophilic' and 'nucleophilic'. The processes may be represented by the following general equations, where the dotted lines indicate the fate of the electron pairs originally forming the covalent bonds which are broken:

Electrophilic substitution
$$\begin{cases} R\text{—}\vdots X + Y\text{—}\vdots Z = R\text{—}Z + X\text{—}Y \\ R\text{—}\vdots X + Z = R\text{—}Z + X \end{cases}$$

Nucleophilic substitution
$$\begin{cases} R\vdots\text{—}X + Y\vdots\text{—}Z = R\text{—}Z + X\text{—}Y \\ R\vdots\text{—}X + Z = R\text{—}Z + X. \end{cases}$$

It is important to realize that the terms 'electrophilic' and 'nucleophilic' have no reference to the electrical (neutral or charged) condition of the reagent, but exclusively to its electron-accepting or electron-donating capacity.[29] This point will be made clear by an

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[26] Kindler, *Annalen*, 1926, **450**, 1; 1927, **452**, 90; 1928, **464**, 278; Ingold and Nathan, *J.C.S.* 1936, 222. In the hydrolysis of an ester R·COOR′, the —OR′ group is removed to form alcohol (as represented in the above scheme). This has been demonstrated by Polanyi and Szabo (*Trans. Faraday Soc.* 1934, **30**, 508), who hydrolysed amyl acetate using water containing an excess of the isotope O^{18}, and found the *normal* isotope ratio in the amyl alcohol produced.

[27] Ingold, ref. 13.

[28] Shoesmith and Slater, *J.C.S.* 1924, **125**, 1312, 2278.

[29] For this reason the terms 'electrophilic' and 'nucleophilic' are here preferred to 'kationoid' and 'anionoid' used by Lapworth and others [see e.g. Robinson, *Outline of an Electrochemical Theory of the Course of Organic Reactions* (Institute of Chemistry, 1932), p. 13]. Compare Ingold, ref. 13 (p. 1121, footnote).

appreciation of the essential similarity of the three processes $NH_3+H^{\oplus} \rightarrow NH_4^{\oplus}$, $BCl_3+NH_3 \rightarrow BCl_3 \cdot NH_3$, and $BF_3+F^{\ominus} \rightarrow BF_4^{\ominus}$. In the first, one of the reagents is charged *positively*, in the second both are *neutral*, while in the last one is a *negative* ion. But the possibility of co-ordination is not connected with these facts; it depends solely upon the ability, in each case, of one reagent to provide electrons and of the other to accept them.

It has frequently been postulated that, in substitution reactions, the removal of the replaced group is preceded by an addition process. This view of the substitution of hydrogen in the benzene nucleus was held by Kekulé, and has had many exponents in later years.[30] A definite addition complex can be formed, however, only by the co-ordination of one of the reacting substances with an unshared electron pair of the other, and this conception meets with considerable difficulties, due mainly to the limitations of valence groups and the lack of polarizability of saturated carbon atoms.[31] The modern view, first expressed by London,[32] visualizes simultaneous addition of the one group and removal of the other.

For either mechanism the substitution will be a bimolecular reaction, proceeding at a speed which is proportional to the concentrations of both the reagent and the substance attacked. This is in agreement with the observed kinetics of the majority of substitutions, both electrophilic and nucleophilic. There are, however, notable examples of such processes which occur with unimolecular kinetics. The work of Olivier and Weber has shown, for instance, that the velocity of hydrolysis of benzyl chloride by alkali hydroxide is dependent upon the concentration of hydroxyl ion, but not in any simple manner, while benzal chloride and benzotrichloride are hydrolysed at speeds which are *independent* of the presence or absence of alkali;[33] the reaction is unimolecular, and the same applies to the hydrolysis of benzhydryl chloride.[34] Hughes and Ingold find, moreover, that the hydrolysis of *iso*propyl and *tert*-butyl halides in

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[30] Compare, for example, Ingold and Ingold's mechanism of nitration, *J.C.S.* 1926, 1313.

[31] Reactions such as ester hydrolysis do not, however, present this difficulty owing to the polarizability of the carbonyl group, and an addition compound of ethyl benzoate with sodium methoxide has actually been isolated (von Pechmann, *Ber.* 1898, **31**, 503).

[32] *Z. Elektrochem.* 1929, **35**, 552. This view is considered more fully in Chap. XI.

[33] *Rec. trav. chim.* 1934, **53**, 869.

[34] Ward, *J.C.S.* 1927, 2285.

60 per cent. aqueous alcohol occurs by a unimolecular mechanism,[35] and they point out that, in cases such as these, the measured speed is probably that of a slow ionization, the complete change being

$$RX \xrightarrow{\text{slow}} R^{\oplus}+X^{\ominus}$$

$$R^{\oplus}+OH^{\ominus} \xrightarrow{\text{rapid}} ROH.$$

They summarize the known facts regarding the kinetics of the hydrolysis of alkyl halides in aqueous media in the following table, where S_N1 and S_N2 represent respectively the unimolecular and bimolecular mechanisms of the nucleophilic substitution.

Mechanism of Hydrolysis of Alkyl Halides, RX (*from Hughes and Ingold*)

Mechanism . . .	S_N2		S_N1	
Group R	$CH_3—$	$CH_3\cdot CH_2—$	$\left.\begin{matrix}CH_3\\CH_3\end{matrix}\right\rangle CH—$	$\left.\begin{matrix}CH_3\\CH_3\\CH_3\end{matrix}\right\rangle C—$
Reaction order . .	2	2	1	1
Velocity	—decrease→		—increase→	

The series shows a 'mechanistic critical point' which, as Hughes and Ingold point out, may change its position with variations of the medium, a strongly ionizing solvent favouring the unimolecular mechanism and vice versa. The electron-repulsive methyl substituent

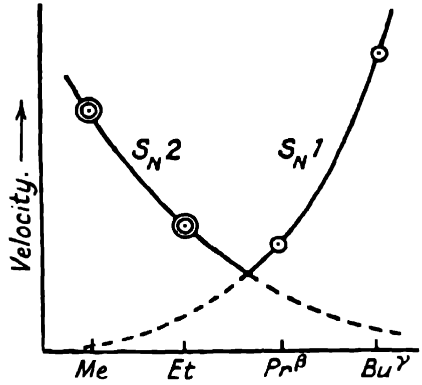

FIG. 5. Velocities of hydrolysis of alkyl halides. (Reproduced from Gleave, Hughes, and Ingold, *J.C.S.* 1935, 238)

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[35] *J.C.S.* 1935, 244, and references there cited. The reader is referred to this paper for a full discussion of the mechanism of substitution reactions, illustrated by numerous examples from the literature. See also later papers by the same authors.

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retards the bimolecular change as in other alkaline hydrolyses, but accelerates the ionization which is the measurable stage of the unimolecular mechanism. There is thus a decrease in velocity from methyl to ethyl halides, and an increase from *iso*propyl to *tert*-butyl halides. Similar variations in velocity and reaction mechanism were observed by the same authors in the degradation of sulphonium salts.[36] The conversion of trimethyl- and triethyl-sulphonium hydroxides to alkyl sulphides ($R_3S^{\oplus}+OH^{\ominus} = R_2S+ROH$) were found to be bimolecular, the latter being the slower, while methyldi*iso*propyl- and dimethyl-*tert*-butyl-sulphonium hydroxides were degraded by a unimolecular mechanism, the latter being the more rapid. The relationships are illustrated in Fig. 5, which is reproduced from the paper by Gleave, Hughes, and Ingold.

In the hydrolysis of benzyl chloride, where the group R is $C_6H_5 \cdot CH_2$—, both mechanisms operate[37] and the velocity is therefore dependent upon but not proportional to the concentration of hydroxyl ion. Either mechanism may predominate, according to the conditions under which the hydrolysis is conducted. This accounts for the substitution (which, of course, is nucleophilic) being a 'Type A' reaction in neutral or acid solution[38] whereas in alkaline solution it is of 'Type B', as would be expected.

The mechanism of substitution reactions is discussed further, from the physical point of view, in Chapter XI.

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[36] Gleave, Hughes, and Ingold, *J.C.S.* 1935, 236.

[37] The effect of phenyl is considered on p. 75.

[38] See p. 52.

V

APPLICATIONS OF THE ELECTRONIC THEORY IN ORGANIC CHEMISTRY. GENERAL DISCUSSION[1]

THE observations described in the preceding chapters lead inevitably to the conclusion that, relatively to hydrogen, the standard of reference, atoms and groups may either repel or attract electrons. This is clearly demonstrated, for example, by the values of the molecular electric moments of organic compounds, by the strengths of acids, bases, and phenols, and by the known facts concerning a large variety of chemical reactions. The effect of this repulsion or attraction of electrons (Flürscheim's 'polar factor') is relayed by induction along a chain of atoms ('inductive effect') and also transmitted through space or the medium ('direct' or 'field' effect), as first visualized by G. N. Lewis in 1916. In either case it diminishes with increasing distance from the source. It is not possible to determine the proportion which is transmitted by either route, and Ingold's term 'inductive effect' is almost invariably employed to denote the whole effect, irrespective of the mode of propagation. It is conventional to represent repulsion and attraction of electrons by positive and negative signs respectively; thus the effect of the group X in $X \rightarrow C$ is designated $+I$, and that of Y in $Y \leftarrow C$ is written $-I$.[2] The most powerful of all inductive effects are those of atoms with which an integral charge is associated, such as nitrogen in a quaternary ammonium salt or oxygen in the phenoxide ion. It must be emphasized that the inductive effect does not involve covalency changes. The electrons do not lose contact with one nucleus, nor do they come under the influence of another; the covalent pair may be regarded as simply drawn nearer to one nucleus, the octets remaining intact. Moreover, the effect represents a *permanent* condition of the molecule, measurable in the electric moment.

Another and distinct type of electronic displacement is possible, however, in suitable systems. This was first postulated by Lowry in 1923,[3] when he ascribed the reactivity of double linkages to a

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[1] See Ingold, *Chem. Reviews*, 1934, **15**, 225; also, idem, *J.C.S.* 1933, 1120; Robinson, *Outline of an Electrochemical Theory of the Course of Organic Reactions* (Institute of Chemistry, 1932).

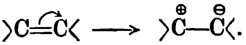
[2] But see p. 40 footnote 34.

[3] *J.C.S.* 1923, **123**, 822.

polarization in which a pair of electrons from the double bond becomes the sole property of one atom. In the case of the olefinic bond this may be represented as follows:

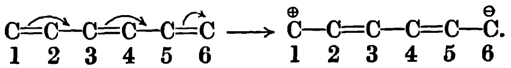
$$\mathrm{C} :: \mathrm{C} \longrightarrow \overset{\oplus}{\mathrm{C}} : \overset{\ominus}{\mathrm{C}} :.$$

Such displacements, in which 'electrons whilst remaining in one octet enter or leave another',[4] are termed 'electromeric', and are denoted by a curved arrow, thus:



$$\rangle\mathrm{C}{=}\mathrm{C}\langle \longrightarrow \rangle\overset{\oplus}{\mathrm{C}}-\overset{\ominus}{\mathrm{C}}\langle.$$

Electromeric displacements may proceed along the full length of a chain of atoms linked by alternate single and double bonds:



$$\underset{1}{\mathrm{C}}{=}\underset{2}{\mathrm{C}}-\underset{3}{\mathrm{C}}{=}\underset{4}{\mathrm{C}}-\underset{5}{\mathrm{C}}{=}\underset{6}{\mathrm{C}} \longrightarrow \overset{\oplus}{\underset{1}{\mathrm{C}}}-\underset{2}{\mathrm{C}}{=}\underset{3}{\mathrm{C}}-\underset{4}{\mathrm{C}}{=}\underset{5}{\mathrm{C}}-\overset{\ominus}{\underset{6}{\mathrm{C}}}.$$

The arrows here indicate that a pair of electrons from the C_1C_2 double bond is released by C_1 and comes under the control of C_3, a double bond between C_2 and C_3 thus being formed; the normal covalency of C_3 is restored by the release of a pair from the C_3C_4 bond; this leads to a double linkage between C_4 and C_5, and finally two electrons from the C_5C_6 double bond become the sole property of C_6. A series of *incomplete* electronic migrations of this kind may be regarded as the electronic analogue of Thiele's conception of 'conjugation'.[5] It is evident that such migrations can occur only in suitable systems such as a chain of alternate single and double bonds or the benzene ring; a chain of saturated carbon atoms would be disrupted by a similar process.

The modern conception of quantum-mechanical resonance, which is a deduction from the equations of wave mechanics, has contributed very materially to our understanding of the significance of

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[4] Ingold, *Rec. trav. chim.* 1929, **48**, 798. The term 'tautomeric' is also employed (idem, *Ann. Reports*, 1926, **23**, 140; ref. 1) since these migrations are involved in a tautomeric change such as $\mathrm{CH_2}\overset{\frown}{=}\mathrm{CH}\cdot\mathrm{CH_2}\cdot\mathrm{COOH} \rightarrow \mathrm{CH_3}\cdot\mathrm{CH}{=}\mathrm{CH}\cdot\mathrm{COOH}$. The *curved* arrow distinguishes electromeric from inductive displacements, which are denoted by a *straight* arrow.

[5] See Chap. VIII. Electromeric displacements were originally described by the term 'conjugation' (Allan, Oxford, Robinson, and Smith, *J.C.S.* 1926, 401). The term 'conjugate system' is commonly applied to those in which such displacements are possible, and will be used in the sequel.

electromeric displacements.[6] In Chapter I the phenomenon of resonance was illustrated by reference to a system of two hydrogen atoms. The energy states of the isolated atoms are determined by the solutions of the appropriate wave equations, but when they interact the combined equation has a solution (representing the hydrogen molecule in its stable or resting state) for which the total energy is a minimum, i.e. less than the sum of the energies of the isolated atoms. A similar treatment is applicable to any molecule which can be represented by two or more structures in which the positions of the nuclei are approximately the same and the energies of the same order of magnitude, but the dispositions of the electrons different.[7] The wave-mechanical equation now reveals the important fact that a minimum of energy, and therefore a maximum of stability, is possessed by a structure intermediate between those which can actually be written by formulae of the usual type. In this structure, also, the distances between the nuclei are somewhat reduced.[8] The molecule will normally exist in this condition of maximum stability, to which Ingold applies the term 'mesomeric state' ('mesomeric' = between the parts). The individual structures which are capable of representation are described as 'unperturbed structures', and are derived the one from the other by electromeric displacements. If they have identical energies, the mesomeric state will be symmetrically related to them; otherwise it will approximate more closely to the form of lower energy (and therefore greater stability). Ingold points out that the unperturbed structures have no existence as states of the molecule, and are of the nature of 'intellectual scaffolding'; the actual condition of the molecule is that represented by the mesomeric form.

As a simple example, the carbon dioxide molecule may be considered. It is linear (zero dipole moment), and can be written by any of the formulae I, II, and III below (unperturbed structures):

$$\begin{array}{ccc} \text{I} & \text{II} & \text{III} \\ \mathrm{O{=}C{=}O} & \overset{\ominus}{\mathrm{O}}\mathrm{{-}C{\equiv}}\overset{\oplus}{\mathrm{O}} & \overset{\oplus}{\mathrm{O}}\mathrm{{\equiv}C{-}}\overset{\ominus}{\mathrm{O}}. \end{array}$$

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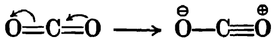
[6] See Ingold, ref. 1; Sidgwick, *Ann. Reports*, 1934, **31**, 37; *J.C.S.* 1936, 533; 1937, 694.

[7] In the case of the hydrogen molecule, the two structures may be represented ($A1+B2$) and ($A2+B1$), where A and B denote the nuclei and 1 and 2 denote the electrons. These structures, of course, have identical energies, and the mesomeric state is therefore symmetrical with respect to them.

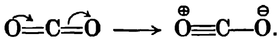
[8] See Sidgwick, ref. 6; Penney and Kynch, *Ann. Reports*, 1036, **33**, 45.

Structures II and III are clearly derived from I by the electromeric displacements

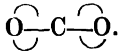


$$O{=}C{=}O \longrightarrow \overset{\ominus}{O}{-}C{\equiv}\overset{\oplus}{O}$$

and

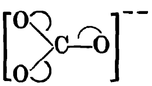


$$O{=}C{=}O \longrightarrow \overset{\oplus}{O}{\equiv}C{-}\overset{\ominus}{O}.$$

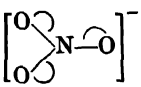
The distances between the atoms in these structures and the energy of formation of each can be calculated, at least approximately, and are almost the same for the three; the distance between the oxygen atoms is about 2·56 A, and the heat of formation is not far removed from 350,000 calories. The necessary conditions for resonance are therefore fulfilled, viz. similarity both in nuclear positions and in energy content; the *same molecule* can be represented by structures having different arrangements of the electrons but not very different energies. The values found experimentally for carbon dioxide are as follows: separation of oxygen atoms, 2·30 A; heat of formation, 380,000 calories. The interatomic distances are thus somewhat less than those calculated for the individual unperturbed structures, and the energy content is very appreciably less. This is in accordance with the predictions of wave mechanics, and the conclusion is therefore reached that the carbon dioxide molecule, in its normal condition, is represented not by any of the structures which can actually be written, but by a mesomeric state of lower energy. This state is conveniently depicted .

Resonance in the carbonate and nitrate ions is indicated by the symmetry of these structures as demonstrated by X-ray and infra-red spectroscopy. The oxygen atoms are equivalent, and hence the ions are to be represented as in IV and V, and not by VI and VII (below).

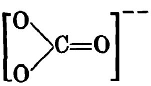
IV



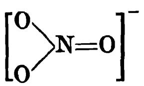
V



VI



VII



The nitro-group provides a very interesting example. Reference has already been made to the evidence obtained from parachor measurements.[9] The zero dipole moments of *p*-dinitrobenzene and *s*-trinitrobenzene, however, prove this group to be symmetrical. The structure VIII (below) would lead to a considerable moment in these com-

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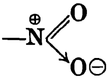
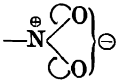
[9] Chap. I, p. 7.

pounds, as is found for *p*-phenylene diamine and its derivatives,[10] since all but one of the possible positions of the nitro-groups would give a definitely polar molecule. The group therefore has the mesomeric structure IX, which is intermediate between the unperturbed forms VIII and X:

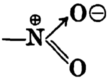
VIII



IX



X



the negative charge being distributed between the two oxygen atoms.

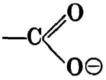
The method described above for carbon dioxide has been applied by Pauling and Sherman to demonstrate the existence of resonance in a number of compounds.[11] They compare the heats of formation, as found experimentally, with those calculated by summation of the 'bond energies' (obtained from thermochemical data), and arrive at the result that, in cases where resonance is to be anticipated, the former are invariably greater than the latter (indicating a *smaller* energy content for the molecule). For example, the heat of formation of the carbonyl bond is unusually high owing to resonance between XI and XII:

XI $\rangle C{=}O$

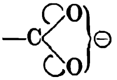
XII $\rangle \overset{\oplus}{C}{-}\overset{\ominus}{O}$

The mesomeric state will here approach much more closely to the normal structure XI than to the structure XII, since the strongly dipolar character of the latter decreases its stability. In the carboxylate ion the resonance energy is considerable, for the mesomeric form XIV, which is reminiscent of the Hantzsch formula for the carboxyl group,[12] will be related symmetrically to the unperturbed structures XIII and XV:

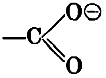
XIII



XIV



XV



Esters and amides show a similar phenomenon, and this resonance accounts satisfactorily for the absence of typical carbonyl properties in carboxylic acids and their derivatives.

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[10] See Chap. II, p. 30.

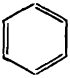
[11] *J. Chem. Physics*, 1933, **1**, 606. See also Pauling and Wheland, ibid., p. 362.

[12] *Ber.* 1917, **50**, 1422.

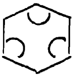
Ethylene no doubt exists in a mesomeric state between $>C{=}C<$, $>\overset{\oplus}{C}-\overset{\ominus}{C}<$, and $>\overset{\ominus}{C}-\overset{\oplus}{C}<$; transformation to one of the dipolar structures probably occurs at the instant of reaction, as postulated by Lowry. The presence of a substituent will facilitate *one* of the electromeric polarizations as in $X\rightarrow CH\overset{\curvearrowright}{=}CH_2$ or $Y\leftarrow C\overset{\curvearrowleft}{H{=}}CH_2$. Similar remarks apply to a chain of alternate single and double bonds. In all these cases, however, the stability of one (or more) of the unperturbed structures is decreased by its dipolar character, and the mesomeric state is relatively near to the non-polar form. But in a cyclic system the electromeric polarizations do not produce a dipolar molecule, and the unperturbed structures of benzene (XVI and XVII below) are completely equivalent. A mesomeric state XVIII, related equally to these, is thus to be anticipated, a conclusion which may be compared with the pre-electronic views of Kekulé and Thiele.

XVI

XVII



XVIII



The calculations of Pauling and his collaborators[11] indicate a considerable resonance energy in aromatic compounds, and the symmetry of benzene has recently been demonstrated by Ingold and his co-workers.[13] It is this resonance which is responsible for the peculiar stability of the aromatic nucleus. Pauling and Sherman observe a similar phenomenon in pyridine, but the resonance energy of pyrrole is smaller, in harmony with its more feebly aromatic character. They also find, as would be anticipated, a higher resonance energy in polynuclear systems such as naphthalene, anthracene, phenanthrene, quinoline, diphenyl, and indole, and in the combined aromatic-olefinic systems of styrene, stilbene, and *as*-diphenylethylene.[14]

It is now possible to discuss a feature of certain groups to which reference has already been made. The considerations outlined in the preceding chapters have made it clear that the influence of a group cannot always be expressed completely in terms of its inductive effect. There are definite indications of the operation of additional factors

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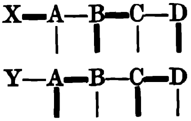
[13] See Chap. II, p. 22.

[14] The lack of aromatic character in cyclo-octatetraene may be due to a non-uniplanar configuration (Penney, *Proc. Roy. Soc.* 1934, **146**, A, 223).

which are distinct from the inductive effect and, since they may even differ from it in sign, must have a different mechanism. Long before the advent of the electronic theory of valency, the necessity for postulating at least *two* independent factors was pointed out by Vorländer,[15] who suggested that the influence of a group is dependent both upon its polar character and upon its 'state of saturation', and the development of this general view may be traced in the writings of Flürscheim, Lapworth, and others. Its translation into electronic terms was achieved mainly by Robinson and Ingold.

In the early years of this century theoretical organic chemistry was influenced very powerfully by the contrast which appeared to exist, in benzene derivatives, between the *ortho* and *para* (2,4,6) positions on the one hand and the *meta* (3,5) positions on the other; great significance was attached to the fact that substitution occurs mainly *either* at the *o*- and *p*-carbon atoms *or* at the *m*-carbon atom. This led to the assumption of an alternation either in the 'affinity contents' of bonds or in the polarities of the carbon atoms of the benzene nucleus (and also, indeed, of a saturated chain). The theory of alternating affinities was used with considerable success by Flürscheim (1902 and later).[16] Adopting the views of Werner, he regarded each atom as being endowed with a definite amount of available affinity; when combination occurred, other atoms claimed varying proportions of this affinity, which was thus utilized to a large extent in forming bonds ('bound affinity'). Some 'residual' or 'free' affinity remained, however, and the reactivity of the combined atom was dependent upon this. These postulates led to the conceptions of alternate bonds of high and low affinity ('strong' and 'weak' bonds) and alternate atoms of high and low residual affinity. This is illustrated in the formulae below, where large and small amounts of affinity are represented by thick and thin lines respectively.



The atom X, having a high 'affinity demand' (i.e. greater than that of hydrogen), forms a 'strong' bond with A (thick line); the available

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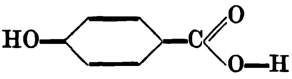
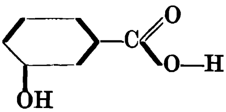
[15] *Annalen*, 1902, **320**, 110.

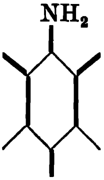
[16] See *J.C.S.* 1909, **95**, 718; *Chem. and Ind.* 1925, **44**, 246, and references there cited.

affinity of A is thus largely utilized in forming the bond, leaving a relatively small amount for the link with B and also a small amount of residual affinity on A (thin lines). B, having used only a small proportion of its affinity in the bond with A, has a high residual affinity and also forms a 'strong' bond with C (thick lines), and so on. The atom Y, on the other hand, has a low affinity demand (less than that of hydrogen), and hence the state of affairs is completely reversed. The effect of this distribution of affinity is termed by Flürscheim the 'quantitative factor', and is regarded as being superimposed upon the 'polar factor'.[17] The following are examples of Flürscheim's use of these conceptions. The fact that *p*-hydroxybenzoic acid is *weaker* than the unsubstituted acid, while its *m*-isomeride is *stronger,* is ascribed to a high affinity demand on the part of hydroxyl, leading to the alternations

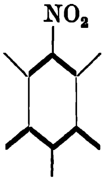




In the *m*-substituted acid the quantitative factor reinforces the polar factor, leading to a stronger acid, while in the *p*-acid it operates against the polar factor and is strong enough to overcome it. Directive influences in aromatic substitution were also ascribed to the varying affinity demands of substituents; a demand greater than that of hydrogen leads to the development of free affinity at the *o*- and *p*-positions where substitution therefore occurs, while conversely a demand less than that of hydrogen leads to *m*-substitution. This is illustrated below.



(*op*-substitution)



(*m*-substitution)

The rival theory postulated the development of positive and negative charges, perhaps permanently, or perhaps at the moment of reaction, on alternate carbon atoms. The theories of Fry[18] and Vorländer[19]

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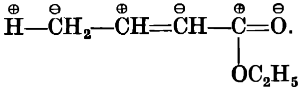
[17] See Chap. III, p. 38.

[18] *The Electronic Conception of Valence* (Longmans, 1921).

[19] *Ber.* 1919, **52**, 263; 1925, **58**, 1898.

were of this type. The alternate polarity view was adopted by Lapworth,[20] who regarded the alternations as being induced by a 'key-atom', and requiring, for their full development, a system of alternate single and double bonds. Lapworth based his theory on arguments such as the following. The addition reactions of the carbonyl group (e.g. cyanohydrin formation) lead to the representation $\rangle\overset{\oplus}{C}=\overset{\ominus}{O}$; this refers to the behaviour of the group at the instant of reaction, and permanent polarization is not postulated. The aldol reaction, in which $\rangle CH-CO-$, for example, takes the place of HCN in cyanohydrin formation, indicates that the hydrogen of this group is positive with respect to the α-carbon, and hence the representation is extended to $\overset{\oplus}{H}-\underset{\wedge}{\overset{\ominus}{C}}-\underset{|}{\overset{\oplus}{C}}=\overset{\ominus}{O}$, which is confirmed by the reaction $\rangle\overset{\oplus}{C}=\underset{|}{\overset{\ominus}{C}}-\underset{|}{\overset{\oplus}{C}}=\overset{\ominus}{O}+HCN=\rangle C(CN)-\underset{|}{C}H-\underset{|}{C}=O$.[21] The resemblance of the γ-hydrogen of ethyl crotonate to the α-hydrogen of ketones[22] leads to the further extension



$$\overset{\oplus}{H}-\overset{\ominus}{CH_2}-\overset{\oplus}{CH}=\overset{\ominus}{CH}-\underset{\substack{|\\OC_2H_5}}{\overset{\oplus}{C}}=\overset{\ominus}{O}.$$

These alternations are regarded as having their origin in the effect of the doubly linked oxygen, which is the 'key-atom'. It is clear that the alternate polarity and alternating affinity views, though based upon different premises, led to much the same interpretation of the processes of organic chemistry.

The expressions 'state of saturation' (Vorländer), 'affinity demand' (Flürscheim), and 'key-atom' (Lapworth) are capable of interpretation in terms of the electronic theory of valency, and the modern standpoint has been reached through the development, on electronic lines, of certain features of the older views, in conjunction first with Lowry's postulate of electromeric displacements and later with the conception of quantum-mechanical resonance. Just as Flürscheim's 'quantitative factor' and Lapworth's 'alternate polarity' were regarded as effects additional to or superimposed upon a 'polar factor' (Flürscheim) or 'general polarity' (Lapworth), so the 'electromeric' and 'mesomeric' effects of present theory represent influences which

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[20] *Mem. Manchester Phil. Soc.* 1920, **64**, No. 3; *J.C.S.* 1922, **121**, 416. Compare Kermack and Robinson, ibid., p. 427.

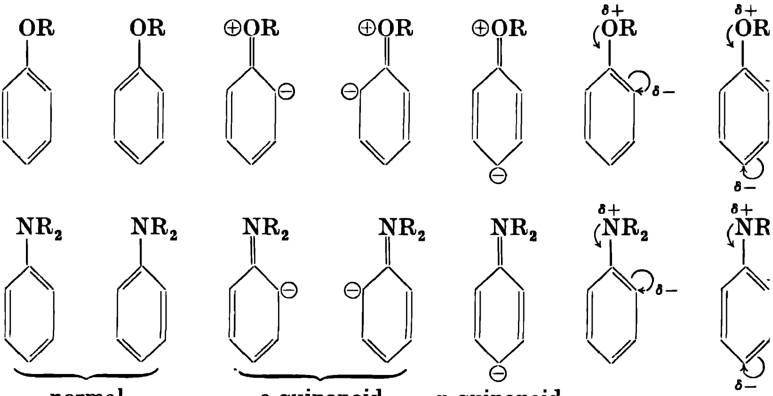
[21] Further reference to this reaction is made in Chap. VIII.

[22] Lapworth, *J.C.S.* 1901, **79**, 1273.

do not exclude but may operate in conjunction with or in opposition to the inductive effect.[23]

One of the most striking features of aromatic substitution is the powerful *op*-directive influence of certain groups which, judging from their effects upon the strengths of saturated aliphatic acids, would be described as electron-attractive (—I). Hydroxyl and groups —OR derived from it are prominent examples. The amino, alkylamino, and dialkylamino groups come into this category, although their influence upon acid dissociation cannot be determined since amino-acids are amphoteric electrolytes. Such groups have one characteristic in common, viz. the atom which is adjacent to the nucleus possesses unshared electrons. If one of these pairs were to enter the bond which links this atom with nuclear carbon, and the normal covalence of the latter were restored by further electromeric displacements in the nucleus, an alternative dipolar structure of a quinonoid type would be formed.[24] This is particularly significant in the case o phenols and anilines (and their derivatives), since compounds having oxygen or nitrogen doubly linked to nuclear carbon (quinones quinone-imines) are well known. The benzenoid and quinonoid structures, in fact, have all the characters necessary for resonance and all the structures I to V (below) participate in the mesomeri

I II III IV V VI VII



normal *o*-quinonoid *p*-quinonoid

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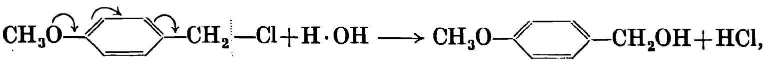
[23] The necessity for postulating two factors of a *polar* character appears to hav first been stated by Kermack and Robinson (*J.C.S.* 1922, **121**, 430) and by Lapwort and Shoesmith (ibid., p. 1391).

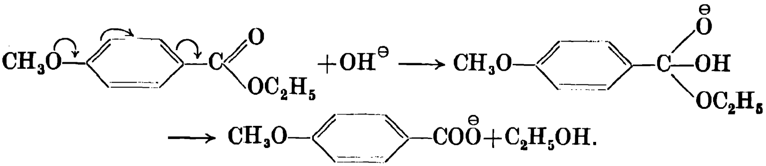
[24] The whole process would, of course, be impossible if the group were attached t a saturated system.

state. In other words, the group, by increasing its covalency with nuclear carbon, sets up permanent (though incomplete) electromeric displacements as represented in VI and VII. Ingold speaks of this as the Mesomeric Effect (+M). Evidence for the existence of such a permanent effect is found in the analysis of dipole moments by Sutton and by Bennett and Glasstone, already referred to.

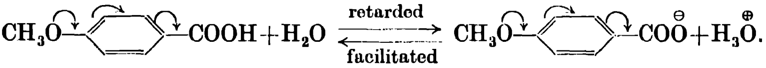
It is clear that the mesomeric effect of a group such as —OR or $—NR_2$ increases the electron-availability at the *o*- and *p*-positions, which acquire a fractional negative charge (indicated by $\delta-$ in VI and VII above). These positions will therefore form the points of attack by an electrophilic reagent, and hence the groups —OR and $—NR_2$ are *op*-directive. The mesomeric effect will also facilitate side-chain reactions of Type A,[25] e.g.



but will operate against Type B reactions, e.g.



The relatively low dissociation constants of *p*-hydroxybenzoic, *p*-anisic, and analogous acids are accounted for similarly, since the mesomeric effect of the group is unfavourable to dissociation and at the same time promotes recombination of the ions, e.g.



Since a *m*-quinonoid form is not possible (it would demand the expansion of the covalency of carbon beyond its limit of eight electrons), the mesomeric effect cannot be transmitted to the *m*-position. Thus *m*-OCH_3, for example, influences a reaction in a side-chain in accordance with its rather weak inductive effect (—I); this is illustrated by the facts that *m*-methoxybenzoic acid is *stronger* than benzoic (just as methoxyacetic is stronger than acetic acid), the order of strengths being *m*-$OCH_3 > H >$ *p*-OCH_3,[26] and that the *m*-substituted ester undergoes alkaline hydrolysis rather more

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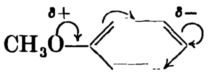
[25] The terms 'Type A' and 'Type B' are explained on p. 52.

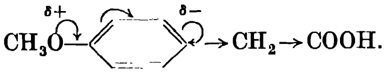
[26] Dippy, Watson, and Williams, *J.C.S.* 1935, 346.

quickly than ethyl benzoate does.[27] The effect of the fractional charge at the *ortho*- and *para*-carbon atoms may, however, be feebly relayed to the *m*-position by an inductive mechanism (VIII below), and a similar relay may occur along a saturated side-chain. For example, in *p*-methoxyphenylacetic acid the mesomeric effect of methoxyl cannot be transmitted *as such* to carboxyl through the intervening methylene group; nevertheless *p*-OCH_3 depresses the dissociation constant, a fact which is interpreted diagrammatically in IX below.[26]

VIII

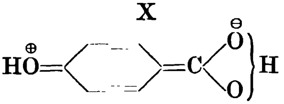


IX

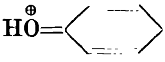


It is not necessary to suppose that the mesomeric effect of a given group is constant in magnitude; Bennett and Glasstone have shown, indeed, that it varies in different systems. For instance, the actual (mesomeric) state of *p*-hydroxybenzoic acid may approach the dipolar form X more closely than phenol approaches XI, and the deviations of some aromatic acids from the $\mu/\log K$ relationship, referred to in Chapter III, may be ascribed to this.[28]

X



XI



When an electrophilic reagent attacks a molecule, moreover, as in nuclear nitration, sulphonation, or halogenation, a further polarization is possible; the change to the quinonoid form, with its full charge at the *o*- or *p*-position, can be completed, and hence the group gives rise momentarily to a much more powerful activating effect. The very strong activation of the *o*- and *p*-positions by —OR and —NR_2 (as illustrated, for example, by the instantaneous bromination of phenol) must be ascribed to the total polarization which occurs as a result of the co-operation of the permanent and time-variable effects. The time-variable factor operates by the same mechanism as the mesomeric effect, but only at the demand of an attacking reagent; its magnitude may therefore vary from reaction to reaction. It is a *polarizability* effect and not a permanent

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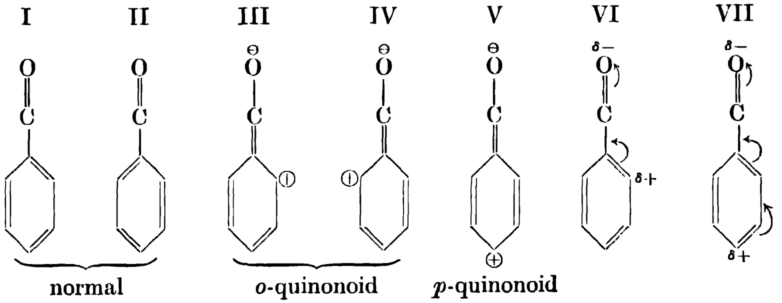
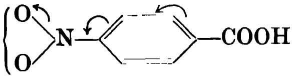
[27] Kindler, *Annalen*, 1926, **450**, 1; 1927, **452**, 90.
[28] See Chap. III, p. 43; also Chap. XI.

polarization. The name Electromeric Effect (+E) is given to this, and the sum of the two effects (M+E) is written with the symbol +T, indicating the tautomeric mechanism. The transmission of both effects will clearly be subject to the same limitation—a 'conjugated' system is necessary. An inductive relay of the electromeric effect is not possible, however, for it will be immediately absorbed by the attacking reagent; nor does the electromeric effect operate *against* a reaction, since it functions only at the demand of a reagent.

Groups such as —NO_2, —COR, —COOH, and —COOR, when linked to the aromatic nucleus, give rise to a state of affairs which is comparable with that produced by —OR and —NR_2, but in which the electromeric displacements are in the reverse direction. Thus, a compound $C_6H_5 \cdot COR$ exists normally in a mesomeric state to which all the forms I to V (below) contribute; the effect of the group is equivalent to the initiation of electromeric displacements *towards* itself (VI and VII). This is written —M.



This effect thus leads to a *decrease* in electron-availability at the *o*- and *p*-positions. The result is that, as regards the attack of an electrophilic reagent, the *o*- and *p*-positions are selectively deactivated, and therefore substitution occurs at the *m*-position. The groups —NO_2, —COR, etc., are therefore *m*-directive. Since these groups also have —I effects, the nucleus is also, to some extent, deactivated as a whole, and *m*-substitution is therefore slow in comparison with *op*-substitution. The latter is due to *activation* of the *o*- and *p*-positions; the former arises through *deactivation* of the whole nucleus and particularly the *o*- and *p*-positions. It is clear that the —M effect will facilitate side-chain reactions of Type B, and retard those of Type A. Like the +M effect, it cannot be transmitted to the *m*-position, and hence *p*-NO_2, for example, influences side-chain processes more powerfully than does *m*-NO_2. Thus, *p*-nitrobenzoic acid is stronger than its *m*-isomeride[26] on account of the process



and the speeds of alkaline hydrolysis of the nitrobenzoic esters stand in the order *p*-NO_2 > *m*-NO_2.[27] At the demand of a reagent the —M effect can develop into a —E effect, and the sum of the two is written —T. This will occur only at the demand of a *nucleophilic* reagent.

Ingold visualizes, in addition to the above polar effects, a time-variable factor, the Inductomeric Effect, which operates by an inductive mechanism. He summarizes the possible polar influences of groups as follows:[29]

Electronic mechanism	*Electrical classification*	
	Polarization	*Polarizability*
General inductive (→) (I) . .	Inductive	Inductomeric
Tautomeric (↷) (T) . . .	Mesomeric (M)	Electromeric (E)

Alkyl Groups. The dipole moments of all saturated aliphatic hydrocarbons are zero, whether the molecule is symmetrical or otherwise; since they are all derived from methane by successive replacements of hydrogen by —CH_3, it follows that such replacement does not confer polar characters upon the hydrocarbon molecule. Similarly, the moments of aliphatic alcohols, ketones, and nitro-compounds are almost constant throughout the homologous series. In the aliphatic nitriles the moments are practically constant after the second member (propionitrile). In alphyl chlorides there is an increase up to the *n*-propyl compound, but the iodides show a larger increase and the limiting value is not reached at *n*-butyl iodide; for bromides the moments increase more than for chlorides but less than for iodides. The following table records the values of the dipole moments of the earlier members of several homologous series of aliphatic compounds RX; they are the mean results of concordant measurements on vapours, as given by Groves and Sugden.[30] Values for R = H are also included.

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[29] *Chem. Reviews*, 1934, **15**, 233.

[30] *J.C.S.* 1937, 158.

Dipole Moments of Aliphatic Compounds RX

X =	Cl	Br	I	CN	NO_2	OH
R = H . . .	1·03	0·78	0·38	2·93	. .	1·84
R = CH_3 . . .	1·87	1·80	1·64	3·94	3·54	1·69
R = C_2H_5 . . .	2·05	2·01	1·87	4·04	3·58	1·69
R = *n*-C_3H_7 . . .	2·10	2·13	2·01	4·05	3·57	1·65
R = *n*-C_4H_9 . . .	2·11	2·15	2·08	4·09	3·55	1·65
R = *iso*-C_3H_7 . .	2·15	2·19	. .	. .	. .	1·63

The values, viewed as a whole, appear to indicate that alphyl groups have a rather feeble capacity for electron release, which increases with the size of the group up to a limit which is imperfectly defined and which varies with the attached group.[31] The sequence $CH_3 < CH_3 \cdot CH_2 < (CH_3)_2CH$ for alphyl chlorides and bromides, where hydrogen atoms are progressively replaced by methyl groups, leads inevitably to the conclusion that methyl is electron-repulsive. A similar electron-repulsion is also indicated by the dissociation constants of the lower saturated aliphatic acids (below).

Acid	$10^5 K_{\text{class}}$
$H \cdot COOH$	21·4
$CH_3 \cdot COOH$	1·82
$CH_3 \cdot CH_2 \cdot COOH$	1·34
$(CH_3)_3C \cdot COOH$	0·98

The influence of methyl upon the reactions of aliphatic compounds is illustrated by the hydrolysis of alphyl halides, to which reference has already been made.[32] Hydrolysis by a unimolecular mechanism ($RX \rightarrow R^{\oplus} + X^{\ominus}$ followed by $R^{\oplus} + OH^{\ominus} \rightarrow R \cdot OH$) will be facilitated by electron release on the part of R, while the reverse will hold for the bimolecular hydrolysis $RX + OH^{\ominus} \rightarrow R \cdot OH + X^{\ominus}$. Hughes and Ingold find that, while the hydrolysis of methyl and ethyl halides is bimolecular, the speed decreasing in the order $CH_3 > C_2H_5$, that of *iso*propyl and *tert*-butyl halides is unimolecular, the latter being the faster.[33] This is clearly to be ascribed to the electron repulsive action of the methyl groups, although the branched chains may also have some specific effect upon the stability of the ion.[34] Among aromatic and unsaturated compounds, examples of the capacity of alphyl groups for electron release are found in their *op*-directive

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[31] In all homologous series, hydrocarbons excepted, the increments in the heat of formation for successive additions of CH_2 grow larger as the series is ascended. See Sidgwick, *The Covalent Link in Chemistry* (Cornell University Press, New York, 1933), p. 115.

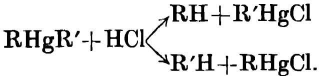
[32] See Chap. IV, p. 54.

[33] *J.C.S.* 1935, 244.

[34] Compare p. 84.

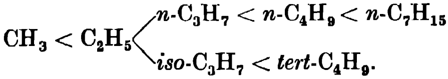
power and their influence upon side-chain reactions, the dipole moments of the homologues of benzene, the lower dissociation constants of *m*- and *p*-toluic acids than of benzoic acid, and the facilitation of the addition of bromine to ethylene by substituent alphyl groups.[35]

No conclusions concerning the *relative* effects of alphyl groups can be drawn from the dissociation constants of aliphatic acids, since the available values lack the accuracy which is necessary in view of the small differences. A comparison of groups extending from methyl to *n*-heptyl has been conducted, however, by Kharasch and Flenner[36] by a method in which they examined the products of decomposition by hydrogen chloride of unsymmetrical mercury dialkyls, RHgR′. Two reactions may occur:



$$RHgR'+HCl \begin{matrix} \nearrow RH+R'HgCl \\ \searrow R'H+RHgCl. \end{matrix}$$

If R is more electron repulsive (electropositive) than R′, hydrogen will combine preferentially with the latter, giving the hydrocarbon R′H in larger quantity than RH, and the product will contain a higher proportion of RHgCl than of R′HgCl. Treatment of various dialkyls in this manner led Kharasch and Flenner to the following order of increasing electron-repulsive character:



$$CH_3 < C_2H_5 \begin{matrix} \diagup\, n\text{-}C_3H_7 < n\text{-}C_4H_9 < n\text{-}C_7H_{15} \\ \diagdown\, \textit{iso-}C_3H_7 < \textit{tert-}C_4H_9. \end{matrix}$$

Experiments of the same type, in which lead tetra-alkyls were employed, have given similar results,[37] viz. $CH_3 < n\text{-}C_4H_9$ and $CH_3 < n\text{-}C_5H_{11}$. Other observations do not lead to such a simple or definite sequence, however, and the reactions of certain compounds in which alphyl groups are linked to the aromatic nucleus appear to indicate the opposite order; these are referred to later. The velocities of iodination of a series of dialkyl ketones R·CO·R′, as found by Dawson and his co-workers,[38] and the stabilities of cyanohydrins of the same ketones, examined by Lapworth and Manske,[39] also do not admit of any simple interpretation.

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[35] These are all referred to in earlier chapters or in Chap. VIII.

[36] *J. Amer. Chem. Soc.* 1932, **54**, 674.

[37] Jones, Evans, Gulwell, and Griffiths, *J.C.S.* 1935, 43.

[38] *J.C.S.* 1910, **97**, 2048; 1911, **99**, 1740.

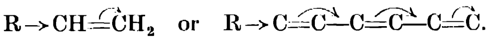
[39] *J.C.S.* 1930, 1976. The mechanism of cyanohydrin formation is dealt with in Chap. VIII.

The capacity of alphyl groups to repel electrons cannot be doubted, however. It must involve an inductive mechanism, since it is observed when the group is attached to a saturated chain; also, unshared electrons such as are possessed by hydroxyl are not here available for the initiation of electromeric displacements. In order to explain the absence of an electric moment in aliphatic hydrocarbons, Ingold suggests that this effect is not an intrinsic property of the bond linking the alphyl group to the remainder of the molecule, but that

> 'alkyl groups will merely exert those polar effects which are impressed on them by the other groups present in the molecule. The important property of alkyl groups is that they are more *polarizable* than hydrogen, and thus —CH_3, although non-polar when CH_3—CH_3 is compared with H—CH_3, becomes an electron-repelling group when the comparison is between CH_3—COOH and H—COOH or between CH_3—CH_2Cl and H—CH_2Cl. Since the majority of substituents commonly encountered are attractors of electrons, alkyl groups generally function as feebly electron-repelling groups.'[40]

A powerful inductive effect such as that of —NO_2 or —COOH is not influenced perceptibly by the environment in which the group finds itself, but when a group is intrinsically almost neutral the environment must be supposed to have an appreciable influence. The electron-repulsive effect (+I) of an alkyl group is therefore detectable only when neighbouring atoms or groups are such as to stimulate its operation.

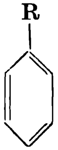
When an alphyl group is linked to an olefinic or conjugate system, the resonance of the system is directed in accordance with the scheme



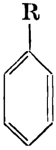
$$R\rightarrow CH{=}CH_2 \quad \text{or} \quad R\rightarrow C{=}C{-}C{=}C{-}C{=}C.$$

The inductive effect of R is probably stimulated here by the electron-attraction of the unsaturated system, whatever be the origin of the latter (see p. 75). Similarly, in an alkyl benzene the unperturbed structures will include III, IV, and V (below) in addition to I and II; in other words, the alkyl group sets up the electromeric displacements represented in VI and VII.

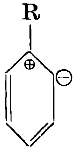
I



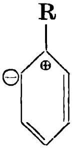
II



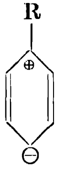
III



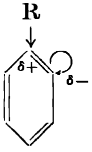
IV



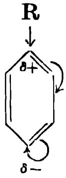
V



VI



VII



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[40] *Chem. Reviews*, 1934, **15**, 238.

It must be emphasized that this effect is different in its origin from the mesomeric effect of groups such as —OR and —NR_2. It does not depend upon an increase in the electron-content of the bond linking the group to nuclear carbon, for alkyl groups have no unshared electrons; it results, nevertheless, in an increased electron-availability at the *o*- and *p*-positions. This leads to activation of these positions towards an electrophilic reagent with consequent *op* substitution. A further consequence is that alkyl groups influence side-chain processes more powerfully from the *p*- than from the *m*-position. Examples are found in the lower dissociation constant of *p*-toluic than of *m*-toluic acid,[41] and the relative speeds of hydrolysis of the corresponding esters, that of the *p*-isomeride being the slower.[42] The complete effect is, of course, permanent, and therefore included in the dipole moment of an alkyl benzene.

The experimental observations already quoted leave no doubt as to the effect of progressive replacements of hydrogen atoms by methyl. The magnitudes of the inductive effects of methyl, ethyl, *iso*propyl, and *tert*-butyl increase in the order

$$CH_3 < CH_3{\cdot}CH_2 < (CH_3)_2CH < (CH_3)_3C.$$

There are cases, however, where the relative powers of electron-release appear to be the reverse of this. In all these instances the alkyl group is linked directly to the aromatic nucleus, and the most familiar is the predominating substitution at the 2-position (i.e. *ortho* to CH_3) in *p*-ethyl, *p*-*iso*propyl, and *p*-*tert*-butyl-toluenes.[43] Baker and Nathan have observed the order $Me > Et > Pr^\beta > Bu^\gamma$ in the reaction of pyridine with *p*-alkylated benzyl bromides, and they postulate a mechanism of electron release by alkyl groups which is distinct from and additional to that which arises from their inductive effects.[44] They suggest that the electron pair (or pairs) linking carbon to hydrogen in one of the groups —CH_3, —CH_2R, or —CHR_2 may come under the influence of the adjacent carbon atom (become 'less localized'), and in a conjugate or aromatic system this will lead to a reinforcement of the electromeric displacements in VI and VII (above). On this view, methyl linked to the benzene nucleus

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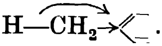
[41] Dippy and Lewis, *J.C.S.* 1936, 644.

[42] Kindler, ref. 27.

[43] Le Fèvre *et al.*, *J.C.S.* 1933, 980; 1934, 1501, 1697. Brady and Day, ibid., p. 114.

[44] *J.C.S.* 1935, 1844. A similar but not identical suggestion was made previously by Burkhardt and Evans (*Mem. Manchester Phil. Soc.* 1933, **77**, 37).

will favour the approach of the system to the forms III, IV, and V by the combined processes which may be represented . Since all three hydrogen atoms of methyl may be concerned, Baker and Nathan's effect will *decrease* in magnitude when they are replaced as in ethyl or *iso*propyl, and will vanish when all three are removed in *tert*-butyl. The order Me > Et > Pr^{β} > Bu^{γ} is thus arrived at. This suggestion has been criticized by Robinson,[45] who points out, *inter alia*, that the dipole moment of *tert*-butylbenzene is greater than that of toluene, in accordance with the order of inductive effects.[46] A complete and satisfactory interpretation of the peculiar behaviour of alkyl groups under some circumstances cannot be expected until further experimental data become available.

Unsaturated Groups. Olefinic, and particularly acetylenic, acids are stronger than the corresponding saturated acids, and this influence of the multiple linkage, like an inductive effect, is transmitted through a chain of saturated atoms and decreases in magnitude with increasing distance of the linkage from the carboxyl group. This is illustrated by the following dissociation constants for olefinic acids:[47]

Acid	$10^5 K_{\text{therm}}$
$CH_3{\cdot}COOH$	1·76
$CH_2{=}CH{\cdot}COOH$	5·56
$CH_2{=}CH{\cdot}CH_2{\cdot}COOH$	4·62
$CH_2{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}COOH$ . . .	2·11
$CH_2{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}COOH$ . .	1·90

Phenyl has a similar effect, $10^5 K$ for phenylacetic and β-phenylpropionic acids being 4·88 and 2·19 respectively.[48] As Ingold points out, 'radicals such as ethenyl and phenyl are to be regarded as intrinsic attractors of electrons. The acetylenyl radical attracts electrons more strongly still. The theory of these effects is at present obscure.'[49]

The influence of phenyl is not described completely in terms of a rather weak effect of an inductive character, however. This effect, for example, cannot be responsible for observations such as the following: (*a*) aryl groups in general are *op*-directive; (*b*) phenyl

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[45] *Chem. and Ind.* 1936, **55**, 962.

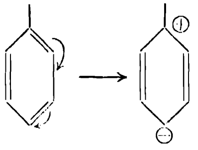
[46] Le Fèvre *et al.*, *J.C.S.* 1935, 488. The dipole-moment values (for benzene solutions) recorded in this paper are toluene 0·34, *tert*-butylbenzene 0·53.

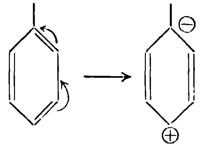
[47] Ives, Linstead, and Riley, *J.C.S.* 1933, 561. Dippy and Lewis, ibid. 1937, 1008.

[48] Dippy and Lewis, loc. cit.

[49] *Chem. Reviews*, 1934, **15**, 239.

linked directly to carbonyl leads to a very great decrease in the stability of the cyanohydrin, whereas it has but little effect if one saturated carbon atom be interposed between the groups;[50] (*c*) certain enols are stabilized by phenyl much as they are by carbonyl or cyano;[51] (*d*) aryl groups have the very specialized property of conferring stability upon free radicals.[52] These and numerous other experimental facts can be understood, however, if it is realized that phenyl can become quinonoid by reason of electromeric displacements in either of two directions, as indicated below, and the sign of the electromeric effect will depend upon the particular system in which the group finds itself.[53] It is perhaps simplest, therefore, to ascribe to phenyl the polar characters represented as —I, ±T.





Halogens. The halogens form very stable anions, and exhibit, to a marked degree, the power of drawing electrons towards themselves. Thus the alkyl halides have dipole moments of the order of 1·6 to 2·2 Debye units, and the halogenoacetic acids are all very much stronger than acetic acid itself. The strengths of these acids fall from fluoro- to iodo-acetic, indicating a decrease in the inductive effects (—I) in the order F > Cl > Br > I, and the proportions of *m*-derivative formed in the nitration of the benzyl halides (decreasing from $C_6H_5 \cdot CH_2F$ to $C_6H_5 \cdot CH_2Br$) point to the same order. The relevant figures are as follows:

X	F	Cl	Br	I	H
$10^5 K_{class}$ for $X \cdot CH_2 \cdot COOH$ . . .	217	155	138	75	1·8
Per cent. *m*-derivative in nitration of $C_6H_5 \cdot CH_2X$[54]	17·5	12	7	..	4

The properties of compounds having halogen linked to a saturated carbon atom thus show that the inductive effects of the halogens (—I) are of considerable magnitude, and fall from fluorine to iodine. The same electron-attractive character is evident when halogen is attached to the benzene nucleus; as a class, halogenated aromatic

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[50] Lapworth and Manske, ref. 39.
[51] See Chap. IX, p. 121
[52] Chap. VI.
[53] See Ingold, *Ann. Reports*, 1928, **25**, 121, 146
[54] Flürscheim and Holmes, *J.C.S.* 1928, 1611; Ingold and Ingold, ibid., p. 2253.

acids and phenols are stronger than the unsubstituted compounds, while bases are weaker; with rare exceptions (see below) the general order $NO_2 > Hal > H$ is maintained. The same applies to a large number of side-chain reactions, both of Type A and of Type B.[55] The *main* influence is still the inductive effect of the halogen. It has already been pointed out, however,[56] that this is now not the *only* effect which operates, a conclusion which is based on the following evidence:

(*a*) The dipole moments of the halogenobenzenes in the gas phase are as follows: C_6H_5F 1·57, C_6H_5Cl 1·73, C_6H_5Br 1·71. These are appreciably smaller than those of the corresponding alphyl halides, e.g. CH_3F 1·81, CH_3Cl 1·87, CH_3Br 1·80, particularly in the case of fluorobenzene.

(*b*) The halogens are *op*-directive. The unusual phenomenon of *op*-substitution accompanied by nuclear *deactivation* is here encountered.

(*c*) The strengths of the halogenated aromatic acids, phenols, and bases are not in the order which would be predicted on the basis of inductive effects.

(*d*) The same applies to the relative velocities of numerous side-chain reactions of nuclear halogenated compounds.

The table which follows gives the data relating to a number of compounds in which halogen is linked to the aromatic nucleus. The numbers refer to the following:

I. Dissociation constants (10^5K) of benzoic acids, $X \cdot C_6H_4 \cdot COOH$, in water at 25°.[57]

II. 10^5K for phenylacetic acids, $X \cdot C_6H_4 \cdot CH_2 \cdot COOH$, in water at 25°.[57]

III. $10^{11}K$ for phenols, $X \cdot C_6H_4 \cdot OH$, in 30 per cent. aqueous alcohol at 25°.[58]

IV. $10^{10}K$ for phenylboric acids, $X \cdot C_6H_4 \cdot B(OH)_2$, in 25 per cent. alcohol at 25°.[59]

V. 10^2k for alkaline hydrolysis of benzoic esters, $X \cdot C_6H_4 \cdot COOC_2H_5$, in 88 per cent. alcohol at 30°.[60]

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[55] These terms are explained on p. 52.

[56] Chap. III, p. 42.

[57] Dippy *et al.*, *J.C.S.* 1934, 161, 1888; 1935, 343; 1936, 644.

[58] Bennett, Brooks, and Glasstone, *J.C.S.* 1935, 1821.

[59] Bettmann, Branch, and Yabroff, *J. Amer. Chem. Soc.* 1934, **56**, 1865.

[60] Kindler, ref. 27; *Annalen*, 1928, **464**, 278.

VI. k for the reaction of benzyl chlorides, $X \cdot C_6H_4 \cdot CH_2Cl$, with potassium iodide in acetone at 20°.[61]

VII. $k_1 + k_2$ for the prototropy of $\alpha\gamma$-diphenylmethyleneazomethines in alcohol at 82° catalysed by sodium ethoxide.[62]

VIII. 10^2k for the hydrolysis of benzyl chlorides in 50 per cent. aqueous acetone at 84·5°.[61]

IX. $10^{12}K$ for anilines, $X \cdot C_6H_4 \cdot NH_2$, in 30 per cent. alcohol at 25°.[58]

The data are all of relatively recent date, and their accuracy may be relied upon. In cases I to VII the inductive effects of the halogens would lead to values *falling* in the order F > Cl > Br > I, while in cases VIII and IX they would be expected to *rise* in this order.

X =	*m*-NO_2	*m*-F	*m*-Cl	*m*-Br	*m*-I	*p*-F	*p*-Cl	*p*-Br	*p*-I	H
I	32·1	13·65	14·8	15·4	14·1	7·22	10·5	10·7	..	6·27
II	10·8	..	7·24	..	6·93	5·68	6·45	6·49	6·64	4·88
III	..	15·1	49·0	43·7	38·9	2·6	13·2	15·5	21·9	3·2
IV	69·0	11·0	13·5	14·6	..	3·66	6·30	7·26	..	1·97
V	311·0	..	36·3	39·5	..	9·39	21·2	24·2	24·9	4·9
VI	4·83	1·84	2·17	2·47	2·34	1·90	2·80	3·12	2·98	1·32
VII	147·0	..	10·7	9·47	7·33	..	7·83	7·09	6·82	..
VIII	2·85	5·51	5·56	4·92	5·02	38·2	13·3	11·6	10·6	23·2
IX	..	10·5	8·51	7·94	7·59	120·0	28·8	21·9	15·1	126·0

An inspection of these figures shows that halogen in the *m*-position is always electron-attractive, though to a lesser extent than the nitro-group; this is in harmony with the order of inductive effects, NO_2 > Hal > H. But the differences between the individual halogens are small, and this approximate equality in their effects points to the operation of a factor which is opposite in sign to the inductive effect, and which decreases from fluorine to iodine (i.e. in the same order as the inductive effects). The necessity for postulating an effect diminishing in this order was first pointed out by Baddeley and Bennett.[63] The strengths of the *m*-halogenophenols (III) present a striking example of its operation, for fluorine here appears to be markedly *less* electron-attractive than the other halogens in the *m*-position; throughout the nine series quoted above, indeed, the order of the *m*-halogen-substituted compounds is rarely that which would be expected on the basis of the inductive effects.

The operation of a second factor is still more evident when the

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[61] Bennett and B. Jones, *J.C.S.* 1935, 1815.

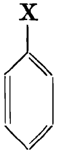
[62] Shoppee, ibid. 1931, 1225; 1932, 696.

[63] *J.C.S.* 1933, 261.

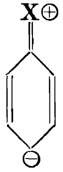
halogen is in the *p*-position. The variations are now more marked and indicate usually an apparent *increase* in electron-attractive character from fluorine to iodine; a complete 'inversion' of the halogen order is the rule rather than the exception. Indeed, in cases III and VIII (above) fluorine in the *p*-position appears to be electron-repulsive relatively to *hydrogen*,[64] and *p*-F behaves throughout as though it were far less powerfully electron-attractive than the remaining halogens (for example, in case IX there is an approximate equality between F and H).

The data, viewed as a whole, make it imperative to postulate the operation of an effect which is electron-repulsive in nature, and which decreases in the order F > Cl > Br > I. The same effect, of course, leads to the *op*-directive influence of the halogens, and the relatively low values of the dipole moments of the halogenobenzenes (particularly of fluorobenzene). It is doubtless a resonance phenomenon, and is therefore spoken of as the 'mesomeric effect' of the halogens. Its influence at the *m*-position may be ascribed to a feeble relay by an inductive mechanism. Thus far there is substantial agreement between different investigators, but no such agreement has been reached with regard to the genesis of the effect. It is usually assumed that halogen is comparable with other groups having unshared electrons, and that resonance occurs between forms such as I and II.[65]

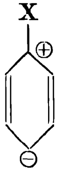
I



II



III



Bennett and his collaborators point out, however,[66] that of the four halogens fluorine must control its valency electrons the most powerfully and iodine, with the largest atom, least powerfully, and hence the magnitude of this effect should vary in the order

$$I > Br > Cl > F;$$

further, covalency increase between the substituent and nuclear carbon is here less probable than in the case of oxygen or nitrogen,

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[64] This peculiarity was first observed by Shoesmith and Slater, *J.C.S.* 1926, 217, in the hydrolysis of *p*-fluorobenzyl bromide.

[65] See, for example, Ingold, refs. 1 and 4; Branch, ref. 59; Robinson, *J.C.S.* 1933, 1114.

[66] Ref. 63, *J.C.S.* 1933, 1112; 1935, 1827.

since quinonoid forms of halogenated benzenes are not known. They therefore suggest that the dipolar unperturbed forms are of the type represented by III. Such a position might arise from the operation of a 'reversed field'. If the positive charge on the carbon atom of the C-Hal dipole is largely distributed throughout the nucleus, halogen will become virtually a negative pole and will thus develop electron-*repulsive* characters decreasing in the same order as the inductive effects. This will lead to the mesomeric state postulated.

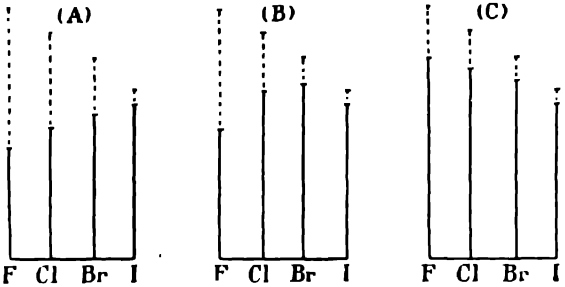

FIG. 6. (From Dippy and Lewis, *J.C.S.* 1936, 649.)

(A) I > Br > Cl > F, e.g. the strengths of *p*-halogenophenylacetic acids.
(B) Br > Cl > I > F, e.g. the strengths of *m*-halogenobenzoic acids.
(C) F > Cl > Br > I, e.g. the tautomeric mobilities of *p*-halogeno-$\alpha\gamma$-diphenylpropenes (Shoppee, *J.C.S.* 1930, 968).

It must be emphasized that, on either view, the magnitude of the mesomeric effect may vary with the system to which halogen is attached, and probably also with external conditions. The attacking reagent may also have some influence (e.g. electromeric effect). The opposition to the inductive effect is thus not a constant quantity, and it is not surprising that the order of the halogens is different in different reactions, even in two reactions of the same compound.[67] Possible combinations of the two effects have been depicted diagrammatically by Dippy and Lewis, and their figure is reproduced above (Fig. 6); the total line represents the inductive effect (F > Cl > Br > I), the dotted part the opposing effect (also F > Cl > Br > I), and the unbroken line the resultant of the two as observed experimentally. There appears to be no reason to expect any simple relationship between the effects of the halogens when they are linked to the aromatic nucleus.

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[67] Compare Dippy, Watson, and Williams, ref. 26. An example of a 'normal' and an 'inverted' order of the halogens in different reactions of the same compound was observed by Baddeley and Bennett, ref. 63.

VI

FREE RADICALS

THE term 'radical' was introduced into chemistry by Lavoisier. His ideas centred around oxygen, and he described inorganic compounds as the oxides of 'simple radicals' (elements) and organic compounds as the oxides of 'compound radicals' (containing at least the two elements carbon and hydrogen). He thus regarded sugar as the oxide of a hydrocarbon radical, and oxalic acid, got from sugar by oxidation, as a higher oxide of the same radical. The compound radical was, of course, purely hypothetical, but before very long examples were observed experimentally. In 1815 Gay-Lussac published the account of his investigation of the cyanogen compounds; he had prepared pure hydrocyanic acid and established its composition, and had further isolated cyanogen gas, which was believed to be the free radical. About seventeen years later Liebig and Wöhler completed their study of the benzoyl radical. Starting from benzaldehyde they obtained a series of compounds in which the group C_7H_5O was present, and Laurent even claimed to have isolated the radical (his product was actually benzil). The third 'pillar' of the radical theory was the work of Bunsen (1839) upon the cacodyl compounds. He prepared a number of derivatives of the group $(CH_3)_2As$, and ultimately isolated cacodyl itself; this was not the radical, however, but had the doubled formula $[(CH_3)_2As]_2$. Aided by these and allied researches, the radical theory continued to dominate organic chemistry, which was actually described by Liebig in 1840 as 'the chemistry of the compound radical'.

The next stage was represented by the attempts of Frankland and Kolbe, between 1840 and 1850, to prepare the simple alphyl radicals. When, on heating ethyl iodide with zinc, Frankland obtained a gas of the empirical formula C_2H_5, he described it as the free ethyl radical, and Kolbe believed the product of the electrolysis of potassium acetate to be free methyl; the substances were actually the paraffins butane and ethane respectively. Although, however, Frankland and Kolbe did not succeed in their quest for the aliphatic radicals, they originated two important methods of synthesizing hydrocarbons; Frankland's method was modified by Wurtz (1854), who employed sodium in place of zinc, and the same process was applied by Fittig (1863) to the preparation of homologues of benzene. Thus there arose the synthetic methods which are familiar to every student of organic chemistry. Frankland's work, indeed, led also to the discovery of the metallic alkyls, and hence to the conception of valency.

Even after it was shown that the densities of the so-called 'radicals' were double those required by the formulae, a number of investigators still maintained that they were different from the 'isomeric' paraffins. It was Schorlemmer (1863) who proved the identity of these two sets of compounds. The terms free 'methyl' and 'ethyl' were then abandoned, and, with the development of the doctrine of valency and the success achieved by the structural theory with its assertion of the invariable quadrivalence of carbon, the conclusion was reached that the free radicals were incapable of existence. There the matter remained until the closing year of the last century.

Triarylmethyls and Allied Radicals.[1] The next phase in the history of the free radical opened with Gomberg's attempt, in 1900, to prepare hexaphenylethane by treatment of triphenylmethyl chloride with metallic silver.[2] The anticipated reaction was

$$2(C_6H_5)_3CCl+2Ag = 2AgCl+(C_6H_5)_3C\cdot C(C_6H_5)_3.$$

In the absence of atmospheric oxygen he obtained a colourless, crystalline solid having the analysis of the desired hydrocarbon. Its properties were quite unexpected, however. It gave yellow solutions in organic solvents, and, far from being a relatively inert substance, exhibited intense chemical reactivity, forming addition products with many elements and compounds. Thus, it gave a peroxide with oxygen, triphenylmethyl halides with halogens, triphenylmethane with hydrogen in presence of platinum, and solid crystalline products with a variety of organic compounds.[3] A determination of its molecular weight in naphthalene[4] gave a value of 415, whereas the molecular weight of hexaphenylethane is 486, and the observations were explained by postulating partial dissociation of the hydrocarbon into triphenylmethyl radicals having 'trivalent' carbon,

$$(C_6H_5)_3C\cdot C(C_6H_5)_3 \rightleftharpoons (C_6H_5)_3C— + —C(C_6H_5)_3,$$

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[1] For excellent reviews of this subject, see Gomberg, *Chem. Reviews*, 1924, **1**, 91; Ingold, *Ann. Reports*, 1924, **21**, 115; 1928, **25**, 150.

[2] *Ber.* 1900, **33**, 3150.

[3] Various papers by Gomberg, Schmidlin, Schlenk, and their collaborators.

[4] Gomberg, *Ber.* 1904, **37**, 2049.

the radical being present to the extent of 10 per cent. under the conditions employed in the cryoscopic measurement. The observed molecular weights in various solvents indicated proportions of the radical varying from 5 to 17 per cent. Further cryoscopic measurements by Schlenk and his collaborators[5] gave results which pointed to still larger percentages of other triarylmethyls in solutions of the corresponding hydrocarbons, e.g.

$$\underset{\text{15 per cent.}}{(C_6H_5\cdot C_6H_4)C(C_6H_5)_2,} \quad \underset{\text{80 per cent.}}{(C_6H_5\cdot C_6H_4)_2\cdot C\cdot C_6H_5,} \quad \underset{\text{100 per cent.}}{(C_6H_5\cdot C_6H_4)_3C.}$$

The demonstration of an equilibrium in these solutions was given by Schmidlin.[6] He found that a freshly made solution of hexaphenylethane was colourless for a few seconds, when a yellow colour developed and reached a permanent intensity; air removed the colour (formation of peroxide), which then reappeared. These changes could be repeated a number of times.

The solutions containing triarylmethyl radicals were of more than one kind.[7] When hexaphenylethane was dissolved in a non-ionizing medium such as benzene, a non-conducting solution resulted, but in liquid sulphur dioxide it was conducting. In the latter case, therefore, the presence of positive and negative ions must be inferred,

$$(C_6H_5)_3C\cdot C(C_6H_5)_3 \rightleftharpoons (C_6H_5)_3C^{\oplus}+C(C_6H_5)_3^{\ominus}.$$

These solutions have different absorption spectra. There are, therefore, three triphenylmethyls, the neutral radical and the two ions. This view is confirmed by the observation that solutions of triphenylmethyl chloride in liquid sulphur dioxide or hydrocyanic acid conduct the current, i.e.

$$(C_6H_5)_3CCl \rightleftharpoons (C_6H_5)_3C^{\oplus}+Cl^{\ominus},$$

and that sodium and potassium form solid red compounds $NaC(C_6H_5)_3$ and $KC(C_6H_5)_3$, which also give conducting solutions (e.g. in liquid ammonia),[8] i.e.

$$NaC(C_6H_5)_3 \rightleftharpoons Na^{\oplus}+C(C_6H_5)_3^{\ominus}.$$

The colours of these different solutions indicate that the neutral triphenylmethyl radical and the kation are yellow, while the anion

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[5] *Annalen*, 1910, **372**, 1; 1912, **394**, 180.

[6] *Ber.* 1908, **41**, 2471.

[7] Gomberg and Sullivan, *J. Amer. Chem. Soc.* 1922, **44**, 1810.

[8] Schlenk and Marcus, *Ber.* 1914, **47**, 1664; Kraus and Kawamura, *J. Amer. Chem. Soc.* 1923, **45**, 2756; Kraus and Rosen, ibid. 1925, **47**, 2739.

is red. The properties and stabilities of the three entities may obviously differ as considerably as do, for example, those of halogen atoms and halide ions.

The triarylmethyl *anion* is not unique, for the negative benzyl ion is found in the red conducting solutions of sodium benzyl in ether.[9] A comparable case is presented by the highly coloured (blue or green) and reactive metal ketyls formed by the interaction of an alkali metal with a diaryl ketone or aryl aldehyde,[10]

$$R_2C{=}O+Na = R_2CONa.$$

The single formula of the compound from potassium and phenyl-*p*-diphenylyl ketone has been demonstrated by molecular weight determinations[11] and by its paramagnetism.[12] Ketyls of the aliphatic series have recently been prepared;[13] examples are those from di-*tert*-butyl and *iso*propyl-*tert*-butyl ketones. Certain acetophenones with branched side-chains also give rise to stable ketyls;[14] branched aliphatic chains thus favour the formation of such compounds, and similar observations have been made with regard to the dissociation of dialphyl-tetra-arylethanes.[15] There would appear to be a connexion between the stabilizing effect of branched alphyl chains upon these radicals and their influence upon the mechanism of hydrolysis of alkyl halides;[16] such a connexion is emphasized by the fact that aryl groups, which are unique in their influence upon the stability of radicals, affect the hydrolysis in the same way as do branched alphyl groups.

Brief reference must be made to examples of 'abnormal valency' exhibited by nitrogen and oxygen. The dissociation of the tetra-arylhydrazines, e.g.

$$(C_6H_5)_2N{-}N(C_6H_5)_2 \rightleftarrows 2(C_6H_5)_2N{-},$$

was first demonstrated by Wieland,[17] who observed that solutions of tetraphenylhydrazine in boiling toluene were green in colour, and gave an addition product with nitric oxide. Hexa-aryltetrazanes

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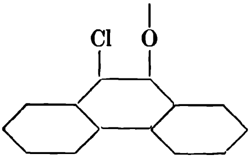
[9] Schlenk and Holtz, *Ber.* 1917, **50**, 262.
[10] Schlenk and Weichel, *Ber.* 1911, **44**, 1182.
[11] Schlenk and Thal, *Ber.* 1913, **46**, 2840.
[12] See below.
[13] Favorski and Nazarov, *Compt. rend.* 1933, **196**, 1229.
[14] Idem, *Compt. rend. Acad. Sci. U.R.S.S.* 1934, **1**, 325.
[15] Conant and Schultz, *J. Amer. Chem. Soc.* 1933, **55**, 2098.
[16] Hughes and Ingold, *J.C.S.* 1935, 244. See p. 54.
[17] Wieland *et al.*, *Annalen*, 1911, **381**, 200; *Ber.* 1912, **45**, 2600; 1915, **48**, 1078.

also give deep blue solutions and combine with nitric oxide, indicating dissociation to hydrazyls,

$$Ar_2N—NAr—NAr—NAr_2 \rightleftarrows 2Ar_2N—NAr—.$$

(Ar = an aryl group)

These radicals have been investigated by Goldschmidt and his collaborators.[18] Diphenyl-picryl-hydrazyl is a remarkably stable radical, forming crystals resembling permanganate; it is reduced instantaneously by hydroquinone, a reaction which enabled Goldschmidt to demonstrate the existence of an equilibrium, by a procedure similar to that used by Schmidlin in the case of triphenylmethyl. Goldschmidt found further[19] that oxidation of guaiacol by lead peroxide gave a green solution, suggesting the presence of $CH_3O \cdot C_6H_4 \cdot O—$; in a phenanthrene derivative the blue radical



and the corresponding compound of doubled formula (colourless) were both isolated, and 69 per cent. dissociation found in solution. Recent work by Schönberg[20] points to the formation of radicals in solutions of diaryl sulphides, $ArS \cdot SAr \rightleftarrows 2ArS—$.

Paramagnetism of Free Radicals.[21] According to Langevin's theory of magnetism (1905), the path of each electron in the atom is equivalent to a magnet of definite moment. When the number of electrons is even, however, the moments may neutralize in pairs, giving a resultant of zero. The electronic movements will then be somewhat modified by an external field, and the phenomenon of diamagnetism arises from this cause. A diamagnetic substance is repelled by a magnet (because a pole of given sign induces a pole of the same sign nearest to itself), and when placed between two poles it increases the field strength. This effect is small, independent of

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[18] *Ber.* 1922, **55**, 616; *Annalen*, 1924, **437**, 194.

[19] *Ber.* 1922, **55**, 3194; *Annalen*, 1924, **438**, 202.

[20] *Ber.* 1932, **65**, 1864; 1933, **66**, 237, 1932; *Trans. Faraday Soc.* 1934, **30**, 17.

[21] For full discussions of magnetic phenomena, see Stoner, *Magnetism and Atomic Structure* (Methuen, 1926); Van Vleck, *The Theory of Electric and Magnetic Susceptibilities* (Oxford University Press, 1932). Useful summaries are found as follows: G. N. Lewis, *Valence and the Structure of Atoms and Molecules* (Chemical Catalog Co., New York, 1923), pp. 52 and 147; Sidgwick, *The Electronic Theory of Valency* (Oxford University Press, 1927), p. 204; Sugden, *Trans. Faraday Soc.* 1934, **30**, 18.

temperature (Curie's law), and common to all matter; for a given compound the diamagnetic susceptibility (magnetic moment acquired by unit mass in a field of unit strength) can be calculated as the sum of the values of the atomic and constitutive constants (Pascal). If, however, the electrons are not 'paired' in the magnetic sense, the atom or molecule will have a resultant moment; it is paramagnetic (or, in a few extreme cases, ferromagnetic); it is *attracted* by a magnet, and in a magnetic field will orient itself in such a way as to *reduce* the field strength. The orientation of the molecules is opposed by thermal agitation (compare molecules with permanent electrical dipoles when placed in an electric field[22]), and hence the paramagnetic susceptibility decreases with rise of temperature. When paramagnetism exists, it completely conceals the diamagnetism on account of its much greater magnitude. The mutual influences of electrons of neighbouring atoms also contribute to the total magnetic susceptibility; the effect is in most cases very small, however, and may be neglected. It is probably responsible for a feeble paramagnetism, not varying with temperature, observed in the permanganates, dichromates, and some complex salts. The molecular magnetic susceptibility is therefore the sum of three terms:

$$\chi_M = \chi_d + \chi_\mu + \chi_r.$$

χ_μ, the paramagnetic contribution, when present is large in comparison with χ_d, the diamagnetic contribution, and is determined by subtraction of χ_d, calculated from atomic constants, from the experimentally observed value of χ_M, χ_r being neglected. χ_M is conveniently measured by the Guoy method,[23] which consists in observation of the apparent loss of weight when one end of a column of the substance (which may be contained in a glass tube) is suspended in a magnetic field.

It was pointed out by G. N. Lewis[24] that an atom or molecule having an odd number of electrons should be strongly paramagnetic, and in accordance with this view copper, silver, gold, sodium, and potassium are paramagnetic, while zinc, cadmium, mercury, tin, and lead have no moment.[25] The 'odd molecules' NO, NO_2, and ClO_2

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[22] See Chap. II, p. 24.

[23] Described by Sugden, *J.C.S.* 1932, 161.

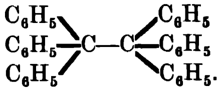
[24] See ref. 21.

[25] The results were obtained by the Stern and Gerlach method, in which a beam of atoms, proceeding from a furnace containing the metal under examination, passes between the poles of an electromagnet, one of which is wedge-shaped (producing a highly inhomogeneous field). The apparatus is highly exhausted, and the tempera-

are also strongly paramagnetic. The paramagnetism of the oxygen molecule forms a striking exception to the rule that 'even' molecules are diamagnetic; it must clearly contain two electrons which are 'unpaired' in the magnetic sense. Bell and Sugden have shown that the hypophosphates are diamagnetic, and therefore derived from $H_4P_2O_6$ and not from H_2PO_3, which is an odd molecule; the result confirms molecular weight determinations on the ethyl ester.[26]

Free radicals such as the triarylmethyls and the metal ketyls are odd molecules, and therefore should be paramagnetic; the substances having the doubled formulae are, of course, even molecules, and a further method of detecting free radicals is thus provided. Of triarylmethyls, $C_{10}H_7C(C_6H_5)_2$ and $(p\text{-}NO_2\cdot C_6H_4)_3C$ have been examined, the former in benzene solution and the latter in the solid state;[27,28] in both cases a large paramagnetism was found. Sugden has also examined two metal ketyls, the products of the reaction of potassium with phenyl-*p*-diphenylyl ketone and benzophenone respectively.[29] In dioxan solution they are strongly paramagnetic; the value of χ_μ in the former case indicates that at least 85 per cent. of the product is present as radical, in accordance with the molecular weight determinations of Schlenk and Thal,[30] and the latter in the solid state shows not less than 70 per cent. of the radical. The paramagnetism of the hydrazyl $(C_6H_5)_2N\cdot NC_6H_2(NO_2)_3$ indicates at least 90 per cent. of the radical in the solid state.[28]

Causes of Radical Stability. The dissociation of the hexa-arylethanes was at one time interpreted in the light of Flürscheim's theory of alternating strong and weak bonds.[31] Phenyl, a powerful *op*-directing group, is ascribed a high affinity demand, and Flürscheim's representation of hexaphenylethane is[32]



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ture of the furnace only about 100° above the melting-point of the metal. The beam is finally received upon a photographic plate, and the deflexion caused by the field is thus observed. Stern, *Z. Physik*, 1921, **7**, 249; Gerlach and Stern, *Ann. Physik*, 1923, **74**, 673; Gerlach, ibid. 1925, **76**, 163; Taylor, *Physical Rev.* 1926, **28**, 576.

[26] References to original papers are given by Sugden, ref. 21.

[27] Taylor, *J. Amer. Chem. Soc.* 1926, **48**, 858.

[28] Allen and Sugden, *J.C.S.* 1936, 440.

✓ [29] Ref. 21. Compare Doescher and Wheland, *J. Amer. Chem. Soc.* 1934, **56**, 2011.

[30] Ref. 11.

[31] *J. pr. Chem.* 1905, **71**, 505. Compare Ziegler *et al.*, *Annalen*, 1923, **434**, 34; 1924, **437**, 227.

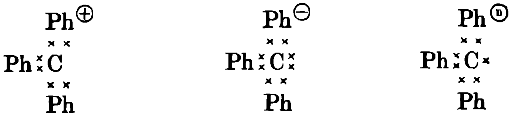
[32] The significance of the thick and thin lines is explained on p. 63.

The stabilizing influence of aryl groups, however, as pointed out by Burton and Ingold,[33] is too specialized a characteristic for interpretation on these grounds, which provide no obvious reason for the absence of the same influence in the case of other *op*-directive groups (e.g. CH_3 and Cl in hexamethyl- and hexachloro-ethanes respectively, neither of which shows any tendency to dissociate). Moreover, Flürscheim's view often predicts a state of affairs which is the reverse of that actually observed; decaphenyl-*n*-butane, for example, which would be represented

$$(C_6H_5)_3\text{—}C\text{—}C(C_6H_5)_2\text{—}C(C_6H_5)_2\text{—}C\text{—}(C_6H_5)_3,$$

actually exists in solution entirely as pentaphenylethyl radicals,[34] and the tri-*p*-nitrophenylmethyl radical is more stable than triphenylmethyl,[35] whereas a smaller stability would be predicted.

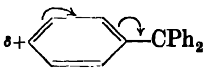
Burton and Ingold point out that the factors tending to the instability of a radical are the incompleteness of the carbon octet (in the kation), the incompleteness of the electron-sharing (in the anion), or both (in the neutral radical), as shown in the following formulae of the three triphenylmethyls:



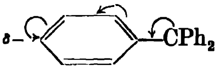
$$\begin{array}{c}\mathrm{Ph}^{\oplus}\\ \times\,\times\\ \mathrm{Ph}\overset{\times}{\underset{\times}{}}\mathrm{C}\\ \times\,\times\\ \mathrm{Ph}\end{array}\qquad\qquad\begin{array}{c}\mathrm{Ph}^{\ominus}\\ \times\,\times\\ \mathrm{Ph}\overset{\times}{\underset{\times}{}}\mathrm{C}\overset{\times}{\underset{\times}{}}\\ \times\,\times\\ \mathrm{Ph}\end{array}\qquad\qquad\begin{array}{c}\mathrm{Ph}^{\textcircled{\tiny D}}\\ \times\,\times\\ \mathrm{Ph}\overset{\times}{\underset{\times}{}}\mathrm{C}\times\\ \times\,\times\\ \mathrm{Ph}\end{array}$$

They then suggest that the unique stabilizing influence of aryl groups (which may also be associated with 'conjugated' open chains) arises from the ability of these groups to permit electromeric displacements in *either* direction.[36] In triarylmethyl radicals, with three groups of this type, the number of possible unperturbed structures is very large and hence the resonance energy considerable. It is this fact which leads to the stability of the radicals. The simplest picture of the existing conditions is obtained by supposing that the positive and negative ions are stabilized by the electromeric displacements represented in I and II (below) respectively, while the operation of both in conjunction stabilizes the neutral radical.

I



II



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[33] *Proc. Leeds Phil. Soc.* 1929, **1**, 421; Ingold, *Trans. Faraday Soc.* 1934, **30**, 52.

[34] Schlenk and Mark, *Ber.* 1922, **55**, 2285.

[35] Ziegler and Boye, *Annalen*, 1927, **458**, 248.

[36] Compare p. 76.

Ingold's interpretation is in harmony with the known increase of stability observed in the series of radicals[37]

phenyl < *p*-diphenylyl < β-naphthyl < α-naphthyl,

since a second nucleus will reinforce the effect of the first (by making possible further unperturbed forms) to a degree determined by the paths available for transmission of electromeric displacements. It also explains the influence of substituents in the aryl groups, and the stability of radicals such as tetraphenylallyl and pentaphenyl*cyclo*pentadienyl;[38] no reference is made, however, to the effect of branched aliphatic chains which has been mentioned above. The view is also applicable, with appropriate modification and extension, to the radicals containing 'bivalent nitrogen' and 'univalent oxygen'. For details of these cases the reader is referred to Ingold's original papers.[33]

Pauling and Wheland[39] and Hückel[40] have put forward wave-mechanical interpretations of a more quantitative type. The treatment given by the former authors resembles that of Ingold, radical stability being attributed to resonance phenomena. Hückel employs the molecular orbital method, and considers the energy of dissociation of the central bond of hexaphenylethane. From a chemical point of view Ingold's descriptive method is the most useful of the three.

Aliphatic Free Radicals. The majority of organic compounds, when heated at temperatures between 500° and 1,000°, decompose into simpler substances,[41] and during the past forty years it has frequently been suggested that the primary change in many of these decompositions is the production of free radicals. Thus Nef,[42] as early as 1897, interpreted a number of thermal decompositions in the light of a free radical mechanism, and Bone and Coward, in 1908,[43] postulated 'residues' such as $-\!\!\!>\mathrm{CH}$, $>\mathrm{CH_2}$, and $-\mathrm{CH_3}$ as intermediates in the pyrolysis of hydrocarbons. Later, Hinshelwood[44]

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[37] Gomberg, Schlenk, *et al.*

[38] Ziegler, *Trans. Faraday Soc.* 1934, **30**, 10, and references there cited.

[39] *J. Chem. Physics,* 1933, **1**, 362.

[40] *Z. Physik,* 1933, **83**, 632; *Trans. Faraday Soc.* 1934, **30**, 40.

[41] See Hurd, *Pyrolysis of Organic Compounds* (Chemical Catalog Co., New York, 1929).

[42] *Annalen,* 1897, **298**, 202.

[43] *J.C.S.* 1908, **93**, 1197. Compare Bone, *Trans. Faraday Soc.* 1934, **30**, 148.

[44] See *Kinetics of Chemical Change in Gaseous Systems* (Oxford University Press, 3rd edition, 1933).

demonstrated the homogeneous and unimolecular character of the thermal decompositions of a number of simple organic compounds including acetone and various ethers, and he represented the *initial stage* in each case as a cleavage of the molecule into radicals.

Alphyl radicals carrying electrical charges have long been recognized in positive ray tubes,[45] but the proof of the existence of free aliphatic radicals under ordinary conditions did not emerge until 1929, when Paneth and Hofeditz[46] showed that lead tetramethyl can be decomposed by heat into metallic lead and free methyl groups. The vapour of the metallic alkyl, largely diluted with pure hydrogen and under a pressure of about 2 mm., was passed through a quartz tube at 500°–600°. A deposit of lead was formed, and the gaseous product removed a lead mirror placed near the outlet to the tube, with production of a compound which again could be decomposed by heat to give metallic lead. Other metals were attacked similarly (tellurium appears to be particularly useful for this purpose), and when zinc was employed the product was identified as zinc dimethyl. Neither hydrogen nor any of the hydrocarbons which were possible products of the decomposition reacted with metallic mirrors in this way, and almost identical results were obtained with nitrogen or helium as transport gas.[47] The demonstration of the real though transitory existence of the methyl radical was complete; its half-life was shown to be of the order 10^{-3} sec. Soon after, the ethyl radical was detected by a similar method;[48] above 600° it decomposes to give methyl.[49] Attempts to observe the higher alphyl radicals were unsuccessful, however, and it appears that they are too unstable for detection under these conditions. The same applies to phenyl and methylene; benzyl was identified, however, in the products of thermal decomposition of tin tetrabenzyl.[50] Paneth and Loleit[49,51] have used the methyl and ethyl radicals in the synthesis of a number of arsenic, antimony, and bismuth alkyls, including the antimony analogue of cacodyl, $[Sb(CH_3)_2]_2$, which has thus been prepared for the first time.

Organo-metallic compounds are not the only sources of free alphyl

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[45] Sir J. J. Thomson, *Rays of Positive Electricity* (Longmans, 1913).

[46] *Ber.* 1929, **62**, 1335.

[47] Paneth and Herzfeld, *Z. Elektrochem.* 1931, **37**, 577.

[48] Paneth and Lautsch, *Ber.* 1931, **64**, 2702.

[49] Paneth and Loleit, *J.C.S.* 1935, 366.

[50] Paneth and Lautsch, *J.C.S.* 1935, 380.

[51] *Trans. Faraday Soc.* 1934, **30**, 179.

radicals. F. O. Rice and his collaborators[52] have shown that radicals are formed in the decomposition of organic compounds of various types, including hydrocarbons, aldehydes, ketones, and ethers. The radicals were identified by allowing them to combine with mercury; the mercury dialkyls thus formed react quantitatively with mercuric halides according to the equation

$$HgR_2 + HgX_2 = 2RHgX,$$

and the alkyl mercuric halides can be isolated as crystalline compounds with definite melting-points. The thermal decompositions were carried out at temperatures between 800° and 1,000°, and the work was simplified on the experimental side by the use of a condensable transport gas such as carbon dioxide or steam. In general, the results of Paneth were confirmed; methyl and ethyl were found to have half-life periods of about 10^{-3} sec., and no higher radicals were observed; methane, ethane, propane, and butane yielded no appreciable quantities of any radical other than methyl, and the same applies to acetone and diethyl ether.[53] The production of the methylene radical from diazomethane, reported by Rice and Glasebrook,[54] has been rendered doubtful by subsequent work in which only methyl radicals were recognized.[55]

Both Paneth and Rice were thus unable to detect alphyl radicals higher than ethyl in the products of decomposition of organic compounds at 500° to 1,000°. During an investigation of a number of alkyl gold cyanides, however, Burawoy and Gibson found that the decomposition of derivatives such as di-*n*-propylmonocyanogold and di-*n*-propyldicyanodigold at temperatures not exceeding 120° gave substantially pure hexane, which was most probably the result of the combination of two *n*-propyl radicals.[56] The previous workers had obtained lower hydrocarbons in cases where these radicals were to be expected, but it would appear that at the temperature of decomposition of the alkyl gold cyanides the *n*-propyl radical exists for a sufficient period of time to permit combination to give hexane.

The formation of radicals in a reaction of quite a different type has been demonstrated by Polanyi and his collaborators.[57] Sodium

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[52] Rice, Johnston, and Evering, *J. Amer. Chem. Soc.* 1932, **54**, 3529.

[53] Rice and Evering, *J. Amer. Chem. Soc.* 1934, **56**, 2105; Rice and Dooley, ibid., p. 2747. Contrast Belchetz, *Trans. Faraday Soc.* 1934, **30**, 170.

[54] *J. Amer. Chem. Soc.* 1934, **56**, 2381.

[55] Rice, *Chem. Reviews*, 1935, **17**, 60.

[56] *J.C.S.* 1935, 1024.

[57] Hartel and Polanyi, *Z. physikal. Chem.* 1930, **11**, 97; Hartel, *Trans. Faraday Soc.* 1934, **30**, 187; Horn, Polanyi, and Style, ibid., p. 189; *Z. physikal. Chem.* 1933, **23**, 291.

vapour, diluted with hydrogen, methane, or nitrogen, was mixed with a gaseous methyl or ethyl halide, and the product allowed to react with chlorine or iodine. The formation of methyl and ethyl radicals was thus demonstrated, e.g. $Na+C_2H_5Br = NaBr+C_2H_5$; they were recognized at distances up to 8 cm. from the source. The detection of the phenyl radical on treatment of chlorobenzene with sodium is also claimed;[58] Dull and Simons also report the presence of phenyl in the products of decomposition of lead tetraphenyl,[59] but in view of Paneth's results these observations require confirmation.

Finally, the production of free radicals in a number of photochemical decompositions has been demonstrated. Investigations of the products of photochemical decomposition of aldehydes and ketones, and of absorption and fluorescence spectra, have led Norrish and his collaborators to the conclusion that the primary change, in some cases at least, consists of a cleavage into radicals.[60] Definite confirmation of this view has been obtained by Pearson and his co-workers, who have been able to show, by the Paneth mirror method, that radicals are produced by the action of ultra-violet light upon acetaldehyde, acetone, and methyl-ethyl, methyl-*n*-propyl, methyl-*iso*propyl, methyl-*n*-butyl, diethyl, di-*n*-propyl, di-*iso*propyl, di-*sec*-butyl, and di-*tert*-butyl ketones.[61] In the case of di-*n*-propyl ketone, the vapours were passed over mercury and the product allowed to react with mercuric bromide. *n*-Propylmercury bromide was formed, the isolation of the *n*-propyl radical thus being demonstrated.[62]

Chain Reactions involving Free Radicals. Reaction chains play an important part in photochemical processes and in certain thermal reactions, the chains being propagated either by activated molecules of the product (as in the reaction of hydrogen with oxygen) or by atoms or radicals (as in Nernst's chain mechanism for the combination of hydrogen and chlorine). In this way, the reaction of the first molecule may lead to that of very many others. The chains may be terminated either by physical deactivation or by chemical reaction of the species by which they are propagated, and chain reactions are therefore characterized by extreme sensitiveness to inhibitors, retardation by increase of the surface area of the containing vessel

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[58] Horn and Polanyi, *Z. physikal. Chem.* 1934, **25**, 151.

[59] *J. Amer. Chem. Soc.* 1933, **55**, 3898.

[60] See *Trans. Faraday Soc.* 1934, **30**, 103; *J.C.S.* 1934, 874, 1456.

[61] *J.C.S.* 1934, 1718; 1935, 1151; 1936, 1777; 1937, 567.

[62] Ibid. 1936, 253.

acceleration by an inactive gas (which increases the distance traversed before a deactivating collision with the wall occurs), and by complicated kinetics.[63] A criterion of a photochemical chain reaction is an abnormally high quantum efficiency (number of molecules decomposed by each quantum of energy); thus, the photochemical decompositions of formaldehyde and acetaldehyde, for which the quantum yields may be as high as several hundred, are regarded as chain reactions, while that of acetone is not, since the quantum yield never rises appreciably above unity.[64]

F. O. Rice has suggested that the thermal decompositions of organic compounds, a number of which have been shown (by Hinshelwood and others) to be unimolecular, are chain reactions involving free radicals.[65] He points out that the radical formed in the primary breakdown of the molecule may *either* decompose *or* withdraw hydrogen from another molecule, giving in each case a new radical; thus a reaction chain could be propagated; e.g.

$$CH_3\cdot CH_2\cdot CH_2\cdot CH_3 \longrightarrow CH_3+CH_3\cdot CH_2\cdot CH_2,$$

$$CH_3\cdot CH_2\cdot CH_2 \longrightarrow CH_3+CH_2{=}CH_2,$$

$$CH_3+CH_3\cdot CH_2\cdot CH_2\cdot CH_3 \longrightarrow CH_4+CH_3\cdot CH_2\cdot CH_2\cdot CH_2,$$

$$CH_3\cdot CH_2\cdot CH_2\cdot CH_2 \longrightarrow CH_3\cdot CH_2+CH_2{=}CH_2,$$

and so on. These free radical mechanisms do not affect the Hinshelwood-Lindemann view of unimolecular reactions, which would still apply to the primary rupture of the molecule. The thermal decompositions of organic compounds do not show the characteristics associated with long chains (see above), but Staveley and Hinshelwood have recently demonstrated the probability that *short* chains are involved in the decomposition of diethyl ether and of propionic aldehyde.[66] The speed of decomposition is reduced to about one-third or one-half by a small quantity of nitric oxide, which must be supposed to break the chains by removing the free radicals from the system. Nitric oxide provides a definite test for the presence of reaction chains (it lowers the speeds of thermal reactions of different

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[63] For an account of the characters of chain reactions, see Hinshelwood, ref. 44.

[64] Leermakers, *J. Amer. Chem. Soc.* 1934, **56**, 1537, 1899. Akeroyd and Norrish, *J.C.S.* 1936, 890.

[65] *J. Amer. Chem. Soc.* 1931, **53**, 1959; 1934, **56**, 284; *Chem. Reviews*, 1932, **10**, 135; 1935, **17**, 53; *Trans. Faraday Soc.* 1934, **30**, 152. F. O. Rice and K. K. Rice, *The Aliphatic Free Radicals* (Baltimore, Johns Hopkins Press, 1935).

[66] *Proc. Roy. Soc.* 1936, **154A**, 335; *J.C.S.* 1936, 812.

types and reduces the quantum yield in the photochemical decomposition of acetaldehyde from several hundred almost to unity), and the absence of inhibition is evidence that a chain mechanism is not involved. This is found in the thermal decomposition of acetaldehyde, where the absence of chains is confirmed by the results of Patat and Sachsse.[67] The available evidence therefore indicates that chains are definitely involved in the decompositions of some, though by no means all, organic compounds.

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[67] *Naturwiss.* 1935, **23**, 247.

VII

COMPOUNDS OF DIVALENT CARBON AND ALLIED PROBLEMS

THE divalency of carbon in carbon monoxide, the carbylamines (isocyanides), and the fulminates, was postulated by Nef,[1] who wrote these compounds as follows:

$$O{=}C, \qquad R{-}N{=}C, \qquad RO{-}N{=}C.$$

A formula with a quadruple link between carbon and nitrogen or oxygen is inadmissible on stereochemical grounds, and is, moreover, inconsistent with the modern covalency rule which limits the valence groups of nitrogen and oxygen to eight electrons. The strongest argument in favour of the Nef formula was the fact that the chemical behaviour of these substances indicates that the unsaturation is confined to the carbon atom, as exemplified by the addition reactions $O{=}C + Cl_2 \rightarrow O{=}CCl_2$ and $R{-}N{=}C + O \rightarrow R{-}N{=}C{=}O$.

An alternative representation, in which carbon shares *six* electrons with oxygen or nitrogen, was first suggested by Langmuir,[2] and was accepted by Lewis,[3] Sugden,[4] and others. Its correctness has recently been demonstrated by Sidgwick and his collaborators.[5] The compounds are therefore formulated

$$O{\geqq}C, \qquad R{-}N{\geqq}C, \qquad RO{-}N{\geqq}C,$$

or

$$\overset{\oplus}{O}{\equiv}\overset{\ominus}{C}, \qquad R{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{C}, \qquad RO{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{C}.$$

In addition to the four-electron bond postulated by the Nef formula, a co-ordinate linkage is formed, the oxygen or nitrogen acting as donor and carbon as acceptor; the octet of the latter is thus completed. The oxygen in carbon monoxide thereby becomes 'oxonium' in character, and the nitrogen of the carbylamines or fulminates has a fully shared octet. The carbon, however, has one unshared pair of

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[1] *J. Amer. Chem. Soc.* 1904, **26**, 1549, and references there cited. The formulae RNC for carbylamines (as opposed to RCN for nitriles) and CNOH for fulminic acid (as contrasted with NCOH for cyanic and HNCO for isocyanic acid) follow from the products of hydrolysis, as is well known.

[2] *J. Amer. Chem. Soc.* 1919, **41**, 1543.

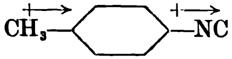
[3] *Valence and the Structure of Atoms and Molecules* (Chemical Catalog Co., New York, 1923), p. 127.

[4] *The Parachor and Valency* (Routledge & Sons, 1930), p. 171.

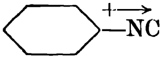
[5] Hammick, New, Sidgwick, and Sutton, *J.C.S.* 1930, 1876; Sidgwick, *Chem. Reviews*, 1931, **9**, 77; Sidgwick and Bowen, *Ann. Reports*, 1931, **28**, 396; Sidgwick, *The Covalent Link in Chemistry* (Cornell University Press, 1933), p. 187.

electrons by means of which it can co-ordinate as donor, while if the co-ordinate bond is ruptured it can also act as acceptor. The formula is thus in harmony with the chemical characters of the compounds, the carbon being the reactive centre.

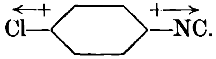
The evidence for these formulae was obtained by a study of parachors and dipole moments, and confirmation is found in the heats of formation, vibrational frequencies, and dimensions of the linkages. The values of the parachors for $N\overset{\rightarrow}{\equiv}C$ and $N=C$ are calculated as 62·3 and 40·5 units respectively, and the mean value observed is 67 units, in fairly good agreement with the former.[6] For carbon monoxide the observed value of 61·6 is much nearer to that for $C\overset{\leftarrow}{\equiv}O$ (69·6) than to that for $C=O$ (48·0).[7] There is some uncertainty here, however, as the effect of the carbon sextet in the Nef formula is unknown. The dipole moment evidence is more convincing. The moment of the $>C=O$ bond in ketones and aldehydes has a relatively high value of between 2 and 3 Debye units; that found for carbon monoxide is indistinguishable from zero, indicating an opposing dipole such as would be anticipated on the basis of an additional co-ordinate bond. In the case of the aryl *iso*cyanides, the dipole of the —NC group has its negative end on carbon; this is shown by the fact that the observed moment of phenyl *iso*cyanide is increased by *p*-CH_3 and decreased by *p*-Cl:[8]



$\mu = 3{\cdot}98$

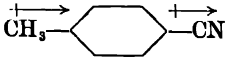


$\mu = 3{\cdot}49$

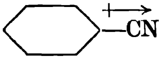


$\mu = 2{\cdot}07$

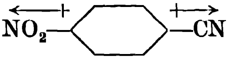
The moments of *p*-substituted benzonitriles, on the other hand, show that the nitrogen is here the negative end of the dipole, $\overset{\oplus}{C}\equiv\overset{\ominus}{N}$; the values are as follows:



$\mu = 4{\cdot}40$



$\mu = 3{\cdot}97$



$\mu = 0{\cdot}66$

This difference between the moments for the cyanide and *iso*cyanide groups can again be attributed to the presence of a co-ordinate bond in the latter. Much additional weight was given to the argument when New and Sutton[9] showed that the dipole moment of *p*-di*iso*-cyanobenzene is indistinguishable from zero. The Nef formula,

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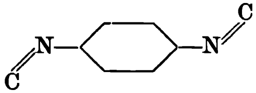
[6] Compare Lindemann and Wiegrebe, *Ber.* 1930, **63**, 1650.

[7] Sugden, ref. 4.

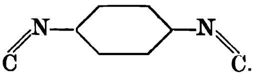
[8] See Chap. II, p. 27.

[9] *J.C*[illegible]. 1932, 1415.

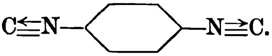
$C=N\cdot C_6H_4\cdot N=C$, would demand an angle of about 125° between the single and double bonds, and any orientation of the group would be possible between the extreme positions



and



A resultant moment as in *p*-phenylene diamine[10] would therefore be anticipated. On the other hand, the six-electron bond gives a linear structure which is therefore non-polar:



The zero moment of nickel carbonyl[11] leads to a similar conclusion for carbon monoxide, since the the link between carbon and oxygen must be collinear with that joining the group to the metal.

Sidgwick points out, in confirmation, that the heats of formation of the links, their vibrational frequencies (about 2,000 cm.$^{-1}$ from Raman Spectra), and, in the case of carbon monoxide, the internuclear distance are all in harmony with those for a six-electron linkage. This structure also accounts for the similarity in physical properties between carbon monoxide and nitrogen gas, which was emphasized by Langmuir.[12]

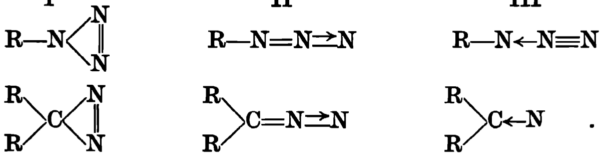
The tautomerism of acetylene, as postulated by Nef,

$$CH\equiv CH \rightleftarrows CH_2=C,$$

cannot be interpreted in this way, since the octet of the first carbon is fully shared; such tautomerism does not appear to be indicated by physical properties.[13] The existence of divalent carbon compounds such as $C(OC_2H_5)_2$ is also very doubtful.[14]

Azides and Aliphatic Diazo-Compounds. The esters of hydrazoic acid, RN_3, and the derivatives of diazomethane, CR_2N_2, also present a structural problem of considerable difficulty. The possible formulae are of three types, viz.

I II III



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[10] Chap. II, p. 30.

[11] Sutton, New, and Bentley, *J.C.S.* 1933, 652.

[12] Ref. 2.

[13] But see de Laszlo, *Trans. Faraday Soc.* 1934, **30**, 825.

[14] Scheibler[illegible] *Ber.* 1926, **59**, 1022; Arbusov, ibid. 1931, **64**, 698.

The original ring formulae (I) were later replaced by open-chain structures on account of the conversion of these substances into open-chain compounds by reduction and addition reactions. The chemical evidence is very inconclusive, however, while parachor values are of little use since those calculated for the alternative structures differ by small amounts only.

The crystal structures of the salts of hydrazoic acid show that the azide ion, $N_3^{\ominus}$, has a linear formula,[15] and Sidgwick's calculation of the heat of formation of the N_3 group, using Roth and Müller's figures[16] for the heats of combustion of phenyl azide, $C_6H_5N_3$, and ethyl azidoacetate, $N_3 \cdot CH_2 \cdot COOC_2H_5$, leads to results which exclude the ring structure I.[17] On the other hand, II and III, each having a co-ordinate bond, are highly polar, whereas the azides and aliphatic diazo compounds are not so. Thus the measured moments of phenyl, *p*-tolyl, and *p*-chlorophenyl azides are 1·55, 1·96, and 0·33 Debye units, and those of diphenyl, di-*p*-tolyl, and di-*p*-chlorophenyl-diazomethanes are 1·42, 1·94, and 0·62 D respectively,[17] whereas moments of about 4 Debye units would be anticipated from the presence of the co-ordinate bond (compare nitro-compounds). Further, the boiling-points of these compounds are similar to those of the corresponding halides, and much lower than those of analogous nitro-compounds.[18] Although, therefore, the ring formula I is excluded, neither of the highly polar representations II and III is in harmony with the facts.

Sidgwick suggests that the compounds are resonance structures between the open-chain forms II and III; the predominant moments, those of the co-ordinate linkages, are equal and opposite, and resonance will lead to a resultant mesomeric structure of small moment.[17] This is the only solution of this complex problem that has yet been offered.

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[15] Hendricks and Pauling, *J. Amer. Chem. Soc.* 1925, **47**, 2904.

[16] *Ber.* 1929, **62**, 1190.

[17] *Trans. Faraday Soc.* 1934, **30**, 801; Sidgwick, Sutton, and Thomas, *J.C.S.* 1933, 406.

[18] Sidgwick, *J.C.S.* 1929, 1108. The effect of a co-ordinate link upon volatility is discussed in *The Electronic Theory of Valency* (Oxford University Press, 1927), p. 123.

VIII

ADDITION TO UNSATURATED COMPOUNDS

THE characteristic properties of the olefinic linkage are its capacity for direct addition of reagents such as halogens, halogen hydrides, and sulphuric acid, and its susceptibility to the attack of oxidizing agents. These are, of course, the basis of the familiar qualitative tests with bromine water and alkaline permanganate, while the identification of the products of oxidation or of ozonolysis provides the standard methods for the location of a carbon to carbon double linkage. Lowry suggested in 1923 that the reactions of the four-electron bond are preceded by the electromeric change[1]

$$\rangle C\overset{\curvearrowright}{=}C\langle \longrightarrow \rangle\overset{\oplus}{C}-\overset{\ominus}{C}\langle;$$

i.e. the molecule is electronically activated and, to use modern terms, takes up or approaches closely to one of the dipolar unperturbed structures. Lowry's view was rendered more probable by the results of an investigation by Norrish of the addition of bromine vapour to ethylene.[2] The reaction occurs entirely at the walls of the containing vessel, and Norrish found that its velocity was dependent upon the chemical nature of the surface. Thus, when the interior of the vessel was coated with different substances, the results shown graphically in Fig. 7 (from Norrish's paper) were obtained; the diminution of pressure, a measure of the extent to which reaction has occurred, is here plotted against time. The speed of addition decreased, with changing surface of the vessel, in the order stearic acid > glass > cetyl alcohol > paraffin wax, i.e. with decrease in the polar character of the surface, the last-named substance slowing it down to about one-seventeenth of its value in an untreated glass vessel. It would appear, therefore, that the effect of the wall is to catalyse some electronic transference such as that postulated by Lowry. Moreover, Davis found that the reaction of bromine with ethylene in pure, dry carbon tetrachloride in the dark is very slow, requiring hours or even days for completion, but is greatly accelerated by small quantities of moisture or by illumination.[3] Some type of activation of the olefin is again indicated.

[1] See Chap. V, p. 58.

[2] *J.C.S.* **1923**, **123**, **3006**.

[3] *J. Amer. Chem. Soc.* **1928**, **50**, **2769**.

The same conclusion is reached by a different line of argument. The reagents which normally form addition products at an olefinic linkage are of the electrophilic type.[4] This is emphasized by the demonstration that, on treatment of ethylene with bromine water containing sodium chloride or nitrate, the addition products $CH_2Br{\cdot}CH_2Cl$ or $CH_2Br{\cdot}CH_2ONO_2$ are formed in addition to $CH_2Br{\cdot}CH_2Br$.[5] Clearly, one atom of bromine adds initially, the remainder of the halogen molecule appearing (in a dissociating solvent) as *anion*, with which other anions can compete in the second stage of the addition process; the formation of ethylene dibromide under these conditions is thus to be represented as follows:

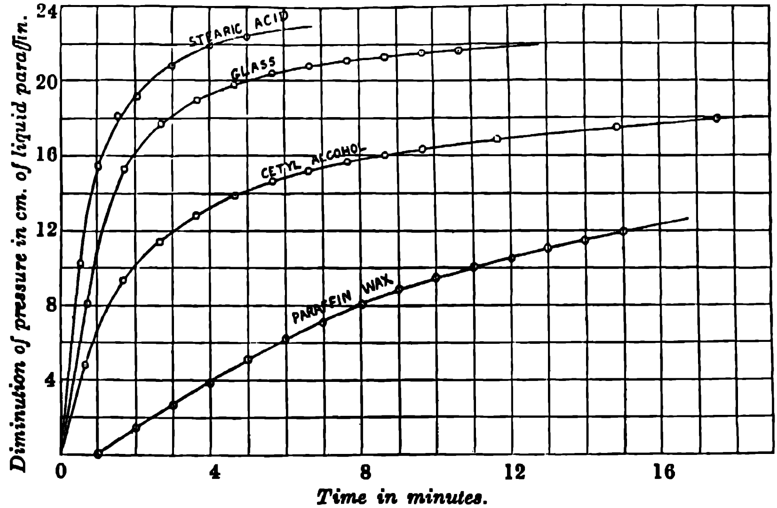

FIG. 7. Effect of the surface of the containing vessel upon the velocity of addition of bromine vapour to ethylene. (Reproduced from Norrish, *J.C.S.* 1923, **123**, 3014.)

$$CH_2{=}CH_2 + Br\vdots{-}Br \longrightarrow CH_2Br{\cdot}CH_2^{\oplus} + Br^{\ominus} \longrightarrow CH_2Br{\cdot}CH_2Br.^{6}$$

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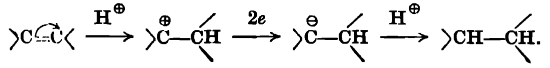
[4] See p. 49.

[5] Francis, *J. Amer. Chem. Soc.* 1925, **47**, 2344.

[6] Burton and Ingold, *J.C.S.* 1928, 912. For the special case of the *reduction* of olefinic compounds (e.g. by sodium amalgam in an aqueous medium), they suggest (ibid. 1929, 2022) a mechanism of the following type:



$$>C{=}C< \xrightarrow{H^{\oplus}} >\overset{\oplus}{C}{-}CH< \xrightarrow{2e} >\overset{\ominus}{C}{-}CH< \xrightarrow{H^{\oplus}} >CH{-}CH<.$$

Unshared electrons are therefore necessary for the formation of the initial covalent bond with bromine, and these can be provided only by means of the mechanism postulated by Lowry, which must either precede or occur simultaneously with the addition; '$\mathrm{C}\overset{\rightarrow}{-}\mathrm{C}$ is not enough; it must be $\mathrm{C}\overset{\curvearrowright}{=}\mathrm{C}$ in which electrons actually dissociate themselves from one of the carbon atoms and become free to be shared with external atoms.'[7]

It is inevitable that the nature of the groups attached to the unsaturated carbon atoms should exert an important influence upon the velocities of addition processes, and this aspect of the subject has been studied by Ingold and Ingold.[8] They point out that a group such as methyl will facilitate the reaction by increasing the electron-availability,

$$\mathrm{CH_3} \rightarrow \mathrm{C}\overset{\curvearrowright}{=}\mathrm{C},$$

while an electron-attractive group (e.g. halogen, carboxyl) will have the opposite influence. This is in harmony with common experience, as instanced by the relative inactivity of αβ-unsaturated acids towards halogens.[9] By means of experiments in which two olefinic compounds (in methylene chloride solution at −35°) were allowed to compete for a limited quantity of bromine, and the mixed product was subsequently analysed, Ingold and Ingold were able to determine the relative speeds of addition. The following are among the values obtained, the rate of addition of bromine to ethylene being taken as unity:

$(CH_3)_2C{=}CH_2$	5·5	$COOH{\cdot}CH{=}CH_2$	0·03
$(CH_3)_2C{=}C(CH_3)_2$	14	$Br{\cdot}CH{=}CH_2$	0·04.

These are in agreement with expectation. It will be observed that groups which render the benzene nucleus more active towards an electrophilic reagent also activate the olefinic linkage, and vice versa.

Coming now to the *products* of addition to double bonds, it is obvious that a symmetrical olefinic compound can give one product only; e.g. $CH_2{=}CH_2 + HBr \longrightarrow CH_3{\cdot}CH_2Br$. The same remark applies to an unsymmetrical compound if the reagent is symmetrical;

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[7] Robinson, *Outline of an Electrochemical Theory of the Course of Organic Reactions* (Institute of Chemistry, 1932), p. 16.

[8] *J.C.S.* 1931, 2354. See also Bauer, *Ber.* 1904, **37**, 3317; 1907, **40**, 918.

[9] See, for example, Sudborough and Thomas, *J.C.S.* 1910, **97**, 715. This has been made the basis of a method of quantitative analysis of a mixture of αβ- and βγ-unsaturated acids (Linstead, *J.C.S.* 1927, 355, 2565).

e.g. $CH_3\cdot CH{=}CH_2 + Br_2 \longrightarrow CH_3\cdot CHBr\cdot CH_2Br$. If, however, both the compound and the reagent are unsymmetrical, there are two possibilities; e.g.

$$CH_3\cdot CH{=}CH_2 + HI \begin{array}{l} \nearrow CH_3\cdot CHI\cdot CH_3 \\ \searrow CH_3\cdot CH_2\cdot CH_2I. \end{array}$$

The famous orientation rule of Markownikoff[10] states that, in the addition of halogen acid to an olefinic linkage, the halogen becomes attached to the carbon carrying the smaller number of hydrogen atoms; thus the main product of the addition of hydrogen iodide to propylene is *iso*propyl iodide. Michael[11] sought to generalize on the basis of the 'principle of maximum neutralization', according to which the electronegative group of the addendum will become attached to the more electropositive of the unsaturated carbon atoms. It is evident that the orientation, as well as the velocity of the addition, may be affected by neighbouring groups by reason of their influence upon the electrons of the double bond;[12] for example, in the compound $CHR{=}CHR'$, either of the polarizations $CHR\overset{\curvearrowright}{=}CHR'$ or $\overset{\curvearrowleft}{CHR{=}}CHR'$ may be favoured by the groups R and R′, the mesomeric form approaching more closely to one or the other of the dipolar unperturbed structures. External factors such as medium, temperature, and illumination may also play a part.[1] The experimental data are exceptionally difficult to interpret, however.

Recent investigations by Kharasch and his collaborators, moreover, have thrown doubt upon the value of many of the recorded observations. In a series of studies of the addition of halogen hydrides to olefinic compounds, they have discovered an important 'peroxide effect'. They first examined the addition of hydrogen bromide to allyl bromide,[14] where the possible products are 1:2-dibromopropane and 1:3-dibromopropane:

$$CH_2{=}CH\cdot CH_2Br + HBr \begin{array}{ll} \nearrow CH_3\cdot CHBr\cdot CH_2Br & (1{:}2) \\ \searrow CH_2Br\cdot CH_2\cdot CH_2Br & (1{:}3). \end{array}$$

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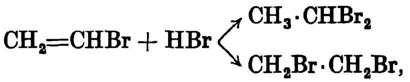
[10] *Annalen*, 1870, **153**, 256. [11] *J. pr. Chem.* 1899, **60**, 341; *Ber.* 1906, **39**, 2138.

[12] This feature has been considered by Lucas and his co-workers, *J. Amer. Chem. Soc.* 1924, **46**, 2475; 1925, **47**, 1459, and by Kharasch and Darkis, *Chem. Reviews*, 1928, **5**, 571.

[13] See Ipatieff, *Ber.* 1903, **36**, 1988; Ingold and Ramsden, *J.C.S.* 1931, 2746; Boorman, Linstead, and Rydon, ibid. 1933, 568; Sherrill, Mayer, and Walter, *J. Amer. Chem. Soc.* 1934, **56**, 928.

[14] Kharasch and Mayo, ibid. 1933, **55**, 2468. An influence of oxygen upon additions

Samples of allyl bromide which had been exposed to air were found to contain peroxidic impurities, which could be recognized by their oxidizing action upon ferrous salts; hydrogen bromide added rapidly to these specimens to give mainly 1 : 3-dibromopropane. On the other hand, if peroxides were completely removed and the addition carried out in absence of air, a slow reaction occurred and 80 per cent. of the product was the 1 : 2-dibromide. When oxygen was bubbled through a peroxide-free specimen for ten minutes, the reaction was again rapid and 70 per cent. of the addition compound was 1 : 3-dibromopropane; passage of hydrogen, nitrogen, nitric oxide, or nitrogen peroxide had no such effect. In presence of an 'antioxidant' such as diphenylamine, hydroquinone, thiophenol, or thiocresol all specimens under all conditions gave 1 : 2-dibromopropane in nearly theoretical yield. In five hundred experiments there was no difference between the behaviour of a peroxide-free specimen and that of one which contained an antioxidant. Kharasch therefore concludes that the 'normal' reaction of allyl bromide with hydrogen bromide produces 1 : 2-dibromopropane, the 1 : 3-dibromide being the result of an 'abnormal' addition catalysed by peroxides; he further expresses the opinion that 'unless conditions are attained which eliminate this oxygen or peroxide effect, no statement as to the direction of addition of hydrogen bromide to a sample of allyl bromide, the peroxide content of which is unknown, is of significance'. Vinyl bromide, which can give either ethylidene dibromide or ethylene dibromide,



$$\mathrm{CH_2{=}CHBr + HBr} \genfrac{}{}{0pt}{}{\nearrow \mathrm{CH_3\cdot CHBr_2}}{\searrow \mathrm{CH_2Br\cdot CH_2Br},}$$

is still more sensitive to the presence of peroxides.[15] The 'normal' reaction leads to ethylidene dibromide, and its speed is about one-tenth of that of the peroxide-catalysed addition producing ethylene dibromide. The presence of an antioxidant is necessary in order to obtain the 'normal' product. Similar remarks apply to vinyl chloride.[16] Propylene, α- and *iso*-butylenes, and α-amylene are less sensitive,[17] and give the 'normal' products unless a peroxide (such as benzoyl peroxide) is introduced, when the addition is reversed.

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to double linkages has also been reported by Dickinson and Leermakers (ibid. 1932, **54**, 3852), by Schultze (ibid. 1934, **56**, 1552), and by Bauer and Daniels (ibid., p. 2014).

[15] Kharasch *et al.*, ibid. 1933, **55**, 2521.

[16] Ibid. 1934, **56**, 712.

[17] Ibid. 1933, **55**, 2531; 1934, **56**, 1212, 1243, 1642.

The 'normal' products are in accordance with Markownikoff's Rule, viz. $CH_3 \cdot CHBr \cdot CH_3$, $CH_3 \cdot CH_2 \cdot CHBr \cdot CH_3$, $(CH_3)_2 \cdot CBr \cdot CH_3$, and $CH_3 \cdot CH_2 \cdot CH_2 \cdot CHBr \cdot CH_3$ respectively. Kharasch considers the peroxide effect to be responsible for many of the conflicting results recorded in the literature, and he believes that variations in the products with changing external conditions (temperature, medium, illumination) are due to the different effects of the conditions upon the velocities of the normal and peroxide-catalysed reactions.[18] The addition of hydrogen iodide always leads to the 'normal' product, even if peroxides are introduced; this is due to its powerful reducing action.[19]

Addition to Conjugated Systems. Numerous observations of the addition of bromine to butadiene and its derivatives, which contain two olefinic linkages separated by a single bond ('conjugated' double linkages), have indicated that the principal product is usually the 1:4 (terminal) dibromide:

$$CH_2{=}CH{-}CH{=}CH_2 + Br_2 \longrightarrow CH_2Br{-}CH{=}CH{-}CH_2Br.$$

Recent investigations confirm the predominance of this type of addition. Thus, Farmer, Lawrence, and Thorpe find the following percentages of the terminal dibromide in the product of addition of bromine to butadiene in different solvents:[20]

Solvent	*Temperature*	*Per cent. 1:4*
Acetic acid	4°	70
Carbon disulphide. . . .	−15°	66
Chloroform	−15°	63
Hexane	−15°	38

The terminal dibromide has also been found in major quantity when bromine is added to $\alpha\delta$-, $\alpha\gamma$-, and $\beta\gamma$-dimethylbutadienes[21] and to isoprene.[22] Muconic acid and $\alpha\delta$-diphenylbutadiene, however, give 1:2 addition of bromine but 1:4 addition of hydrogen.[23]

Thiele's Theory of Partial Valencies[24] was an attempt to interpret 1:4 addition. The reactivity of the olefinic linkage was attributed to the incomplete saturation of the affinities of the doubly bound

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[18] *J. Amer. Chem. Soc.* 1936, **58**, 57.

[19] Ibid. 1934, **56**, 1782.

[20] *J.C.S.* 1928, 729.

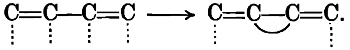
[21] Farmer, Lawrence, and Scott, ibid. 1930, 510.

[22] Staudinger *et al.*, *Helv. Chim. Acta*, 1922, **5**, 756.

[23] Strauss, *Ber.* 1909, **42**, 2866; Chandrasena and Ingold, *J.C.S.* 1922, **121**, 1306.

[24] *Annalen*, 1899, **306**, 87. Thiele's application of his theory to benzene is well known.

carbon atoms, which were thus regarded as possessing free 'partial valencies'. In the case of a compound such as butadiene, the partial valencies of the central carbon atoms might then neutralize each other by 'conjugation', leaving free partial valencies only at the terminal atoms:



$$C{=}C{-}C{=}C \longrightarrow C{=}C{-}C{=}C.$$

All cases of 1:2 addition to compounds of the butadiene type formed exceptions to Thiele's theory, and various ingenious interpretations were suggested to account for them. The theory immediately met with violent criticism,[25] and it was clearly incapable of embracing even a majority of the experimental observations.

In 1922 Gillet suggested[26] that 1:2 addition always occurred first, and might be followed by migration of halogen to the 4-position by what is now known as an 'anionotropic' change.[27] The work of Farmer, Lawrence, and Thorpe[20] showed, however, that this change, while it can occur, is far too slow to account for the high proportion of the 1:4 derivative in the product. Accordingly, Burton and Ingold modified Gillet's mechanism.[28] Starting from Francis's demonstration that one atom of halogen adds initially,[29] they suggested the following scheme for the addition of bromine to conjugated double bonds under conditions which permit ionization:

$$\begin{tikzcd}
\text{Olefinic compound} + Br_2 \arrow[r] & \text{Ions of 1:2 dibromide} \arrow[r, shift left] \arrow[d, shift left] & \text{1:2 dibromide} \arrow[l, shift left] \\
 & \text{Ions of 1:4 dibromide} \arrow[r, shift left] \arrow[u, shift left] & \text{1:4 dibromide.} \arrow[l, shift left]
\end{tikzcd}$$

The isomeric change occurs in the kation, and not in the dibromide itself. For butadiene the series of changes would be

$$CH_2{=}CH{-}CH{=}CH_2 + Br_2 \longrightarrow CH_2Br{-}\overset{\oplus}{C}H{-}CH{=}CH_2 + Br^{\ominus}$$

followed by *either*

$$CH_2Br{-}\overset{\oplus}{C}H{-}CH{=}CH_2 + Br^{\ominus} \rightleftarrows CH_2Br{-}CHBr{-}CH{=}CH_2$$

or

$$CH_2Br{-}\overset{\oplus}{C}H{-}CH{=}CH_2 \rightleftarrows CH_2Br{-}CH{=}CH{-}\overset{\oplus}{C}H_2$$

$$CH_2Br{-}CH{=}CH{-}\overset{\oplus}{C}H_2 + Br^{\ominus} \rightleftarrows CH_2Br{-}CH{=}CH{-}CH_2Br.$$

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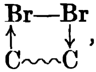
[25] Michael, *J. pr. Chem.* 1899, **60**, 467; Erlenmeyer, *Annalen*, 1901, **316**, 43; Hinrichsen, ibid. 1904, **336**, 168. The presence of the 1:2 dibromide in the product of addition of bromine to butadiene, originally claimed by Griner (*Compt. rend.* 1893, **116**, 723; **117**, 553) was later admitted by Thiele himself (see Straus, *Ber.* 1909, **42**, 2872).

[26] *Bull. Soc. Chim. Belg.* 1922, **31**, 365. See also *Bull. Soc. Chim.* 1927, **41**, 927. Compare Prévost, *Compt. rend.* 1927, **185**, 132.

[27] See Chap. IX, p. 130.

[28] *J.C.S.* 1928, 910; Ingold, *Ann. Reports*, 1928, **25**, 131.

[29] See p. 100.

The positive ion is actually, of course, a mesomeric structure. Provided the above ionic equilibria are established, the proportions of the dibromides formed will depend upon their relative stabilities, that is, upon the difficulty with which a bromide ion is detached, and this will clearly be influenced by substituents.[30] On the other hand, in a non-ionizing solvent such as hexane the equilibria will presumably not be established. The attack of the second bromine will commence while it is still attached to the first, and the complex thus formed, of the type  $\begin{matrix}Br—Br \\ \uparrow \quad \downarrow \\ C\sim\sim C\end{matrix}$, will be that which leads to a ring with the minimum of strain. The results of Farmer, Lawrence, and Thorpe (p. 104) point to the preferential formation of the 1:2-dibromide under these conditions.[31]

Addition of Nucleophilic Reagents. The olefinic linkage forms addition products with a whole group of electrophilic reagents such as halogens and halogen hydrides; the carbonyl bond, $\rangle C=O$, on the other hand, exhibits reactivity towards a quite distinct group of substances, typified by hydrogen cyanide and sodium bisulphite, which do not normally add to olefinic compounds. In these addition reactions of the carbonyl group, hydrogen always becomes linked to oxygen and the anionic portion of the reagent to carbon.[32] The natural inference is that, in its addition reactions, the carbon to oxygen double bond is polarized in the direction $\rangle C\overset{\curvearrowright}{=}O$; indeed, the energy of formation of the carbonyl group indicates resonance between $\rangle C=O$ and $\rangle\overset{\oplus}{C}—\overset{\ominus}{O}$,[33] and the existence of a *permanent* dipole is demonstrated by the high electric moments of ketones and aldehydes (of the order 2·8 D).

Lapworth's observations of the effects of acids, alkalis, and alkaline cyanides upon the addition of hydrocyanic acid to ketones have shown that the initial stage in the process is the relatively slow co-ordination of cyanide ion to produce the complex anion $\rangle C(CN)\overset{\ominus}{O}$,

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[30] The preponderance of one isomeride when addition of bromine occurs, and of the other when hydrogen is added (e.g. in muconic acid or αδ-diphenylbutadiene) is due to the different mechanisms involved. The mesomeric ion is positive and negative respectively (see ref. 6, p. 100), and hence groups have opposite effects.

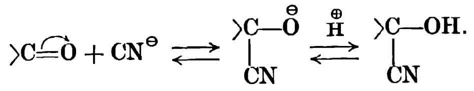
[31] The above suggestions were made to the author by Professor Ingold in a private communication.

[32] Similarly, in reactions with metal alkyls and Grignard reagents, and in the Reformatzky reaction, the metal becomes linked to oxygen and an alkyl group to carbon.

[33] See p. 61.

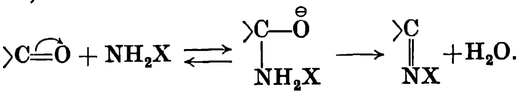
this being followed by instantaneous combination with hydrogen ion to give the cyanohydrin.[34] This view of the reaction, which ascribes to cyanohydrins the characters of weak acids, was confirmed by the isolation of crystalline products (salts) by the action of potassium cyanide upon benzaldehyde and camphorquinone.[35] The distinction between the additive reactions of the olefinic linkage and those of the carbonyl bond now becomes clear; the former adds electrophilic reagents, and the latter nucleophilic reagents.

Since the covalency of carbon is limited to four, the addition of the cyanide ion to carbonyl carbon must be accompanied by the *complete* transfer of a pair of electrons to the sole control of oxygen, and the mechanism of cyanohydrin formation is therefore



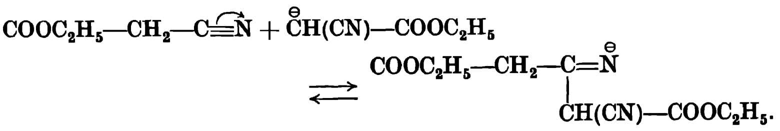
$$>\overset{\frown}{C\!=\!O} + CN^{\ominus} \rightleftharpoons \begin{array}{l}>C-\overset{\ominus}{O}\\ \;\;|\\ \;\;CN\end{array} \overset{\overset{\oplus}{H}}{\rightleftharpoons} \begin{array}{l}>C-OH.\\ \;\;|\\ \;\;CN\end{array}$$

This is no doubt typical of the manner in which addition products are normally formed by the carbonyl group. The process is reversible, and Lapworth and Manske have determined the equilibrium constants for a considerable number of cyanohydrins;[36] reversibility appears, indeed, to be a characteristic of the additions of nucleophilic reagents to unsaturated systems. The production of compounds such as oximes and hydrazones is doubtless to be included among addition reactions,[37] the second stage (not reversible) now being the elimination of the elements of water, accompanied by a readjustment of covalencies,



$$>\overset{\frown}{C\!=\!O} + NH_2X \rightleftharpoons \begin{array}{l}>C-\overset{\ominus}{O}\\ \;\;|\\ \;\;NH_2X\end{array} \longrightarrow \begin{array}{l}>C\\ \;\;\|\\ \;\;NX\end{array} + H_2O.$$

Further, the addition of a nucleophilic reagent to the carbon to nitrogen triple linkage (Thorpe Reaction)[38] must involve a process of an exactly similar type, e.g.



$$COOC_2H_5-CH_2-\overset{\frown}{C\equiv N} + \overset{\ominus}{C}H(CN)-COOC_2H_5$$
$$\rightleftharpoons \begin{array}{l}COOC_2H_5-CH_2-C=\overset{\ominus}{N}\\ \qquad\qquad\qquad\quad\;\; |\\ \qquad\qquad\qquad\quad\;\; CH(CN)-COOC_2H_5.\end{array}$$

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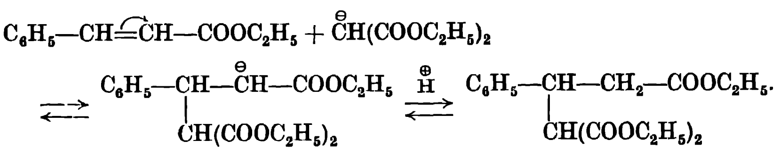
[34] *J.C.S.* 1903, **83**, 995. [35] Ibid. 1904, **85**, 1206. [36] Ibid. 1928, 2533; 1930, 1976.

[37] An addition compound of chloral and hydroxylamine has been isolated by Hantzsch (*Ber.* 1892, **25**, 702).

[38] *J.C.S.* 1904, **85**, 1726; 1906, **89**, 1906. The above formulation of the reaction

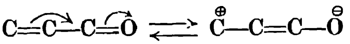
In a number of instances an *olefinic* linkage exhibits the capacity for addition of nucleophilic reagents.[39] The compounds in which such reactivity is observed are αβ-unsaturated ketones, aldehydes, esters, and nitriles. The olefinic linkage is here far *less* reactive than normally towards electrophilic reagents,[40] while the carbonyl bond shows a decreased reactivity towards nucleophilic reagents. Lapworth[41] has studied the addition of hydrocyanic acid to the olefinic linkages in phorone, mesityl oxide, and benzylidenebenzyl cyanide, and finds that the conditions which favour the reaction in each case are exactly those which facilitate cyanohydrin formation. The best-known instance of such addition, however, is the Michael Reaction,[42] as exemplified by the addition of ethyl sodio-malonate to cinnamic ester:



$$C_6H_5{-}CH{=}CH{-}COOC_2H_5 + \overset{\ominus}{C}H(COOC_2H_5)_2$$

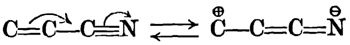
$$\rightleftarrows \begin{array}{l} C_6H_5{-}CH{-}\overset{\ominus}{C}H{-}COOC_2H_5 \\ \qquad\;\; | \\ \qquad\;\; CH(COOC_2H_5)_2 \end{array} \xrightleftarrows{\overset{\oplus}{H}} \begin{array}{l} C_6H_5{-}CH{-}CH_2{-}COOC_2H_5. \\ \qquad\;\; | \\ \qquad\;\; CH(COOC_2H_5)_2 \end{array}$$

It is significant that all compounds in which nucleophilic reagents add to the olefinic linkage contain one of the groupings C=C—C=O or C=C—C≡N. The electromeric changes



$$C{=}C{-}C{=}O \rightleftarrows \overset{\oplus}{C}{-}C{=}C{-}\overset{\ominus}{O}$$

and



$$C{=}C{-}C{\equiv}N \rightleftarrows \overset{\oplus}{C}{-}C{=}C{=}\overset{\ominus}{N}$$

are here possible, and the compounds are actually resonance structures. This accounts for the depression of the *normal* additive reactivity both of carbonyl carbon (which is rendered less susceptible to the attack of a nucleophilic reagent since its deficiency of electrons is supplied from the olefinic linkage) and of the olefinic bond (where the provision of unshared electrons is made more difficult). At the same time, there is provided a point of attack for a nucleophilic reagent at the carbon atom situated in the β-position with respect to the carbonyl or nitrile group,[43] and it is to this carbon that the anion invariably adds.

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as the addition of the anion of the cyanoacetic ester is justified by the findings of Holden and Lapworth (*J.C.S.* 1931, 2368).

[39] Lapworth, *J.C.S.* 1904, **85**, 1214.

[40] Compare p. 101.

[41] References 34 and 39.

[42] *J. pr. Chem.* 1887, **35**, 349.

[43] Compare Cooper, Ingold, and Ingold, *J.C.S.* 1926, 1868.

Catalysed Additions of Nucleophilic Reagents. It remains to consider the large group of reactions in which the addition of a nucleophilic reagent occurs only in presence of a catalyst. In all of these the reagent is a compound possessing 'incipiently ionized' hydrogen, that is, hydrogen which is 'loosened' in such a way that its removal as proton is relatively easy. This condition is brought about by the influence of neighbouring electron-attractive groups.[44] The *catalysed* addition of such a molecule may be distinguished from the *uncatalysed* addition of an anion such as $CN^{\ominus}$ in the examples described above. It may occur at $>C{=}O$ (aldol reaction), and also at $>C{=}C<$ or $—C{\equiv}N$ (analogues of the Michael and Thorpe reactions), when these groups are suitably placed. Like cyanohydrin formation, these additions are reversible.[45]

The simplest aldol condensation is that between two molecules of acetaldehyde to give β-hydroxybutaldehyde,

$$CH_3—CHO + HCH_2—CHO \rightleftarrows CH_3—CH(OH)—CH_2—CHO,$$

a product which loses the elements of water with great facility producing crotonaldehyde, $CH_3—CH{=}CH—CHO$. This loss of water is a characteristic of aldols, which as a consequence frequently cannot be isolated. It is thus a very reasonable supposition that aldol addition precedes the formation of the product actually isolated in the Claisen reaction (aldehyde+aldehyde or ketone in presence of alkali),[46] the Knoevenagel reaction (aldehyde or ketone+malonic, acetoacetic or cyanoacetic ester or a nitro-compound in presence of an organic base),[47] the Perkin reaction (aldehyde+salt of carboxylic acid in presence of acid anhydride),[48] and the acetoacetic ester condensation (ester, or ester+ketone, in presence of sodium ethoxide).[49] In some cases where the subsequent loss of water is not possible, no reaction is observed (e.g. between benzophenone and cyanoacetic ester),[50] and this is probably due to the instability of the aldol phase, the equilibrium favouring the reagents almost entirely.

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[44] Holmes and Ingold, ibid. 1926, 1305. Compare Lapworth, *Mem. Manchester Phil. Soc.* 1920, **64**, No. 3, p. 3; E. H. Ingold, *Chem. and Ind.* 1923, **42**, 1246; Higginbotham and Lapworth, *J.C.S.* 1922, **121**, 2823.

[45] Ingold and Perren, *J.C.S.* 1921, **119**, 1582, 1865; E. H. Ingold, ibid. 1923, **123**, 1717; 1924, **125**, 1319.

[46] Claisen, *Ber.* 1881, **14**, 2471.

[47] Knoevenagel, ibid. 1904, **37**, 4461.

[48] Perkin, *J.C.S.* 1877, **32**, 389.

[49] e.g. Claisen, *Ber.* 1887, **20**, 646. For recent views on the mechanism of this reaction, see Kon, *Ann. Reports*, 1934, **31**, 200.

[50] Haworth, *J.C.S.* 1909, **95**, 480.

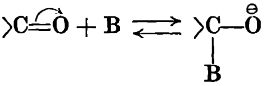
Ethyl malonate and similar compounds will also add to the $\rangle C{=}C\langle$ bond if an organic base is present as catalyst,[47] and sodium ethoxide catalyses addition to the $—C{\equiv}N$ linkage.

The function of the catalyst in these changes has been much discussed, and two distinct views have been expressed:

(1) That the catalyst first reacts with the unsaturated compound. This view is based upon the isolation of products such as $R\cdot CH(OH)\cdot NHR'$, $R\cdot CH(NHR')_2$, and $R\cdot CH(NR'R'')_2$, which undergo reaction with malonic ester and similar compounds.[51] The catalytic effect of *tertiary* bases here remains unexplained, however, and the fact that the compounds can be isolated is no proof that they are intermediates in the processes now under discussion.

(2) That the catalyst removes incipiently ionized hydrogen from the ethyl malonate or other reagent, forming an anion which then adds to the unsaturated compound as in cyanohydrin formation.[52] This view accounts for the action of organic bases and anions such as hydroxyl, but gives no explanation of the catalytic influence of *acids* which is frequently observed in the aldol and other condensations in which carbonyl compounds take part.

The catalysed additions here considered may perhaps all be included in a single scheme which resembles that put forward recently to represent the action of acid and basic catalysts upon prototropic changes.[53] In cyanohydrin formation the *first* step is the addition of the cyanide anion to carbonyl carbon, and alkaline hydrolysis of esters must involve a similar addition of hydroxyl ion. This process is of necessity accompanied by the electromeric change $\rangle C\overset{\frown}{=}O \rightarrow \overset{\oplus}{C}—\overset{\ominus}{O}$. By analogy, the aldol and allied condensations may be regarded as initiated by the attack of a base or anion in the following manner:



$$\rangle C\overset{\frown}{=}O + B \rightleftarrows \rangle \underset{\displaystyle B}{\underset{|}{C}}—\overset{\ominus}{O}$$

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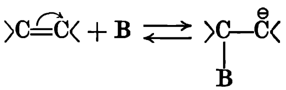
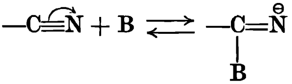
[51] Knoevenagel, *Ber.* 1898, **31**, 2596; Claisen, ref. 49; Dimroth and Zoeppritz, *Ber.* 1902, **35**, 984; Dilthey, ibid. 1929, **62**, 1603, 1609.

[52] Hann and Lapworth, *J.C.S.* 1904, **85**, 46; Cooper, Ingold, and Ingold, ref. 43.

[53] Watson, Nathan, and Laurie, *J. Chem. Physics*, 1935, **3**, 170. The application to prototropy is given in Chap. IX, where a general discussion of acid and base catalysis will also be found.



$$>C\overset{\frown}{=}C< + B \rightleftharpoons >\underset{\displaystyle B}{\underset{|}{C}}-\overset{\ominus}{C}<$$

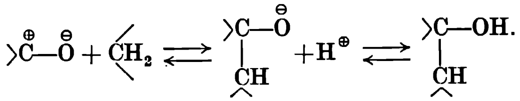


$$-C\overset{\frown}{\equiv}N + B \rightleftharpoons -\underset{\displaystyle B}{\underset{|}{C}}=\overset{\ominus}{N}$$

Similarly, the oxygen atom of the carbonyl group can co-ordinate with a proton (becoming 'oxonium' in character), as in the compounds of acetone with halogen acids isolated by Archibald and McIntosh,[54] and Reddelien's addition products of various ketones (e.g. acetophenone, benzophenone) with nitric and picric acids.[55] The combination of esters with mineral acids has also been demonstrated by Kendall and Booge,[56] and J. W. Baker has shown, both by partition experiments and from a study of the products of nitration, that benzaldehyde, acetophenone, and ethyl benzoate form complexes with sulphuric acid.[57] Acid catalysis of the aldol and similar reactions may therefore be ascribed to the activation of the carbonyl group due to co-ordination of hydrogen ion at the *oxygen* atom,

$$>C\overset{\frown}{=}O + H^{\oplus} \rightleftharpoons >\overset{\oplus}{C}-OH$$

(this is not, of course, applicable to C=C which has no unshared electrons and is not basic). In both types of catalysis the actual bond linking the catalyst to the unsaturated compound may be of a transient nature; its formation provides, however, an efficient means for the communication, to the carbonyl or other group, of the energy necessary to make the electromeric change possible. The essential function of the catalyst is thus the conversion of the double bond to its semipolar form. This being accomplished, the reaction will proceed readily, the approach of the molecule having incipiently ionized hydrogen being accompanied by the withdrawal of the proton, as in the scheme



$$>\overset{\oplus}{C}-\overset{\ominus}{O} + \overset{/}{\underset{\backslash}{C}}H_2 \rightleftharpoons \begin{array}{l}>C-\overset{\ominus}{O}\\ \;\;|\\ \;\;CH\\ \;\wedge\end{array} + H^{\oplus} \rightleftharpoons \begin{array}{l}>C-OH.\\ \;\;|\\ \;\;CH\\ \;\wedge\end{array}$$

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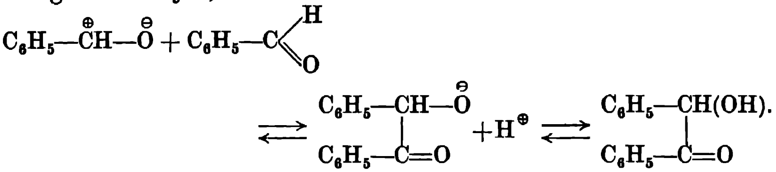
[54] *J.C.S.* 1904, **85**, 924. Later, Maass and McIntosh (*J. Amer. Chem. Soc.* 1912, **34**, 1273) prepared an unstable compound of ethyl acetate with hydrogen bromide.

[55] *Ber.* 1912, **45**, 2904; *J. pr. Chem.* 1915, **91**, 213.

[56] *J. Amer. Chem. Soc.* 1916, **38**, 1712.

[57] *J.C.S.* 1931, 307; Baker and Moffitt, ibid., p. 314; Baker and Hey, ibid. 1932, 1226.

The benzoin reaction falls into line with the others, cyanide ion now being the catalyst;[58]



$$C_6H_5-\overset{\oplus}{C}H-\overset{\ominus}{O} + C_6H_5-C\begin{array}{l}\diagup H\\ \diagdown\!\!\diagdown O\end{array}$$

$$\rightleftharpoons \begin{array}{l}C_6H_5-CH-\overset{\ominus}{O}\\ \qquad\quad\ |\\ C_6H_5-C=O\end{array} + H^{\oplus} \rightleftharpoons \begin{array}{l}C_6H_5-CH(OH).\\ \qquad\quad\ |\\ C_6H_5-C=O\end{array}$$

This view of the influence of catalysts upon the addition reactions under consideration is not proved experimentally, but it is attractive on account of its wide applicability. It ascribes a similar mechanism to all the catalysed reactions of carbonyl compounds, whether the catalyst be basic or acidic, and brings them into line with other analogous changes. The catalyst is visualized as an additive reagent, exactly similar to the cyanide ion in cyanohydrin formation or to the group co-ordinated with oxygen in an oxonium compound, and its function is essentially the activation of the multiple linkage.

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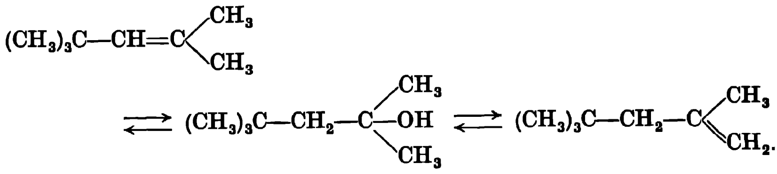
[58] Compare Lapworth, ref. 34.

IX

TAUTOMERIC CHANGE

THE meaning now associated with the word 'tautomerism' is stated with admirable clearness in the following definition:[1] '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.' An obvious demonstration of tautomeric character is the formation, by a single compound, of *two* sets of isomeric derivatives, as exemplified in nitriles and carbylamines or in Baeyer's two ethyl isatins;[2] in each case only *one* parent substance can be isolated. Again, the hydrolysis of β-bromopropylene and vinyl bromide leads to acetone and acetaldehyde respectively, whereas the products anticipated would be the alcohols $CH_2{=}C(OH)CH_3$ and $CH_2{=}CHOH$ which are isomeric with these carbonyl compounds; this is also an instance of tautomerism.

In 1877 Butlerow[3] interpreted the production of two isomeric *iso*dibutylenes in the reaction of sulphuric acid with *tert*-butyl alcohol as indicating the equilibrium



$$(CH_3)_3C{-}CH{=}C(CH_3)_2 \rightleftarrows (CH_3)_3C{-}CH_2{-}C(CH_3)_2{-}OH \rightleftarrows (CH_3)_3C{-}CH_2{-}C(CH_3){=}CH_2.$$

He suggested further that all substances which give rise to isomeric derivatives might themselves be equilibrium mixtures of isomerides; in such cases they would exhibit the reactions of both forms and yield derivatives of each. A quite different view was expressed by Laar,[4] to whom we owe the term 'tautomerism'. In all the known examples the parent substances (e.g. HCN and HNC) differed from each other in the position of a hydrogen atom, and Laar suggested

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[1] 'Oxford definition.' See Lowry, *Chem. Reviews*, 1927, **4**, 231.

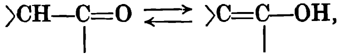
[2] *Ber.* 1883, **16**, 2188.

[3] *Annalen*, 1877, **189**, 44.

[4] *Ber.* 1885, **18**, 648.

that this hydrogen was in a state of continuous oscillation between these positions (similarly to the double bonds in the Kekulé benzene formula). Laar's view was, of course, directly opposed to Butlerow's conception of an equilibrium between isomerides, for the forms giving rise to the different derivatives were regarded as being not isomeric but identical.

Definite evidence in support of Butlerow's theory was obtained in 1896, when the ketonic and enolic forms of certain diketones and ketonic esters were isolated[5] and shown to be easily convertible to the same mixture. The equilibrium in the 'keto-enol' system may be written, in general,



$$>CH{-}\overset{}{\underset{|}{C}}{=}O \rightleftharpoons\ >C{=}\underset{|}{C}{-}OH,$$

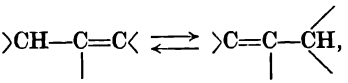
and among the individual isomerides isolated were those of acetyldibenzoyl methane,

$$CH_3\cdot CO\cdot CH(CO\cdot C_6H_5)_2 \rightleftharpoons CH_3\cdot C(OH){=}C(CO\cdot C_6H_5)_2,$$

and of ethyl formylphenylacetate,

$$CHO\cdot CH(C_6H_5)\cdot COOC_2H_5 \rightleftharpoons CH(OH){=}C(C_6H_5)\cdot COOC_2H_5.$$

In the same year, too, Hantzsch and Schultze isolated a solid isomeride of phenylnitromethane,[6] which was clearly responsible for the acidic character of the nitro-compound, and which changed spontaneously to the liquid isomeride; the forms are written $C_6H_5\cdot CH_2\cdot NO_2$ and $C_6H_5\cdot CH{=}NO(OH)$ respectively. Reference should also be made to Fittig's discovery[7] of the interconversion of the ions of $\alpha\beta$- and $\beta\gamma$-unsaturated acids in hot alkaline solution, e.g. $CH_3\cdot CH{=}CH\cdot COO' \leftrightarrows CH_2{=}CH\cdot CH_2\cdot COO'$. This is an example of 'three-carbon tautomerism',



similar to that of the *iso*dibutylenes, but differing from the other cases referred to above in that the individual isomerides are both stable substances under ordinary conditions, and are converted to the equilibrium mixture only under the influence of a powerful reagent.

Meanwhile, the problem of the constitution of ethyl acetoacetate,

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[5] Claisen, *Annalen*, 1896, **291**, 25; Wislicenus, ibid., p. 117; Knorr, ibid. **293**, 70.

[6] *Ber.* 1896, **29**, 699, 2251.

[7] Ibid. 1891, **24**, 82, and later; cf. Linstead, *J.C.S.* 1927, 362.

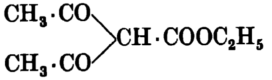
the classic and most widely investigated example of a tautomeric substance, awaited solution. The ester was first prepared in 1863 by Geuther, who assigned to it the enolic formula

$$CH_3\cdot C(OH){=}CH\cdot COOC_2H_5.$$

Frankland, however, preferred the ketonic representation

$$CH_3\cdot CO\cdot CH_2\cdot COOC_2H_5,$$

which was accepted by Wislicenus,[8] whose investigation of the formation and decomposition of the mono- and di-alkyl derivatives of the ester laid the foundation of the extensive uses of the 'aceto-acetic ester synthesis'. The metallic derivatives show none of the properties of the organo-metallic compounds, in which a metal is linked to carbon; moreover, the ester can be liberated by addition of acid to these substances, which doubtless have an enolic structure, e.g. $CH_3\cdot C(ONa){=}CH\cdot COOC_2H_5$. They react with alkyl and acyl halides giving products in which the alkyl or acyl group can usually be shown to be linked to *carbon*, i.e. $CH_3\cdot CO\cdot CHR\cdot COOC_2H_5$ and $CH_3\cdot CO\cdot CRR'\cdot COOC_2H_5$, although acetyl chloride, under different conditions, gives both



$$\begin{matrix} CH_3\cdot CO \\ CH_3\cdot CO \end{matrix}\!\!>\!CH\cdot COOC_2H_5 \quad \text{and} \quad CH_3\cdot C(O\cdot COCH_3){=}CH\cdot COOC_2H_5,$$

ethyl chloroformate produces $CH_3\cdot C(O\cdot COOC_2H_5){=}CH\cdot COOC_2H_5$, and ammonia and amines yield esters of the type

$$CH_3\cdot C(NR_2){=}CH\cdot COOC_2H_5.$$

Acetoacetic ester itself gives acetone with dilute acids or alkalis, and *iso*nitrosoacetone, $CH_3\cdot CO\cdot CH{=}NOH$, with nitrous acid; it also reacts with hydrocyanic acid, sodium bisulphite, hydroxylamine, and phenylhydrazine in accordance with the ketonic formula. On the other hand, it gives a violet coloration with ferric chloride, and is converted to ethyl β-chlorocrotonate, $CH_3\cdot CCl{=}CH\cdot COOC_2H_5$, by phosphorus pentachloride. It is a typically tautomeric substance in terms of the definition given at the beginning of this chapter.

The rival formulae were, however, the subject of heated controversy until 1911, when Knorr succeeded in isolating the individual isomerides.[9] He crystallized the ketonic form from solutions of the ester in organic solvents at −78°; it gave no immediate colour with

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[8] *Annalen*, 1877, **186**, 163.

[9] Knorr, Rothe, and Averbeck, *Ber.* 1911, **44**, 1138.

ferric chloride (absence of hydroxyl), nor reaction with bromine (absence of C=C). Treatment of the sodium derivative with dry hydrogen chloride at −78° gave the enol, which reacted instantaneously both with ferric chloride and with bromine. Either form gave the equilibrium mixture with the utmost ease, Knorr's successful separation of the isomerides being made possible by the use of a very low temperature at which the speed of interconversion was relatively small. K. H. Meyer later separated the forms by aseptic distillation,[10] consisting in fractionation from a Jena glass or silica vessel previously treated to ensure absence of traces of impurities which catalysed the attainment of equilibrium. Butlerow's original conception of an equilibrium between isomerides was thus finally established in a case where the interconversion is exceedingly easy and rapid.

The composition of the equilibrium mixture of ketonic and enolic forms has been investigated by observations of physical properties (e.g. refractivity), but the outstanding method is that devised by K. H. Meyer;[11] it is of a chemical nature, and depends upon the instantaneous reaction of bromine with the enol. Other chemical methods (e.g. the standard processes for determination of —OH) are inapplicable, owing to the rapid transformation of one form to the other. In Meyer's procedure an alcoholic solution of the tautomeric compound is treated with bromine, also in alcohol, and the excess of the halogen immediately removed by addition of a phenol (e.g. β-naphthol or *m*-cresol); the process up to this stage occupies only fifteen seconds, and is carried out at a temperature below 0°. On addition of potassium iodide and acid, the brominated product is reduced in accordance with the equation

$$\text{—CHBr—} + 2\text{HI} = \text{—CH}_2\text{—} + \text{HBr} + \text{I}_2,$$

and the iodine is determined with thiosulphate. The method clearly depends upon the *quantitative* liberation of iodine, which usually occurs with brominated β-diketones and β-ketonic esters (which have the grouping $\text{—CO—CH}_2\text{—CO—}$ in common). Meyer found that pure acetoacetic ester normally contains 7 per cent. of enol in equilibrium with the ketonic form, and other compounds have much

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[10] Meyer and Schoeller, *Ber.* 1920, **53**, 1410.

[11] Ibid. 1911, **44**, 2718; 1912, **45**, 2843. Direct titration with alcoholic bromine is an alternative to the process here described; it is more widely applicable, but probably less accurate.

higher proportions, e.g. acetylacetone (80 per cent.) and benzoylacetone (98 per cent.). In solutions the proportions vary widely. Enol is not detectable in ethyl malonate, in spite of its many similarities to acetoacetic ester.

Although the β-diketones and β-ketonic esters provide the best-known examples of keto-enol tautomerism, another well-established case is that of the α-diketones. The existence of these compounds in the two tautomeric forms has been indicated in a number of investigations,[12] and Dufraisse and Moureu have more recently isolated the pure ketonic and enolic forms of methylbenzylglyoxal, phenylbenzylglyoxal, and phenyl-*p*-methoxybenzylglyoxal.[13] The ketonic forms were obtained by distillation from an alkaline catalyst (sodium carbonate), and the enols by crystallization, also in presence of an alkali or organic base. The isomerides are remarkably stable, and show no tendency to form the equilibrium mixture in the absence of added catalysts.[14] The separation of the tautomeric forms of an α-ketonic ester was achieved by Gault and Weick, who isolated the ketonic and two stereoisomeric enolic isomerides of ethyl phenylpyruvate.[15]

Thus far reference has been made only to cases of mobile hydrogen tautomerism, now usually described by Lowry's term 'prototropy'.[16] Until a relatively recent date, in fact, the term 'tautomerism' was used exclusively to denote the migration of hydrogen.[17] The similar migration of anionic atoms or groups is now recognized, however; this is termed 'anionotropy', and is included under the more general title 'tautomerism'.[18] There is, moreover, no distinction in principle between the tautomerism of crotonic and vinylacetic acids, where interconversion does not proceed at all readily, and that of acetoacetic ester, where it is a matter of great difficulty to isolate either individual form;[19] nor is there any fundamental difference between

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[12] Widman, *Ber.* 1916, **49**, 484; Jörlander, ibid. 1917, **50**, 406; Malkin and Robinson, *J.C.S.* 1925, **127**, 369.

[13] See Moureu, *Trans. Faraday Soc.* 1928, **24**, 562, and references there cited. Also *Compt. rend.* 1929, **188**, 504.

[14] Compare Lowry, Moureu, and MacConkey, *J.C.S.* 1928, 3167.

[15] *Compt. rend.* 1920, **170**, 1392.

[16] *J.C.S.* 1923, **123**, 828; ref. 1.

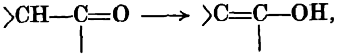
[17] As, for example, in K. H. Meyer's famous definition, *Annalen*, 1913, **398**, 49.

[18] No reference is here made to terms such as 'desmotropy', 'merotropy', 'pseudomerism', 'cryptomerism', or 'dynamic isomerism', which have in the past appeared extensively in the literature. They seem now to be quite unnecessary, and indeed confusing.

[19] The most stable specimen of the enol of acetoacetic ester which has been

examples where the equilibrium mixture consists almost entirely of one isomeride and those which normally exist as mixtures of measurable proportions of each. No attempt is made here to describe the individual characters of the various prototropic systems which have been investigated; twelve such systems are possible by different combinations of the three atoms carbon, nitrogen, and oxygen (e.g. C—C—C, C—N—O, C—C—O, etc.). The object of the present chapter is the consideration of the more general theoretical aspects of tautomeric change, and reference will be made only to the better known examples, particularly the keto-enol system. For a fuller account of the subject the reader is referred to J. W. Baker's recent work,[20] in which the individual tautomeric systems are described.

Evidence of Prototropy in the Halogenation of Carbonyl Compounds. The tautomeric nature of α- and β-diketones and ketonic esters is evident from the foregoing; in a number of cases these compounds have been proved to exist normally as equilibrium mixtures, and the individual ketonic and enolic forms have frequently been isolated. No such clear demonstration is available for monoketones, although any carbonyl compound having at least one hydrogen atom situated in the α-position is *formally* capable of enolization,



$$\rangle CH-\underset{|}{C}=O \longrightarrow \rangle C=\underset{|}{C}-OH,$$

and β-bromopropylene, for example, which yields acetone on hydrolysis, is a derivative of the enol. Further, an enolic constitution was ascribed by Freer[21] to certain metallic derivatives of acetone, and the presence of enol in alkaline solutions has been inferred from the nature of the oxidation products.[22] But the main evidence that monoketones can undergo prototropic change has been derived from a study of the kinetics of their reactions with halogens.

It was first suggested by Lapworth[23] that the characteristic replacement of the α-hydrogen atom of a carbonyl compound might involve a preliminary change to enol. The suggestion was based upon

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prepared had a half-life period of 500 hours (Rice and Sullivan, *J. Amer. Chem. Soc.* 1928, **50**, 3048).

[20] Baker, *Tautomerism* (Routledge & Sons, 1934). This work contains, *inter alia*, an account of the investigations of the three-carbon system carried out by Kon, Linstead, and their collaborators at Imperial College, London.

[21] *Amer. Chem. J.* 1891, **13**, 322, and later; cf. Evans and Nicoll, *J. Amer. Chem. Soc.* 1925, **47**, 2789.

[22] Witzemann, ibid. 1917, **39**, 2657; cf. Denis, *Amer. Chem. J.* 1907, **38**, 561.

[23] *J.C.S.* 1904, **85**, 30.

his discovery that bromine reacts with acetone in dilute aqueous solution at a rate which is proportional to the concentration of the ketone but independent of that of the halogen. It was clear that the reaction must occur in at least two stages, that in which the halogen is involved being too rapid for measurement. The further observation that the velocity of bromination was increased very greatly by the introduction of mineral acid led Lapworth to suggest that a relatively slow change to the enolic form (catalysed by acids) is followed by very rapid reaction of the latter with bromine:

$$CH_3\cdot CO\cdot CH_3 \xrightarrow{\text{(slow)}} CH_2{=}C(OH)\cdot CH_3 \xrightarrow{Br_2\text{(rapid)}} CH_2Br\cdot CO\cdot CH_3+HBr.$$

On Lapworth's view, therefore, the velocity actually measured is that of the prototropic change; a convenient method of determining the speeds of such changes is thus provided. Subsequent investigations, by Dawson and his collaborators,[24] of the iodination of various ketones and of acetaldehyde, confirmed the view that these compounds react with halogens in their enolic forms. A similar demonstration has since been given for typical α- and γ-ketonic acids (pyruvic and laevulinic),[25] and the conclusion may be drawn that, with certain reservations indicated below, compounds containing a carbonyl group with at least one hydrogen atom situated in the α-position with respect to this group react with halogens in their enolic forms.

It is important to realize that it is the ketonic carbonyl group and not that of carboxyl or carbethoxyl which is concerned in the prototropy of ketonic acids and their esters, and, in view of the absence, in carboxylic acids such as acetic and its homologues, of the properties which are characteristic of ketones, it is unsafe to force an analogy between the two types of compounds. Nevertheless, the α-bromination of saturated aliphatic acids appears to bear some resemblance to that of typical carbonyl compounds. At a somewhat elevated temperature one α-hydrogen is replaced, and if no α-hydrogen is present halogenation does not occur, as, for example, in the case of trimethylacetic acid.[26] Moreover, the reaction is catalysed by hydrogen chloride and hydrogen bromide, and Lapworth suggested tentatively that here also enolization might precede halogenation. This view received much support.[27] Subsequent

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[24] Ibid. 1909, **95**, 1860; 1910, **97**, 2048; 1911, **99**, 1740; 1912, **101**, 1503; 1914, **105**, 1275.

[25] Hughes and Watson, ibid. 1929, 1945.

[26] Reformatzsky, *Ber.* 1890, **23**, 1594.

[27] e.g. Aschan, ibid. 1912, **45**, 1913; 1913, **46**, 2162; Ward, *J.C.S.* 1922, **121**, 1161; 1923, **123**, 2207.

investigations,[28] however, have shown that in the bromination of acetic acid and its homologues (*a*) the velocity is dependent upon the concentration of the halogen,[29] (*b*) the catalytic effect of halogen acids is specific, and not common to acids in general, and (*c*) a small quantity of the acid bromide accelerates the bromination enormously, the velocity now being proportional to the concentrations of both acid bromide and bromine. It has long been known that the bromides of carboxylic acids react with halogens more rapidly than do the acids themselves, the well-known Hell-Volhard method of bromination being based upon this fact, and the observations noted above are in harmony with the following scheme for the bromination of the acids. The bromine first reacts with the acid bromide, the brominated *acid* then being formed as the result of a reaction between the unsubstituted acid and the brominated bromide,[30]

$$R\cdot CH_2\cdot COBr + Br_2 = R\cdot CHBr\cdot COBr + HBr,$$

$$R\cdot CHBr\cdot COBr + R\cdot CH_2\cdot COOH \rightleftharpoons R\cdot CH_2\cdot COBr + R\cdot CHBr\cdot COOH.$$

The acid bromide is then free to go through the same series of reactions again. This scheme brings into harmony all recorded observations of the catalysed bromination of carboxylic acids, the actual role of all accelerators (such as phosphorus, acetic anhydride, or halogen acid) being the production of a small quantity of the acid bromide. Chlorination follows a similar course.[31]

In spite, however, of the absence of any tendency on the part of the saturated monocarboxylic acids to undergo prototropic change, malonic acid reacts with halogens in its enolic form, the velocity being, as in the case of acetone, independent of the concentration of the halogen.[32] Moreover, Meyer has demonstrated the presence of enol in the product when an alcoholic solution of ethyl sodiomalonate is acidified, although the ester itself normally contains no detectable quantity of this isomeride. There are also indications that

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[28] Watson, *J.C.S.* 1925, **127**, 2067; *Chem. Reviews*, 1930, **7**, 173.

[29] Compare Hell and Urech, *Ber.* 1880, **13**, 531.

[30] For further evidence in support of this mechanism see ref. 28. The second reaction actually occurs in two stages, involving the production of a mixed anhydride as intermediate (Watson and Gregory, *J.C.S.* 1929, 1373). When no catalyst is added the change may commence by the reaction of bromine with a trace of moisture present.

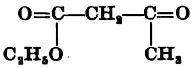
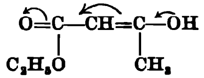
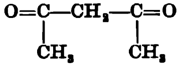
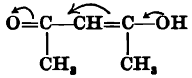
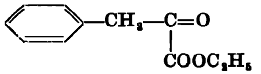
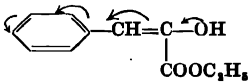
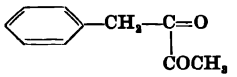
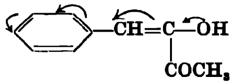
[31] Watson and Roberts, *J.C.S.* 1928, 2779.

[32] Meyer, *Ber.* 1912, **45**, 2864; West, *J.C.S.* 1924, **125**, 1277. The latter author suggests that in the bromination of monobromomalonic acid *rapid* enolization is followed by a *measurable* reaction with bromine, the change being bimolecular.

succinic acid may be brominated through its enolic form, the reaction being catalysed by mineral acids.[33]

The available data indicate, therefore, all grades of stability of the enol, extending from those instances where it is isolatable and present normally in equilibrium with the ketonic form in measurable, and sometimes major quantity, to cases where its stability is so small that it cannot even function as an intermediate in halogenation and other processes. An interpretation of these vast differences in stability may be found in the light of Pauling's conception of quantum-mechanical resonance, which has been outlined in Chapter V.

In all enols which are known to have considerable stability the system is terminated by one of the groups C=O, C≡N, or C_6H_5, and this group is separated from hydroxyl by a chain of alternate double and single linkages.[34] Resonance will therefore occur, as indicated by the curved arrows in the formulae of the table which follows:

Compound	*Ketonic form*	*Enolic form*
Acetoacetic ester	 $\underset{C_2H_5O}{O{=}C}{-}CH_2{-}\underset{CH_3}{C{=}O}$	
Acetylacetone	 $\underset{CH_3}{O{=}C}{-}CH_2{-}\underset{CH_3}{C{=}O}$	
Ethyl phenylpyruvate		
Methylbenzylglyoxal		

All these enols must therefore have considerable resonance energies, which will lead to an increase in stability. It has further been pointed out by Sidgwick,[35] with regard to acetylacetone and acetoacetic ester, that the greater solubility of the enols in non-aqueous solvents, and their greater volatility as compared with the ketonic isomerides, indicates the formation of a 'hydrogen bond' between the hydroxyl and the carbonyl groups; a free hydroxyl group would be expected to lead to a *smaller* solubility in non-hydroxylic solvents,

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[33] Hughes and Watson, *J.C.S.* 1930, 1733.

[34] Compare Watson and Yates, ibid. 1933, 221.

[35] Ibid. 1925, **127**, 907; cf. Lowry and Burgess, ibid. 1923, **123**, 2114.

and also to association, with a consequent *decrease* in volatility. Such formation of a 'hydrogen bond' will result in a further increase of resonance energy and therefore of stability.[36]

In the saturated monocarboxylic acids, on the other hand, transformation to enol, $-\mathrm{C}\Big\langle{}^{\mathrm{O}}_{\mathrm{O}}\Big\}\mathrm{H} \longrightarrow =\mathrm{C}\Big\langle{}^{\mathrm{OH}}_{\mathrm{OH}}$, would destroy the carboxyl group, with a *loss* of the resonance energy associated with it,[37] and a consequent loss of stability. It is not surprising, therefore, that they are never found to undergo prototropic change. Dicarboxylic acids, such as malonic and succinic, however, can change to enol while retaining the resonance energy due to *one* carboxyl group,[38] e.g. $\mathrm{COOH{-}CH_2{-}COOH} \longrightarrow \mathrm{COOH{-}CH{=}C}\Big\langle{}^{\mathrm{OH}}_{\mathrm{OH}}$. The halides of the monocarboxylic acids, such as acetyl chloride and bromide, also show no indication of prototropy, and they are brominated at a rate which is proportional to the concentration of halogen.[39] Direct reaction of the halogen with the ketonic form is therefore probable, and must be due to the influence of halogen attached directly to carbonyl. No clear interpretation of this case has been given, however.

Acid and Base Catalysis. An important feature of the majority of prototropic changes is the catalytic influence of *both* acids and bases; this is observed also in certain other reactions, such as the hydrolysis of esters and some addition processes described in the preceding chapter. Ostwald and Arrhenius attributed such catalysis exclusively to hydrogen and hydroxyl ions, a view which was based upon the observation by the former (1884–7) that there was an approximate proportionality between the catalytic influence of an acid or base and its electrical conductivity. The relationship was demonstrated for thirty-four acids by measurements of the velocity of hydrolysis of methyl acetate or the inversion of cane sugar, and for four alkalis and thirteen nitrogenous bases by a study of their catalytic effects upon the hydrolysis of ethyl acetate. In spite of the approximate nature of this relationship, and of the absence of any interpretation of the observed effects of neutral salts, the Ostwald-Arrhenius conception was not seriously challenged for twenty years. From 1907 onwards, however, a whole series of observations have

[36] See Chap. XII, p. 202.

[37] See Chap. V, p. 61.

[38] Watson, Nathan, and Laurie, *J. Chem. Physics*, 1935, 3, 170.

[39] Watson, *J.C.S.* 1928, 1137.

shown that a much broader view must be taken, and the catalytic effects of a variety of molecules and ions are now recognized.

The first step was the inclusion of undissociated molecules of acids as catalysts,[40] but this so-called 'dual theory' of catalysis (a term introduced by Dawson) was very soon extended. The work of Brönsted upon the decomposition of nitroamide,[41] and of Dawson upon the iodination of acetone[42] made it necessary to ascribe catalytic influences to the anions of weak acids (of which hydroxyl is clearly a special example). Finally, a definite, though relatively small catalytic action of water molecules has been observed in at least two reactions,[43] and the velocity of an acid-base catalysed change in an aqueous medium is therefore represented

$$v = v_{\mathrm{H}}+v_{\mathrm{OH}}+v_{\mathrm{M}}+v_{\mathrm{A}}+v_{\mathrm{H_2O}}$$

(where the suffixes indicate catalysis by hydrogen ion, hydroxyl ion, undissociated acid, anion of weak acid, and water respectively).

These catalysts are divisible into two classes, viz. those which can release a proton (e.g. $H_3O^{\oplus}$, undissociated acid), and those which can unite with a proton (e.g. hydroxyl ion, anion of weak acid, organic bases). Water has both properties ($H_3O^{\oplus} \leftarrow H_2O \rightarrow OH^{\ominus}$). In accordance with a suggestion made independently by Lowry[44] and by Brönsted[45] in 1923, the terms 'acid' and 'base' are now endowed with a wider significance, and include all these substances. According to this generalized conception, an 'acid' is a proton donator and a 'base' is a proton acceptor. Brönsted expresses the relationship between 'acids' and 'bases' as

$$\text{Acid} \rightleftarrows \text{Base}+H^{\oplus};$$

the 'acid' can release a proton to give the 'conjugate base', and, conversely, a 'base' can combine with a proton forming the 'conjugate

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[40] Acree and Johnson, *Amer. Chem. J.* 1907, **37**, 410; **38**, 258; Lapworth, *J.C.S.* 1908, **93**, 2197; Goldschmidt and Thuesen, *Z. physikal. Chem.* 1910, **70**, 627; 1912, **81**, 30; Bredig, Miller, and Braune, *Z. Elektrochem.* 1912, **18**, 535; Snethlage, ibid., p. 539; Dawson and Powis, *J.C.S.* 1913, **103**, 2135; Dawson and Reiman, ibid. 1915, **107**, 1426.

[41] Brönsted and Pedersen, *Z. physikal. Chem.* 1924, **108**, 185. Brönsted and Duus, ibid. 1925, **117**, 299.

[42] Dawson and Carter, *J.C.S.* 1926, 2282.

[43] Brönsted and Guggenheim, *J. Amer. Chem. Soc.* 1927, **49**, 2554; Dawson and Kay, *J.C.S.* 1928, 543. Compare Hudson, *J. Amer. Chem. Soc.* 1907, **29**, 1571.

[44] *Chem. and Ind.* 1923, **42**, 43.

[45] *Rec. trav. chim.* 1923, **42**, 718. Compare *J. Phys. Chem.* 1926, **30**, 777; *Chem. Reviews*, 1928, **5**, 231; *Trans. Faraday Soc.* 1928, **24**, 630.

acid'. It is interesting to note that, in the light of this conception, ammonia is a base while ammonium ion is an acid, $NH_4^{\oplus} \rightleftarrows NH_3 + H^{\oplus}$. The modern theory of acid and base catalysis thus substitutes, for the 'hydrogen ion' and 'hydroxyl ion' of the Ostwald-Arrhenius conception, the terms 'acid' and 'base', defined in the generalized manner.

It is evident that, if a reaction is catalysed both by acids and by bases, its velocity must have a minimum value for a certain composition of the catalysing medium, and as early as 1893 such a minimum was observed in the velocity of hydrolysis of methyl acetate.[46] A similar 'minimum point' has more recently been observed in the iodination of acetone, the mutarotation of glucose, and the hydrolysis of various esters.[47] The conditions existing at the minimum point have been calculated by Dawson and Dean in the following way.[48] They consider an acid-base catalysed reaction proceeding in aqueous solution in presence of a constant concentration c of a weak acid HA (e.g. acetic acid), and a variable concentration of its salt. Unless the amount of salt is very great, catalysis by hydroxyl may be neglected, as may also the very small catalytic effect of the water molecules. The velocity equation thus becomes

$$v = v_H + v_A + v_M = k_H[H^{\cdot}] + k_A[A'] + k_M[HA]. \tag{1}$$

Assuming the Ostwald Dilution Law,

$$[H^{\cdot}][A'] = K(c - [H^{\cdot}]),$$

whence
$$v = k_H[H^{\cdot}] + \frac{k_A K(c - [H^{\cdot}])}{[H^{\cdot}]} + k_M(c - [H^{\cdot}])$$

$$= (k_H - k_M)[H^{\cdot}] + \frac{k_A Kc}{[H^{\cdot}]} + k_M c - k_A K, \tag{2}$$

the last term being negligible.

At the minimum point $dv/d[H^{\cdot}] = 0$, and hence the concentration of hydrogen ion at this point becomes

$$[H^{\cdot}]_i = \sqrt{\left(\frac{k_A Kc}{k_H - k_M}\right)}. \tag{3}$$

Substituting in (2), the velocity at the minimum point is

$$v_i = 2\sqrt{\{(k_H - k_M)k_A Kc\}} + k_M c. \tag{4}$$

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[46] Wijs, *Z. physikal. Chem.* 1893, **11**, 492.

[47] Dawson and Carter, ref. 42; Dawson and Lowson, *J.C.S.* 1927, 2444; Groocock, Ingold, and Jackson, *J.C.S.* 1930, 1039; Lowry and Smith, ibid. 1927, 2539; Euler *et al.*, *Z. anorg. Chem.* 1925, **146**, 45; 1926, **152**, 113.

[48] *J.C.S.* 1926, 2872; cf. Dawson, *Trans. Faraday Soc.* 1928, **24**, 640.

From (2) and (4) it is evident that

$$(v_{\mathrm{H}})_i = (v_{\mathrm{A}})_i = \sqrt{\{(k_{\mathrm{H}}-k_{\mathrm{M}})k_{\mathrm{A}}\mathrm{K}c\}},$$

and the minimum point is thus characterized by the equality of the effects of the hydrogen ions and the anions.

Considering, now, two *equal* velocities, one on each side of the minimum ('isocatalytic') point, where the concentrations of hydrogen ions are $[\mathrm{H}^{\cdot}]_1$ and $[\mathrm{H}^{\cdot}]_2$ respectively, equation (2) leads to the relationship

$$(k_{\mathrm{H}}-k_{\mathrm{M}})[\mathrm{H}^{\cdot}]_1+\frac{k_{\mathrm{A}}\mathrm{K}c}{[\mathrm{H}^{\cdot}]_1} = (k_{\mathrm{H}}-k_{\mathrm{M}})[\mathrm{H}^{\cdot}]_2+\frac{k_{\mathrm{A}}\mathrm{K}c}{[\mathrm{H}^{\cdot}]_2}$$

which, on dividing throughout by $(k_{\mathrm{H}}-k_{\mathrm{M}})$ and rearranging, becomes

$$[\mathrm{H}^{\cdot}]_1[\mathrm{H}^{\cdot}]_2 = \frac{k_{\mathrm{A}}\mathrm{K}c}{k_{\mathrm{H}}-k_{\mathrm{M}}} = [\mathrm{H}^{\cdot}]_i^2$$

or

$$(\mathrm{pH})_1+(\mathrm{pH})_2 = 2(\mathrm{pH})_i.$$

The plot of velocity against pH[49] is therefore a symmetrical curve. It is actually a catenary, as shown in Fig. 8, which is reproduced from Dawson and Dean's paper; the total velocity is represented by the unbroken curve, and the dotted lines represent the partial velocities due to catalysis by hydrogen ion, anion, and undissociated acid respectively. Excellent agreement between theory and experiment has been obtained by Dawson and his collaborators, both for the acetone-iodine reaction and for ester hydrolysis.[47,48] For each value of c, the constant concentration of acid, there is a separate catenary, and the reaction velocities for *all* possible mixtures of a weak acid and its salt are represented by a series of curves which form a catenary surface, the co-ordinates of which are expressed in terms of the velocity, the hydrogen ion concentration, and the acid concentration.[50] Dawson and Key have shown that the conclusions reached are not invalidated by the influence of the ionic strength of the medium upon the reaction velocity.[51] Neutral salt effects were observed by Arrhenius, and are accounted for by Brönsted's theory of reaction velocity in solution.[52] Dawson and Key's results for sodium chloride solutions up to 4 M in concentration are closely similar, however, to those obtained in the absence of the catalytically inert salt.

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[49] pH is the hydrogen ion exponent, representing $-\log[\mathrm{H}^{\cdot}]$.

[50] Dawson, *J.C.S.* 1927, 213, 756.

[51] Ibid. 1928, 1248.

[52] *Z. physikal. Chem.* 1922, **102**, 169; 1925, **115**, 337; cf. ref. 45.

An investigation of the bromination of a series of halogenated acetones in 50 per cent. and 75 per cent. acetic acid medium has revealed a very notable influence of substituents upon the isocatalytic point.[53] As the number of halogen atoms is increased (e.g. from acetone to tetrabromoacetone), this point occurs at continuously higher acid concentration. Thus, in the case of acetone, the medium itself is on the acid side of the isocatalytic point, and introduction of mineral

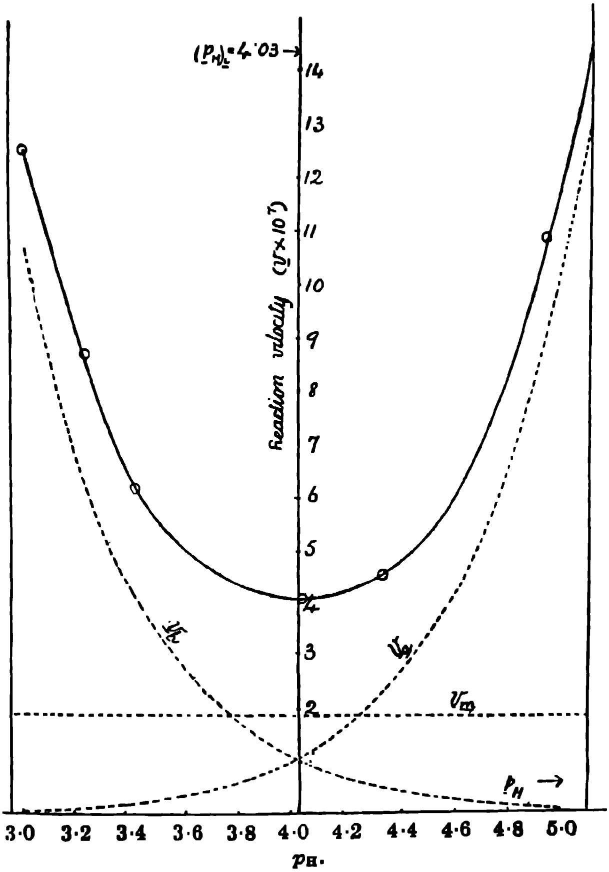

FIG. 8. The catalytic catenary for the acetone-iodine reaction in presence of acetic acid and varying concentrations of sodium acetate. (Reproduced from Dawson and Dean, *J.C.S.* 1926, 2875.)

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[53] Watson and Yates, *J.C.S.* 1932, 1207.

acid leads to a continuous increase of velocity. For monobromo-, *as*-dibromo-, and *s*-dibromo-acetones, however, addition of acid at first causes a *decreased*, and later an increased speed; the point of minimum velocity is reached, in the three cases, by introduction of hydrochloric acid at concentrations of 0·002 M, 0·2 M, and 0·45 M respectively. The influence of acid upon the bromination of ααα-tribromo- and *as*-tetrabromo-acetones is very striking; the speed is *decreased* by acid up to 2 M concentration, and the isocatalytic point must therefore occur at a higher acidity even than this. This movement of the minimum point into regions of higher acidity clearly indicates a decrease in the effectiveness of acid catalysts as compared with basic catalysts, i.e. a decrease in the ratio k_H/k_A. It is brought about by the presence of *electron-attractive* substituents (halogens) in the molecule, and is to be expected since such a substituent will facilitate attack by a base (nucleophilic reagent) and operate against the attack by an acid (electrophilic reagent).[54]

Mechanism of Prototropic Change. As early as 1890 the suggestion was made that tautomeric change is preceded by the ionization of the mobile hydrogen,[55] and some confirmation was found in the discovery that the interconversion of tautomerides was facilitated by solvents of good ionizing power.[56] The development of this view has been admirably summarized by Professor J. F. Thorpe in his Presidential Address to the Chemical Society, 1931,[57] and he concludes with the following criticism:

> 'the large differences between organic and inorganic chemistry and the fact that the former is so largely the "chemistry of the covalencies" must always introduce an element of reserve into the reception of any theory postulating complete ionic reaction in virtually non-conducting media. Such considerations undoubtedly influenced the earlier supporters of the dissociation hypothesis and led them to qualify their views by such expressions as "a weak kind of dissociation", "a species of dissociation", "a phase of disorganization", and so on.'

Whatever be the exact mechanisms involved, it is obvious that a prototropic change which is catalysed both by acids and by bases must proceed by *two* distinct routes. This was pointed out in 1902 by Lapworth and Hann,[58] who suggested two series of changes which, in their essentials, have usually been accepted. Taking the proto-

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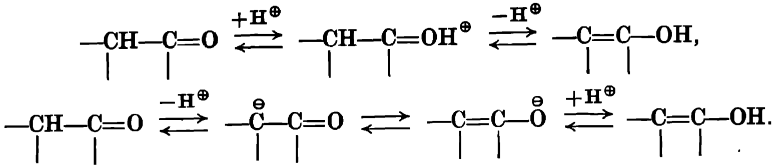
[54] See p. 52.
[55] Goldschmidt, *Ber.* 1890, **23**, 257.
[56] e.g. Claisen, *Annalen*, 1896, **291**, 86; Brühl, *Ber.* 1899, **32**, 2326.
[57] *J.C.S.* 1931, 1015.
[58] Ibid. 1902, **81**, 1512.

tropy of a carbonyl compound as an example, these 'acid' and 'basic' mechanisms may be written as follows:



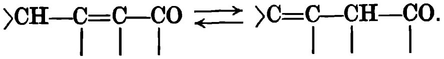
$$-\underset{|}{\text{CH}}-\underset{|}{\text{C}}=\text{O} \overset{+\text{H}^{\oplus}}{\rightleftharpoons} -\underset{|}{\text{CH}}-\underset{|}{\text{C}}=\text{OH}^{\oplus} \overset{-\text{H}^{\oplus}}{\rightleftharpoons} -\underset{|}{\text{C}}=\underset{|}{\text{C}}-\text{OH},$$

$$-\underset{|}{\text{CH}}-\underset{|}{\text{C}}=\text{O} \overset{-\text{H}^{\oplus}}{\rightleftharpoons} -\underset{|}{\overset{\ominus}{\text{C}}}-\underset{|}{\text{C}}=\text{O} \rightleftharpoons -\underset{|}{\text{C}}=\underset{|}{\text{C}}-\overset{\ominus}{\text{O}} \overset{+\text{H}^{\oplus}}{\rightleftharpoons} -\underset{|}{\text{C}}=\underset{|}{\text{C}}-\text{OH}.$$

The initial step is thus either addition of proton at carbonyl oxygen (acid catalysis), or removal of α-hydrogen as proton (basic catalysis). Evidence that the former can occur has been given in the preceding chapter;[59] the latter has no definite experimental evidence in its support, however. This 'basic mechanism' is actually a restatement of the earlier 'ionization theory' of tautomeric change, and in more recent years the series of transformations

ionization—rearrangement of ion—addition of proton

has been postulated by Ingold, Shoppee, and Thorpe for three-carbon tautomerism,[60] and by Lowry for the keto-enol change.[61] In the former case the interconversion is observed only when the system is activated by a group, such as CO, $COOC_2H_5$, or CN, which causes electron-recession by electromeric displacements, e.g.



$$\rangle\text{CH}-\underset{|}{\text{C}}=\underset{|}{\text{C}}-\underset{|}{\text{CO}} \rightleftharpoons \rangle\text{C}=\underset{|}{\text{C}}-\underset{|}{\text{CH}}-\underset{|}{\text{CO}}.$$

The most powerful catalysts are those of the basic type, but acid catalysis has been observed,[62] and it may be concluded that the C=O or C≡N group provides the point of attack for the acid catalyst.

While the first step in these mechanisms of prototropy is either the addition or the removal of a proton, each scheme is completed by the reverse change, i.e. the removal (in acid catalysis) or addition (in basic catalysis) of a proton. This is in harmony with Lowry 'sview that prototropic changes can proceed only in the presence of both a proton donator (acid) and a proton acceptor (base).[63] As early as 1899 experiments on the prototropy of nitrocamphor,

$$\rangle\text{CH}-\text{NO}=\text{O} \rightleftharpoons \rangle\text{C}=\text{NO}-\text{OH},$$

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[59] p. 111.

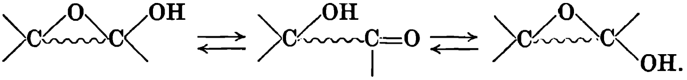
[60] *J.C.S.* 1926, 1477.

[61] Ibid. 1927, 2557; cf. Hsu and Wilson, ibid. 1936, 623.

[62] Kon, ibid. 1931, 248; 1934, 623.

[63] Ibid. 1925, 1371. At an earlier date (ref. 44) Lowry had correlated the observed arrests in the mutarotation of nitrocamphor with the lack of acidity of pure liquids and the universal solvation of the hydrogen ion in solution, all of which he ascribed to the 'extreme reluctance of a hydrogen nucleus to lead an isolated existence'

which can be followed polarimetrically, had shown that the mutarotation, usually complete in three days, is sometimes arrested in a pure anhydrous solvent for long and variable periods of time extending up to two or three weeks.[64] At a later date similar observations were made during a study of the mutarotation of tetramethylglucose,[65] which probably involves two prototropic changes,



For example, one experiment in chloroform medium showed no change after ten days. It was finally demonstrated that, while neither pyridine (proton acceptor) nor cresol (proton donator) individually catalysed the mutarotation, the two in conjunction formed a powerful catalyst.[66] Lowry therefore concluded that prototropic changes require the presence of a reagent to provide a proton, and also of one to remove a proton, and he defined the period of induction observed in mutarotation as a 'period of time during which a pure material is taking up the impurities that are needed to promote the change'. Similar arrests of variable duration have been observed in the bromination of acetone and of ketonic acids in anhydrous solvents; there is a period of induction which may vary from ten minutes to several hours.[67]

The series of changes first suggested by Lapworth and Hann to represent acid- and base-catalysed prototropy have thus met with general acceptance, and it is a tribute to the insight displayed by these authors that more than thirty years of intensive research have led to no results which are contrary to their postulated mechanisms. Recently, however, a view has been put forward which gives a more precise physical significance to their scheme, and to some extent modifies it.[68] The attack of the catalyst is visualized in the manner already described in connexion with the addition of nucleophilic reagents at double bonds;[69] co-ordination at carbonyl carbon (for base catalysis) or oxygen (for acid catalysis) leads to the energized semipolar form $>\overset{\oplus}{C}—\overset{\ominus}{O}$, or to a disposition of electrons approaching

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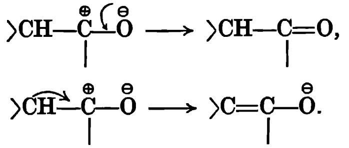
[64] Lowry, *J.C.S.* 1899, **75**, 211.
[65] Lowry and Richards, ibid. 1925, **127**, 1385.
[66] Lowry and Faulkener, ibid., p. 2883.
[67] Hughes and Watson, ref. 25.
[68] Watson, Nathan, and Laurie, ref. 38.
[69] Preceding chapter, p. 110.

this closely. This will be immediately transformed to a more stable structure, a change which may occur in either of two ways, viz.



$$\rangle CH-\overset{\oplus}{C}-\overset{\ominus}{O} \longrightarrow \rangle CH-C=O,$$

$$\rangle CH-\overset{\oplus}{C}-\overset{\ominus}{O} \longrightarrow \rangle C=C-\overset{\ominus}{O}.$$

The first leads to the original ketone, and the second to the ion of the enol, which can immediately add a proton (provided a proton-donator is present), or, like the enol itself, react with halogen. The velocity of the prototropic change will depend, according to this view, on two factors, viz. the rate of reaction of ketone and catalyst, and the proportion of the activated form which is transformed to enol.[70] The presence of a proton acceptor is always necessary, of course, for the removal of the α-hydrogen. The same mechanism is applicable, with appropriate modification, to three-carbon and other types of prototropy, and it may be noted that mobility is conferred upon the three-carbon system by the same groups which promote the addition of nucleophilic reagents at the olefinic linkage.[71]

This view has not as yet received direct experimental confirmation. Thus, the known facts regarding base-catalysed prototropy and the effects of substituents upon the position of the isocatalytic point are interpreted equally well whether the initial step be the addition of the catalyst (as here postulated) or the removal of proton (as in Lapworth and Hann's mechanism). The new mechanism has the virtue, however, that it brings into line all the reactions which are typical of the carbonyl group, and correlates them with other instances of prototropy, with additions to double bonds, and with catalysed changes such as esterification and hydrolysis.[72]

Anionotropy. Tautomeric changes involving the migration of an anion have not been subjected to such extensive investigation as

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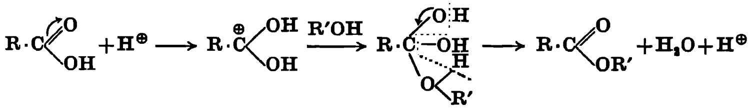
[70] The influence of substituent groups upon these two factors is discussed by Evans, Morgan, and Watson, *J.C.S.* 1935, 1167.

[71] See p. 108.

[72] On this view, the mechanism of esterification catalysed by hydrogen ion is



(compare Evans, Morgan, and Watson, ref. 70, p. 1171).

have prototropic changes. Nevertheless, the general rules governing anionotropy have been laid down by Burton and Ingold[73] as the result of their study of the interconversion of esters of α-phenylallyl alcohol, $C_6H_5\cdot CH(OH)\cdot CH{=}CH_2$, and cinnamyl alcohol, $C_6H_5\cdot CH{=}CH\cdot CH_2OH$. The *p*-nitrobenzoate of the former was found to pass smoothly into that of the latter in boiling acetic anhydride medium,

$$C_6H_5\cdot CHX\cdot CH{=}CH_2 \longrightarrow C_6H_5\cdot CH{=}CH\cdot CH_2X$$
$$(X = p\text{-}NO_2\cdot C_6H_4\cdot COO^{\ominus}).$$

In presence of tetramethylammonium acetate, however, the product was a mixture of cinnamyl acetate and cinnamyl *p*-nitrobenzoate; this observation indicated that complete removal of the anion X had occurred, and the stages of the anionotropic change may therefore be represented as follows:

$$R\cdot CHX\cdot CH{=}CH_2 \longrightarrow X^{\ominus} + R\cdot \overset{\oplus}{C}H\cdot CH{=}CH_2$$
$$\longrightarrow X^{\ominus} + R\cdot CH{=}CH\cdot \overset{\oplus}{C}H_2 \longrightarrow R\cdot CH{=}CH\cdot CH_2X.$$

It may be noted that such a change differs from prototropy in that anions in solution are not universally solvated as protons are.

In accordance with this mechanism, the ease with which the conversion occurs is found to be governed by three factors:

(*a*) The ability of X to form a stable anion, as indicated by the strength of the acid HX. Thus the alcohols (X = OH) were not interconvertible, whereas acetic anhydride (producing the corresponding acetates, $X = O\cdot COCH_3$) gave an easy conversion, and hydrogen bromide (producing bromides, X = Br) gave exclusively cinnamyl bromide. The order of mobility, $OH < O\cdot COCH_3 < Br$, is that of increasing acidity of HX.

(*b*) The ionizing power of the medium (as indicated by its dielectric constant), e.g. benzonitrile > xylene.

(*c*) The capacity of the group R to supply electrons, thus conferring additional stability on the cation. Variation of R gave the order *p*-chlorophenyl > *p*-tolyl > phenyl > methyl > H.

These observations of anionotropic change formed the basis of Burton and Ingold's view of additions to conjugated olefinic compounds, to which reference has been made in the preceding chapter.

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[73] *J.C.S.* 1928, 904, 1650.

X

MIGRATIONS FROM SIDE-CHAIN TO NUCLEUS AND OTHER REARRANGEMENTS[1]

INVESTIGATIONS of the behaviour of aromatic compounds having atoms or groups linked to nitrogen in the side-chain have revealed a number of instances where, in the presence of acid, this group leaves the nitrogen and becomes attached to a carbon atom of the nucleus: $C_6H_5 \cdot NXR \rightarrow X \cdot C_6H_4 \cdot NHR$, where X is Halogen, NO_2, NO, OH, SO_3H, CH_3, NHC_6H_5, $N_2C_6H_5$, etc. In spite of the apparent similarity of these processes, however, there appear to be important differences in mechanism.

The transformations of aromatic chloroamines (a general term for compounds having chlorine attached to nitrogen) to nuclear-substituted anilines have been studied very fully. Acetylchloroaminobenzene (*N*-chloroacetanilide, $C_6H_5 \cdot NCl \cdot COCH_3$), prepared by the action of hypochlorite solutions on acetanilide,[2] is converted almost quantitatively by hydrochloric acid to a mixture of *o*- and *p*-chloroacetanilides (*C*-chloroacetanilides). Hydrochloric acid is the only agent which brings about the transformation,[3] and the proportions of the *o*- and *p*-isomerides produced are the same as in the direct chlorination of acetanilide.[4] Moreover, Orton and W. J. Jones[5] established the existence, in aqueous acetic acid solutions, of the equilibrium

$$C_6H_5 \cdot NCl \cdot COCH_3 + HCl \rightleftarrows C_6H_5 \cdot NH \cdot COCH_3 + Cl_2,$$

and it is therefore clear that the 'chloroamine transformation' occurs in two stages, the chlorine formed in the above reversible process acting as a substituting agent,

$$Cl_2 + C_6H_5 \cdot NH \cdot COCH_3 = Cl \cdot C_6H_4 \cdot NH \cdot COCH_3 + HCl.$$

The formation of *o*- and *p*-chloroacetanilides is due to the *op*-directive

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[1] Only some of the better known rearrangements are dealt with here. For more details of the subject up to 1927, and numerous references to the original papers, see Porter, *Molecular Rearrangements* (Chemical Catalog Co., New York, 1928).

[2] Chattaway and Orton, *J.C.S.* 1899, **75**, 1046; 1901, **79**, 274.

[3] Armstrong, ibid. 1900, **77**, 1047.

[4] Orton and Bradfield, ibid. 1927, 986.

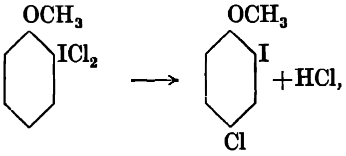
[5] Ibid. 1909, **95**, 1456; *Rep. Brit. Assoc.* 1910, p. 85. See also Orton, Soper, and Williams, *J.C.S.* 1928, 998.

influence of the acetylamino group. The whole series of reactions may be written as follows:

$$\begin{tikzcd}
C_6H_5\cdot NCl\cdot COCH_3+HCl \arrow[dr, shift left] & \\
& C_6H_5\cdot NH\cdot COCH_3+Cl_2. \arrow[ul, shift left] \arrow[dl] \\
Cl\cdot C_6H_4\cdot NH\cdot COCH_3+HCl &
\end{tikzcd}$$

The quantitative conversion of *N*-chloroacetanilide to the nuclear-substituted anilides depends upon the non-reversibility of the *C*-chlorination. A still more convincing proof of the two-stage mechanism is obtained from observations of the 'wandering' of the chlorine to a 'foreign' nucleus; a chloroamine in presence of hydrochloric acid forms an excellent chlorinating agent for anilines, anilides, and phenols.[6] This makes it evident that, at some stage of the process, the chlorine must be free; the transformation is thus definitely *inter*molecular. *N*-chloroacetanilide is also transformed to *o*- and *p*-chloroacetanilides by heating at 100°, and here again there is evidence that free chlorine appears at an intermediate stage.[7] Recent work by R. P. Bell and his co-workers[8] has indicated, however, that the analogous rearrangements of *N*-bromoacetanilide and *N*-iodoformanilide (to give *p*-bromoacetanilide and *p*-iodoformanilide respectively) in *anhydrous* solvents (e.g. chlorobenzene, anisole) are one-stage, or *intra*molecular processes. Thus carboxylic acids and phenols catalyse these rearrangements. Moreover, no free halogen could be detected in the system in the case of *N*-bromoacetanilide, while the iodination of formanilide by a small quantity of iodine present in the *N*-iodoformanilide solutions was shown to be far too slow to account for the rate of production of *p*-iodoformanilide.

The wandering of chlorine from *iodine* to nuclear carbon in the aryl iodide dichlorides is an *inter*molecular process. Thus *o*-iodoanisole dichloride is converted to 4-chloro-2-iodoanisole,



the chlorine substituting the hydrogen situated *para* to methoxyl, the

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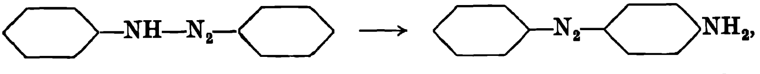
[6] Orton and King, ibid. 1911, **99**, 1185.

[7] Bradfield, ibid. 1928, 351.

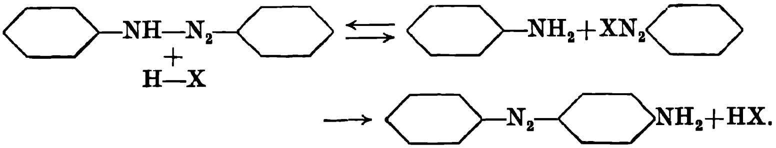
[8] Bell, *Proc. Roy. Soc.* 1934, **143A**, 377; Bell and Levinge, ibid. 1935, **151**, 211; Bell, *J.C.S.* 1936, 1154; Bell and Brown, ibid., p. 1520.

more powerful of the two *op*-directing groups, and the chlorination of acetanilide by an aryl iodide dichloride has been accomplished.[9]

There is also evidence of the *inter*molecular character of the conversion of aromatic diazoamino compounds to the isomeric aminoazobenzenes. Diazoaminobenzene, the product of the condensation of benzene diazonium chloride with aniline, is transformed, in presence of aniline hydrochloride, to *p*-aminoazobenzene,



the group $N_2C_6H_5$ migrating from side-chain nitrogen to nuclear carbon. In diazoaminotoluene, CH$_3$⬡—NH—N$_2$—⬡CH$_3$, the *p*-position is occupied, and in presence of *p*-toluidine hydrochloride a product having the migrating group *ortho* to NH$_2$ is obtained in small yield. On heating diazoaminotoluene with aniline or *o*-toluidine hydrochloride, however, the group migrates to the 'foreign' nucleus to give CH$_3$⬡—N$_2$—⬡NH$_2$ or CH$_3$⬡—N$_2$—$\underset{CH_3}{⬡}$NH$_2$.[10] A study of the kinetics of the diazoaminobenzene transformation by Goldschmidt and Reinders[11] has shown that the velocity is proportional to the concentration of aniline hydrochloride; also, if the hydrochloride be replaced by another aniline salt, the speed varies with the strength of the combined acid. It has therefore been suggested[9] that the transformation is brought about by the free acid in accordance with a scheme such as



The Hofmann-Martius rearrangement of alkyl anilines[12] is a transformation of very considerable importance, since it provides an excellent method for preparing homologues of aniline. On heating the hydrochloride, hydrobromide, or hydriodide of an alkyl or dialkyl aniline, or a phenyltrialkylammonium salt at 250°–350°, the alkyl groups migrate to the *o*- and *p*-positions in the nucleus. A similar transformation occurs if the amine is heated with certain metallic

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[9] Ingold, Smith, and Vass, *J.C.S.* 1927, 1245.

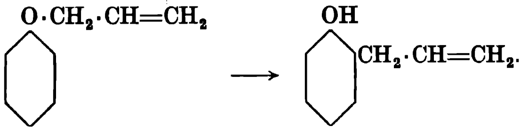
[10] Nietzki, *Ber.* 1877, **10**, 662.

[11] Ibid. 1896, **29**, 1369, 1899.

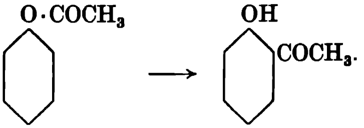
[12] Ibid. 1871, **4**, 742, and later.

salts such as the chlorides of zinc, cadmium, or cobalt.[13] One, two, or three alkyl groups may thus be introduced into the nucleus. Different views have been held regarding the mechanism of the rearrangement; dissociation to produce an alkyl halide has frequently been postulated as an intermediate step, and it has recently been suggested that the alkyl group may first be expelled as a positive ion.[14] The available facts are not easy to interpret, however, and lead to no definite conclusion.

Claisen has recorded a number of examples of the migration of an alkyl group from *oxygen* to nuclear carbon;[15] thus, phenyl allyl ether, on heating above 200°, is transformed to *o*-allylphenol,



The *acyl* group of a phenol ester also migrates to the nucleus when the compound is treated with aluminium chloride or zinc chloride, the product being an *o*- or *p*-hydroxy aromatic ketone. This is known as the Fries Reaction, and is exemplified by the conversion of phenyl acetate to *o*-hydroxyacetophenone,



Fries, von Auwers, and their co-workers, who have studied numerous reactions of this type, consider the rearrangement to be *intra*-molecular.[16] It is claimed, on the other hand, that experimental evidence indicates the liberation of the acid chloride followed by a reaction of the Friedel-Crafts type; for example, treatment of a mixture of *m*-tolyl acetate and *m*-chlorobenzoyl chloride with zinc chloride yields a derivative of benzophenone, acetyl chloride being displaced:[17]

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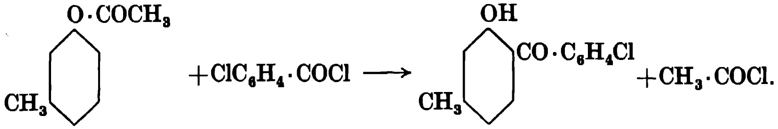
[13] Reilly and Hickinbottom, *J.C.S.* 1920, **117**, 103.

[14] Hickinbottom, ibid. 1934, 1700. In the case of alkyl groups higher than propyl, olefin appears to be an intermediate product; see idem, ibid. 1937, 404, and references there cited.

[15] *Ber.* 1912, **45**, 3157; *Annalen*, 1919, **418**, 69. Analogous migrations from oxygen to carbon may occur in aliphatic compounds.

[16] Fries *et al.*, *Ber.* 1908, **41**, 4272, and later; von Auwers *et al.*, *Annalen*, 1926, **447**, 162; 1928, **460**, 240; *Ber.* 1928, **61**, 1495.

[17] Skraup and Poller, ibid. 1924, **57**, 2033. Compare Cox, *J. Amer. Chem. Soc.* 1930, **52**, 352 (this paper contains a useful summary of suggested mechanisms).



A reaction between two molecules of the phenol ester has also been suggested.[18] These mechanisms have been criticized by von Auwers and Mauss,[19] and no agreement has been reached.

Nothing is known regarding the mechanism of the migration of the sulphonic acid group, as in the transformation of phenylsulphamic acid (in presence of a little sulphuric acid) to aniline *o*- and *p*- sulphonic acids,

$$C_6H_5 \cdot NH \cdot SO_3H \longrightarrow SO_3H \cdot C_6H_4 \cdot NH_2.$$

At temperatures above 180° sulphanilic (aniline *p*-sulphonic) acid is formed exclusively; moreover, on heating the *o*-sulphonic acid with sulphuric acid at 180°–190° it is converted to sulphanilic acid,[20] and a series of changes involving two migrations may be involved in the familiar preparation of this acid from aniline, viz. aniline sulphate → phenylsulphamic acid → aniline *o*-sulphonic acid → aniline *p*-sulphonic acid.

The transformations of aromatic nitroamines to nitroanilines have been studied by Orton and his collaborators.[21] The nitroamines are obtained[22] by treatment of the appropriate aniline with a mixture of nitric acid and acetic anhydride (the nitrating agent being acetyl nitrate, $CH_3 \cdot CO \cdot ONO_2$), and they are converted to *o*- and *p*-nitroanilines under the influence of *any* acid; the nitro group may even displace another group (e.g. Br) already present in the *o*- or *p*-position. There is some evidence of the migration of the group to a foreign nucleus, but, as Bradfield and Orton point out, 'no nitrating agent invariably and normally appears in the system in which a nitroamine is undergoing isomeric change, whereas the presence of chlorine can always be demonstrated during the isomeric change of a chloroamine'. They conclude that 'the facts are in harmony with the view that in the transformation of the nitroamines to nitroanilines

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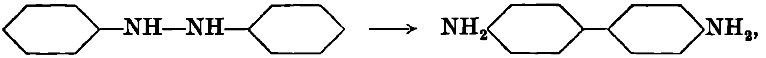
[18] Rosenmund and Schnurr, *Annalen*, 1928, **460**, 56.   [19] Ibid. 1928, **464**, 293.

[20] Bamberger *et al.*, *Ber.* 1897, **30**, 654, 2274. Such a change of nuclear position is unusual, and is, of course, assumed to be absent when the orientation of an aromatic compound is deduced by a relative method. It occurs, however, in certain reactions at rather high temperatures, e.g. the production of resorcinol by fusion with alkali of benzene *p*-disulphonic acid or of any of the bromobenzenesulphonic acids.

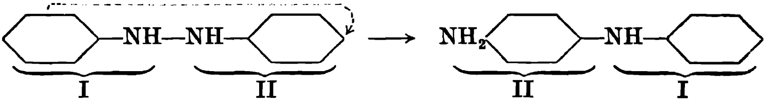
[21] *Rep. Brit. Assoc.* 1912, p. 117; Bradfield and Orton, *J.C.S.* 1929, 915, and references there cited.   [22] Orton, ibid. 1902, **81**, 806.

an *intra*molecular process plays the important part'. The distinction between such a process and the *inter*molecular processes already described may be expressed in the statement that the group comes within the sphere of influence of the nuclear carbon atom before its link with nitrogen is actually broken; it is therefore at no stage free.

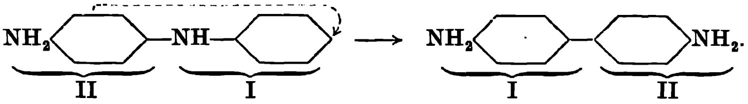
There are two migratory processes which appear to be definitely *intra*molecular. These are the rearrangements of arylhydroxylamines and diarylhydrazines (hydrazobenzenes), where the wandering groups are —OH and —NHAr respectively. Phenylhydroxylamine is transformed by acids to *p*-aminophenol, $C_6H_5 \cdot NH \cdot OH \rightarrow HO \cdot C_6H_4 \cdot NH_2$. Ingold and his collaborators have made many attempts to realize the transference of the hydroxyl to a foreign nucleus, with definitely negative results.[9] The same applies to the rearrangement of hydrazobenzenes. The criteria which have indicated that other processes are *inter*molecular are here absent, and, if the migrating group were at any stage free, the tests to which the systems have been subjected would almost certainly have detected it. Positive evidence of the *intra*molecular nature of the rearrangement of hydrazobenzenes has recently been obtained. Under the influence of acids, hydrazobenzene itself gives mainly benzidine (4:4′-diaminodiphenyl),



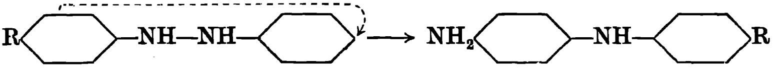
a rearrangement which may be regarded as the result of two transformations. First the group I migrates to the *p*-position in the nucleus II,



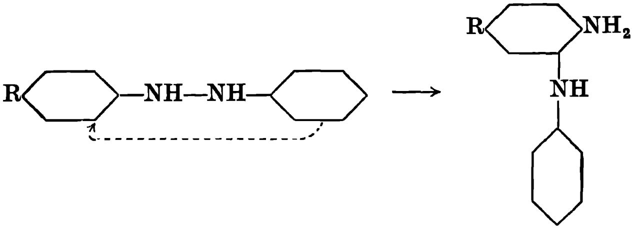
and then the group II wanders to the *p*-position in I,



If in one of these changes the migrating group takes up the *o*-position, the product is diphenyline (2:4′-diaminodiphenyl), which is formed to some extent from hydrazobenzene. When substituents are present in either or both nuclei, the benzidine conversion may be replaced largely or completely by other processes such as the transformation to *o*- and *p*-semidines, in which one only of the above changes has occurred, e.g.

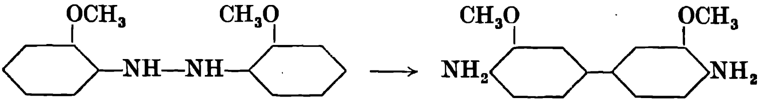


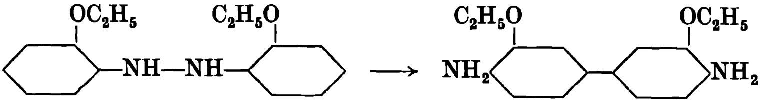
(*p*-semidine)



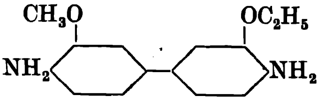
(*o*-semidine)

Various rearrangements may therefore occur simultaneously, leading to a mixed product, and the isomeric changes of a large number of hydrazobenzenes have been studied by Jacobsen and his co-workers.[23] The compounds 2:2′-dimethoxy- and 2:2′-diethoxy-hydrazobenzene, however, undergo no rearrangement other than that of the benzidine type, and they change at comparable speeds. A study of the transformations of these compounds *in the same solution* has enabled Ingold and Kidd to demonstrate the truly *intra*molecular nature of this transformation.[24] Such a rearrangement would give rise to *two* products only, by the reactions





If, however, the migrating group were at any time free, the compound



would be formed also. By a method of thermal analysis the product

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[23] Summarized in *Annalen*, 1922, **428**, 76.

[24] *J.C.S.* 1933, 984.

was shown to consist of *two* benzidines only, and positive evidence of the *intra*molecular character of the benzidine conversion was thus obtained.

The Beckmann Rearrangement

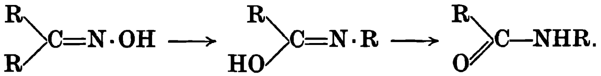
The transformation of an oxime into an acid amide,

$$\left.\begin{matrix}R\\R\end{matrix}\right>C=N-OH \longrightarrow R-CO-NHR,$$

was first observed by Beckmann in 1886.[25] It occurs under the influence of a number of reagents, which include phosphorus pentachloride and oxychloride, sulphuric acid, hydrochloric acid, acetyl and benzenesulphonyl chlorides, and the chlorides of antimony and of a number of metals. The majority of ketoximes undergo this rearrangement, and also the *N*-ethers of aldoximes and sometimes aldoximes themselves; in certain rather rare cases an abnormal rearrangement occurs.[26]

The existence of unsymmetrical ketoximes in two forms was interpreted by Hantzsch and Werner as an instance of geometrical isomerism.[27] The isomeric ketoximes rearrange to give different amides, and it was assumed that a *cis*-interchange of groups occurred. The configurations of the oximes were then deduced from the nature of the products, on the basis of this assumption.[28] The postulate of a *cis*-interchange rested on no experimental foundation, however, and more recent work has shown that *trans*-interchange takes place usually if not invariably.[29] Mills has pointed out, indeed, that *trans*-exchange is probable on stereochemical grounds,[30] and any complete theory of the mechanism of the Beckmann Rearrangement must be applicable to such exchange.

Beckmann himself regarded the transformation as involving an exchange of positions by the alkyl and hydroxyl groups, giving the 'pseudo' form of the amide, followed by the migration of hydrogen:[31]



$$\left.\begin{matrix}R\\R\end{matrix}\right>C=N\cdot OH \longrightarrow \left.\begin{matrix}R\\HO\end{matrix}\right>C=N\cdot R \longrightarrow \left.\begin{matrix}R\\O\end{matrix}\right>C-NHR.$$

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[25] *Ber.* 1886, **19**, 988.

[26] For an excellent summary of the literature relating to the Beckmann Rearrangement up to 1932, see Blatt, *Chem. Reviews*, 1933, **12**, 215.

[27] *Ber.* 1890, **23**, 11. See Chap. XII.

[28] Hantzsch, *Ber.* 1891, **24**, 13, 51.

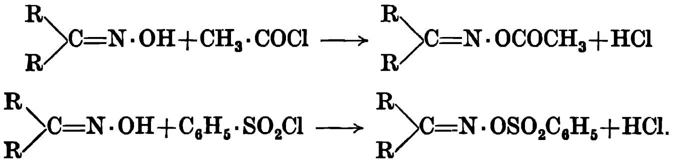
[29] Meisenheimer, ibid. 1921, **54**, 3206, and later. The evidence is summarized in Chap. XII.

[30] Presidential Address to Brit. Assoc., 1932; *Chem. and Ind.* 1932, **51**, 750.

[31] *Ber.* 1894, **27**, 300.

Nothing is here postulated concerning the mechanism by which the actual interchange occurs. Lachman suggested later that the process takes place in the ion of the hydrochloride or other salt of the oxime, a view which was confirmed by his observation of the rearrangement of benzophenoneoxime in aqueous hydrochloric acid.[32] On the other hand, an investigation of the transformations of acyl derivatives (esters) of oximes led Kuhara to the conclusion that these substances (or their salts) were the entities which were capable of rearrangement.[33]

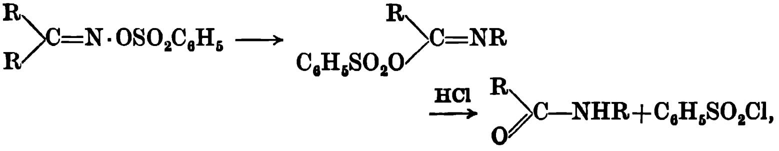
Kuhara found that the speed of rearrangement of benzophenoneoxime under the influence of different acid chlorides varied in the same order as the electron-attractive character of the acyl group as indicated by the dissociation constant of the corresponding acid, e.g. $C_6H_5{\cdot}SO_2Cl > CH_2Cl{\cdot}COCl > CH_3{\cdot}COCl$. Moreover, while the presence of hydrogen chloride was necessary to promote the rearrangement of the acetate of the oxime, the benzenesulphonate rearranged on melting and even on standing. An *alkaline* solution of benzophenoneoxime, in fact, rearranged on treatment with benzenesulphonyl chloride. The transformation of an oxime was ascribed, therefore, to the formation of an ester, e.g.



$$\left.\begin{array}{l}R\\R\end{array}\right\rangle C{=}N{\cdot}OH + CH_3{\cdot}COCl \longrightarrow \left.\begin{array}{l}R\\R\end{array}\right\rangle C{=}N{\cdot}OCOCH_3 + HCl$$

$$\left.\begin{array}{l}R\\R\end{array}\right\rangle C{=}N{\cdot}OH + C_6H_5{\cdot}SO_2Cl \longrightarrow \left.\begin{array}{l}R\\R\end{array}\right\rangle C{=}N{\cdot}OSO_2C_6H_5 + HCl.$$

If this is the ester of a strong acid (e.g. benzenesulphonic), it rearranges spontaneously,



$$\left.\begin{array}{l}R\\R\end{array}\right\rangle C{=}N{\cdot}OSO_2C_6H_5 \longrightarrow \left.\begin{array}{r}R\\C_6H_5SO_2O\end{array}\right\rangle C{=}NR \xrightarrow{HCl} \left.\begin{array}{l}R\\O\end{array}\right\rangle C{-}NHR + C_6H_5SO_2Cl,$$

whereas the ester of a weak acid rearranges only in the form of its ion:

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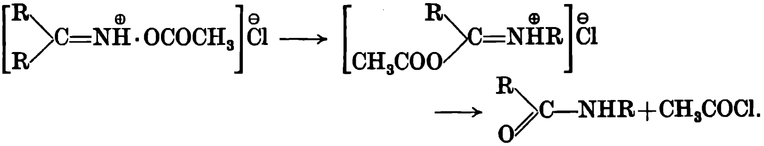
[32] *J. Amer. Chem. Soc.* 1924, **46**, 1477; 1925, **47**, 260. Stieglitz had previously postulated salt-formation (ibid. 1914, **36**, 272).

[33] M. Kuhara, *On the Beckmann Rearrangement* (Imperial University of Kyoto, Tokio, 1926). Sluiter made a similar suggestion at an earlier date (*Rec. trav. chim.* 1905, **24**, 372), but without experimental justification.



$$\left[\begin{matrix}R\\R\end{matrix}\!\!>C{=}\overset{\oplus}{N}H\cdot OCOCH_3\right]\overset{\ominus}{Cl} \longrightarrow \left[\begin{matrix}R\\CH_3COO\end{matrix}\!\!>C{=}\overset{\oplus}{N}HR\right]\overset{\ominus}{Cl} \longrightarrow \begin{matrix}R\\O\end{matrix}\!\!>C{-}NHR+CH_3COCl.$$

The spontaneous transformation of the derivatives of oximes with strong acids has been confirmed by Chapman, in a study of oxime picryl ethers, $\begin{matrix}R\\R\end{matrix}\!\!>C{=}N\cdot OC_6H_2(NO_2)_3$. These rearrange on heating without the intervention of a catalyst, the change being unimolecular. There is no evidence of dissociation into ions, and Chapman, like Kuhara, concludes that the reagents which normally bring about the Beckmann Transformation give rise to such derivatives, which then undergo spontaneous intramolecular rearrangement.[34] The effect of hydrogen chloride was difficult to reconcile with this view, since Stieglitz and Peterson had found that the ester $CR_2{=}NCl$ does not rearrange,[35] and Chapman therefore carried out a thorough examination of the transformation of benzophenoneoxime,

$$(C_6H_5)_2C{=}N\cdot OH \longrightarrow C_6H_5\cdot CO\cdot NHC_6H_5,$$

in ethylene dichloride solutions of hydrogen chloride.[36] He found that an initial period of low velocity was followed by a rapid change at almost constant speed; autocatalysis was thus indicated. The presence of benzanilide (the reaction product) reduced the initial slow period, which was completely removed by the introduction of a very small quantity of the imidochloride of the anilide, $C_6H_5\cdot CCl{=}NC_6H_5$ (the chloride of the 'pseudo' form). The presence of hydrogen chloride was necessary, however, in addition to the imidochloride. Chapman's results will be best understood by reference to Fig. 9, which is reproduced from his paper. He concludes therefrom that the Beckmann Rearrangement of benzophenoneoxime in presence of hydrogen chloride involves the following series of changes: (*a*) production of a small quantity of benzanilide (slow change),

$$(C_6H_5)_2C{=}N\cdot OH \longrightarrow C_6H_5\cdot CO\cdot NHC_6H_5;$$

(*b*) reaction of benzanilide with hydrogen chloride to give the imidochloride,

$$C_6H_5\cdot CO\cdot NHC_6H_5+HCl \longrightarrow C_6H_5\cdot CCl{=}NC_6H_5+H_2O;$$

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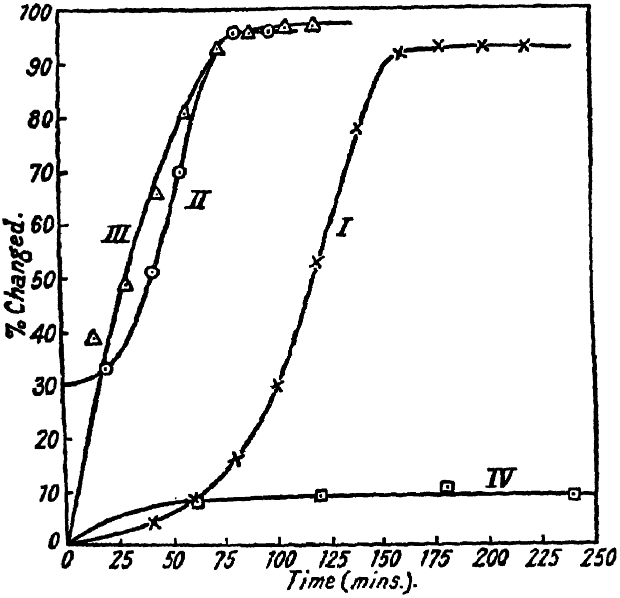
[34] *J.C.S.* 1933, 806; 1934, 1550; 1936, 448.

[35] *Ber.* 1910, **43**, 782.

[36] *J.C.S.* 1935, 1223.

(*c*) condensation of oxime and imidochloride,

$$(C_6H_5)_2C{=}N{\cdot}OH + C_6H_5{\cdot}CCl{=}NC_6H_5 \longrightarrow (C_6H_5)_2C{=}N{\cdot}OC(C_6H_5){=}NC_6H_5 + HCl;$$



I. 0·42 *Mol.* HCl: *starting from pure oxime.*
II. 0·42 *Mol.* HCl: *starting from* 30% *anilide,* 70% *oxime.*
III. 0·41 *Mol.* HCl + 0·002 *mol. benzanilideimidochloride.*
IV. 0·002 *Mol. benzanilideimidochloride.*

FIG. 9. Velocity of the Beckmann Transformation of benzophenoneoxime. Effect of hydrogen chloride as catalyst. (Reproduced from Chapman, *J.C.S.* 1935, 1224.)

(*d*) conversion of this oxime ether to cation,

$$(C_6H_5)_2C{=}N{\cdot}OC(C_6H_5){=}NC_6H_5 + H^{\oplus} \longrightarrow (C_6H_5)_2C{=}N{\cdot}OC(C_6H_5){=}\overset{\oplus}{N}HC_6H_5.$$

The positive charge on this cation will have the effect of rendering the ether group $—C(C_6H_5){=}\overset{\oplus}{N}HC_6H_5$ electron-attractive, like the anion of a strong acid. Chapman confirmed the above mechanism by the preparation and examination of the condensation product from benzophenoneoxime and benzanilideimidochloride; when treated with aqueous hydrogen chloride it was converted quantitatively to benzanilide, and it also catalysed the rearrangement of the oxime to the same extent as an equivalent quantity of benzanilideimidochloride. The rapid rearrangement brought about by hydrogen chloride is thus capable of interpretation as due to the spontaneous transformation of an oxime derivative which is of the same type as the derivatives formed with strong acids, and hence hydrogen chloride falls into line with the other reagents. There remains, of course, the slower change by which the first small quantity of anilide is formed, and Chapman ascribes this to a far less rapid rearrangement of the *salt*. Nevertheless, the transformation proceeds mainly through the intermediate formation of an ester-like compound which is capable of undergoing spontaneous rearrangement.

Chapman's work upon the Beckmann Transformation of oxime ethers has also provided important information concerning the effect of changes in the solvent and in the concentration and chemical character of the ether. His results are as follows:

(1) Solvents of high dipole moment increase the velocity. Thus, in different media, the speeds are in the order $CCl_4 < CHCl_3 < C_2H_4Cl_2$, while addition of other solvents to carbon tetrachloride increased the velocity in the order

$$C_6H_{14}\,(\mu = 0) < C_6H_5Cl\,(\mu = 1{\cdot}5) < C_2H_4Cl_2\,(\mu = 1{\cdot}8)$$
$$< CH_3{\cdot}CO{\cdot}CH_3\,(\mu = 2{\cdot}8) < CH_3{\cdot}NO_2\,(\mu = 3) < CH_3{\cdot}CN\,(\mu = 3{\cdot}2).$$

(2) Increase in the initial concentration of ether produces more than a proportionate increase in speed. The ether thus appears to act catalytically, and, since the unimolecular velocity coefficient remained constant throughout any one experiment, the same must apply to the product. This may be a medium effect similar in nature to (1).

(3) Electron-repulsive substituents in the R groups of $CR_2{=}NOX$ increase the speed of transformation, and vice versa; this is more pronounced when the substituent is in the migrating group than when it is in the other.

(4) Electron-attractive substituents in the group X increase the ease of rearrangement. Thus, while the 2:4-dinitrophenyl ether of benzophenoneoxime [$X = C_6H_3(NO_2)_2$] does not rearrange at 100°,

the picryl ether [$X = C_6H_2(NO_2)_3$] changes at temperatures as low as 40°.

These observations throw some light upon the actual mechanism by which the oxime derivative undergoes transformation. It has already been pointed out that there is no reason to suppose that the migrating groups are at any time free; the rearrangement is best regarded as *intra*molecular, in accordance with the views of Beckmann, Kuhara, and Chapman. Mechanisms dependent upon the withdrawal of water to give a cyclic[37] or a univalent nitrogen compound[38] are further inadmissible, since they are not applicable to the transformation of the aldoxime *N*-ethers[39] or to the Beckmann change in aqueous solutions, and suffer from various other disadvantages.[40]

A survey of the whole position indicates that the actual transformation may occur in an ester (or similar derivative), or in a salt of the oxime or of its ester. The rearrangement of esters is demonstrated by the work of Kuhara and Chapman. The observation, by the former, that the presence of hydrogen chloride is necessary for the transformation of an acetate, but not of a benzenesulphonate, indicates further that an oxime ester of a weak acid can rearrange only as salt. Chapman has shown, moreover, that the rearrangement when catalysed by hydrogen chloride does not proceed *entirely* through an ester-like intermediate, while salt-formation must occur when an oxime changes in an aqueous solution of hydrochloric acid, as observed by Lachman. Again, it is not easy to visualize the formation of esters by the *N*-ethers of aldoximes, and it is significant that the corresponding *C*-ethers, which have no basic characters, do not undergo rearrangement.[39]

It seems simplest to suppose[41] that the rearrangement is made possible by the tendency of the group OX to dissociate as anion (in esters of strong acids), *or* by the electron-attraction of a co-ordinated proton (in salts),[42] *or* by both (in salts of esters). In some cases all of

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[37] Wallach, *Annalen*, 1906, **346**, 272.

[38] Stieglitz, *Amer. Chem. J.* 1896, **18**, 751.

[39] Brady and Dunn, *J.C.S.* 1926, 2411.

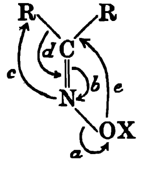
[40] For a critical survey of these theories, see ref. 26.

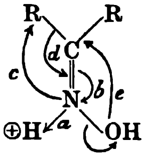
[41] This is probably an expression, in other terms, of previous views such as those of Bücherer, Biltz, Meisenheimer, and Ramart-Lucas (see ref. 26). Cf. also Chapman, *J.C.S.* 1936, 450.

[42] It seems unnecessary to assume that the proton is effective only when co-ordinated with oxygen of OH or OX (cf. Chapman, *J.C.S.* 1935, 1226).

these may contribute to the complete rearrangement. Electrons are thus drawn away from the nitrogen atom (process *a* below), and the electromeric change *b* thereby initiated. Clearly, the more powerful the electron attraction of OX and the greater the ionizing influence of the medium, the greater will be the tendency for process *b* to occur; it will also be facilitated by electron-repulsion in the R groups. All these deductions are in harmony with the facts. When change *b* has been initiated (but *not completed*, since the free rotation about the single bond so created would lead to an identical product from stereoisomeric oximes[43]), the molecule is in an activated state, and the actual rearrangement occurs as the result of several further processes which are probably simultaneous. R comes under the influence of the nitrogen atom (process *c*, where the arrow indicates the reaction of the nitrogen electrons with R, and not the movement of R), and begins to relinquish the electron pair linking it to carbon (process *d*), this being facilitated by electron-repulsive substituents in R; substituents in the migrating group therefore have a greater effect than similar substituents in the other group. At the same time, the hydroxyl or OX group comes under the influence of carbon (process *e*; this group moves with its electrons), and continues the process of breaking away from nitrogen. The completion of these various processes gives the rearrangement of I and II to III and IV; if X is the anion of a weak acid, the combination of both the processes marked *a* is necessary.

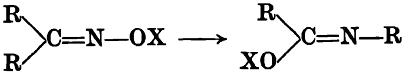
I.
(ester)





II.
(salt)

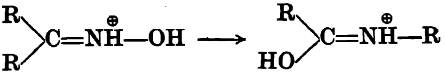
I.



$$\begin{matrix}R\\R\end{matrix}\!\!>\!C{=}N{-}OX \longrightarrow \begin{matrix}R\\XO\end{matrix}\!\!>\!C{=}N{-}R$$

III.

II.



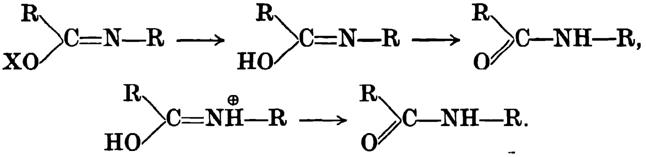
$$\begin{matrix}R\\R\end{matrix}\!\!>\!C{=}\overset{\oplus}{N}H{-}OH \longrightarrow \begin{matrix}R\\HO\end{matrix}\!\!>\!C{=}\overset{\oplus}{N}H{-}R$$

IV.

---

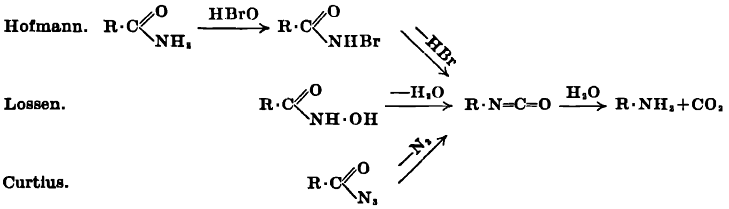
[43] Compare Montagne's criticism of Stieglitz's univalent nitrogen theory, *Ber.* 1910, 43, 2014.

Hydrolysis of III and loss of proton from IV give the amides which are the ultimate products:



The Hofmann, Lossen, and Curtius Degradations[44]

These processes lead to the production of amines from acid amides ($R \cdot CO \cdot NH_2$), hydroxamic acids ($R \cdot CO \cdot NHOH$), and acid azides ($R \cdot CO \cdot N_3$, acyl derivatives of hydrazoic acid) respectively. In each case an isocyanate has been shown to be an intermediate,[45] and the formation of this compound involves the migration of an alkyl group from carbon to nitrogen. The processes may be written as follows:



Resemblances between these processes and the Beckmann Transformation are obvious, and were pointed out by Stieglitz, who represented the rearrangements by his univalent nitrogen mechanism.[46] Unlike the Beckmann change, however, they proceed in *alkaline* media, and they probably depend upon the attack of the carbonyl group by hydroxyl ion (compare alkaline hydrolysis of esters, etc.).[47] When the molecule is in this way activated, processes similar to those designated *c* and *d* on the preceding page must occur; the group R comes under the influence of the unshared electron pair of the nitrogen (process *c*), and releases its covalency electrons to the control of carbon and nitrogen (process *d*). Simultaneously the

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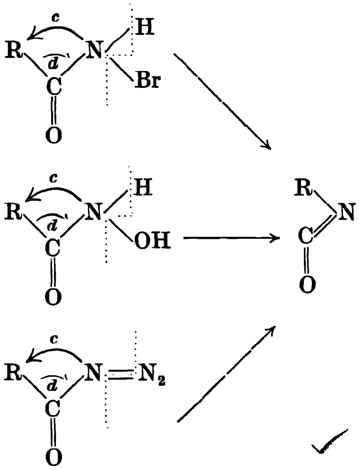
[44] Hofmann, *Ber.* 1882, **15**, 407; Lossen, *Annalen*, 1877, **186**, 1; Curtius, *J. pr. Chem.* 1901, **63**, 428.

[45] Hofmann, ref. 44; Tiemann, *Ber.* 1891, **24**, 4162; Mauguin, *Compt. rend.* 1909, **149**, 790; Schroeter, *Ber.* 1909, **42**, 2336, 3356; Forster, *J.C.S.* 1909, **95**, 433.

[46] *Amer. Chem. J.* 1896, **18**, 751; 1903, **29**, 49. Cf. Jones, ibid. 1912, **48**, 1.

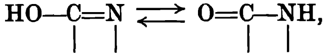
[47] Chap. VIII, p. 110.

ejection of halogen acid, water, or nitrogen takes place, as shown below (the dotted lines indicate the fate of the electron pair originally linking nitrogen to the group eliminated).



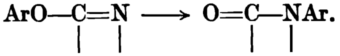
Rearrangements of Imino-ethers and Amidines

The imino-aryl ethers, $\mathrm{Ar\cdot C}\begin{smallmatrix}\nearrow \mathrm{NAr} \\ \searrow \mathrm{OAr}\end{smallmatrix}$, derivatives of the 'pseudo' forms of acid amides, are transformed at temperatures above 220° to isomeric derivatives of the 'normal' acid amides,[48] $\mathrm{Ar\cdot C}\begin{smallmatrix}\nearrow \mathrm{NAr_2} \\ \searrow \mathrm{O}\end{smallmatrix}$. Prototropic change in the amido-imidol system,



$$\mathrm{HO{-}\underset{|}{C}{=}\underset{|}{N}} \rightleftarrows \mathrm{O{=}\underset{|}{C}{-}\underset{|}{N}H},$$

has long been recognized (e.g. in simple acid amides, uric acid, cyanic acid),[49] and the rearrangement of the imino-aryl ethers involves the migration of an aryl group in the same system,



$$\mathrm{ArO{-}\underset{|}{C}{=}\underset{|}{N}} \longrightarrow \mathrm{O{=}\underset{|}{C}{-}\underset{|}{N}Ar}.$$

A similar rearrangement occurs in the amidine system,

$\mathrm{Ar\underset{|}{N}{-}\underset{|}{C}{=}\underset{|}{N}} \rightleftarrows \mathrm{\underset{|}{N}{=}\underset{|}{C}{-}\underset{|}{N}Ar}$ (compare $\mathrm{\underset{|}{N}H{-}\underset{|}{C}{=}\underset{|}{N}} \rightleftarrows \mathrm{\underset{|}{N}{=}\underset{|}{C}{-}\underset{|}{N}H}$),[50]

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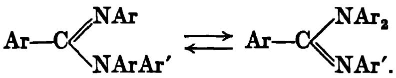
[48] Wheeler and Johnson, *Ber.* 1899, **32**, 35; Wislicenus and Goldschmidt, ibid. 1900, **33**, 1467.

[49] See Baker, *Tautomerism* (Routledge & Sons, 1934), pp. 136 ff.

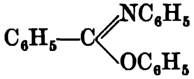
[50] Ibid., p. 140.

as in



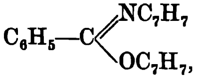
$$\mathrm{Ar{-}C({=}NAr)NArAr' \rightleftharpoons Ar{-}C(NAr_2){=}NAr'}.$$

These transformations have been studied by Chapman.[51] While the amidine rearrangement is reversible, the same equilibrium mixture being obtained by heating either isomeride at a temperature exceeding 300°, the imino-ether transformation goes to completion as far as can be ascertained; if it is reversible, the amount of imino-ether present at equilibrium is too small for detection. The corresponding imino-*thio*ethers, however, appear to rearrange reversibly.[52] The velocities of the transformations were measured by determination of the proportions of the isomerides, after heating for definite time intervals, by thermal analysis. The changes were shown to be unimolecular. Their *intra*molecular character was demonstrated by heating a mixture of two imino-ethers or amidines at the temperature at which rearrangement occurs. Under these conditions, the ethers



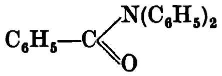
$$\mathrm{C_6H_5{-}C({=}NC_6H_5)OC_6H_5}$$

and



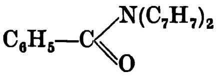
$$\mathrm{C_6H_5{-}C({=}NC_7H_7)OC_7H_7},$$

for example, gave the two products



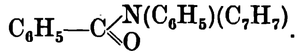
$$\mathrm{C_6H_5{-}C(N(C_6H_5)_2){=}O}$$

and



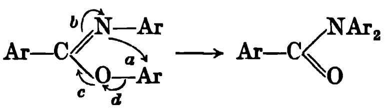
$$\mathrm{C_6H_5{-}C(N(C_7H_7)_2){=}O}$$

and no trace of the mixed product



$\mathrm{C_6H_5{-}C(N(C_6H_5)(C_7H_7)){=}O}$. There was no interchange of groups; the rearrangements of the ethers occurred independently, and hence the migrating group was not at any stage free, in contrast with prototropic changes in the same systems.

The transformations of both imino-ethers and amidines are facilitated by electron-attractive substituents in the migrating nucleus, and by electron-repulsive substituents in the other aryl groups. All these facts, together with the results of observations of the equilibrium positions for various amidines, are in harmony with a mechanism of the following type:[53]



$$\mathrm{Ar{-}C({=}N{-}Ar)O{-}Ar \longrightarrow Ar{-}C(NAr_2){=}O}$$

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[51] *J.C.S.* 1925, **127**, 1992; 1927, 1743; 1929, 2133; 1930, 2458, 2462.

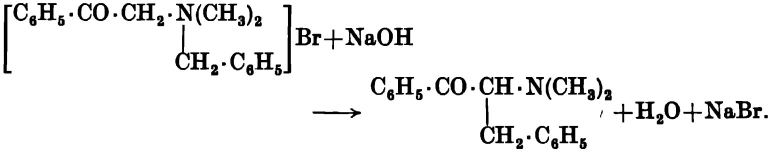
[52] Ibid. 1926, 2296.

[53] Bennett and Chapman, *Ann. Reports*, 1930, **27**, 121; Chapman and Perrott, *J.C.S.* 1930, 2465.

(in the amidine transformation, OAr is replaced by NArAr′). The change is probably initiated by the attraction of the mobile aryl group for the unshared electrons of the nitrogen (process *a*); the electronic displacements *b* and *c* are thereby set up, and finally the aryl group breaks away from the oxygen (process *d*) and processes *a*, *b*, and *c* become complete, giving the isomeric compound.

The Stevens Rearrangement of Quaternary Ammonium Salts[54]

In 1928 Stevens and his collaborators observed a transformation in which a benzyl group migrates from the nitrogen atom of a quaternary ammonium salt to the adjacent carbon atom. The process occurs in alkaline solution, being promoted by alkali hydroxides or alkoxides. The first example recorded was the following:



$$\left[C_6H_5\cdot CO\cdot CH_2\cdot \underset{\displaystyle CH_2\cdot C_6H_5}{\underset{|}{N}}(CH_3)_2\right]Br+NaOH \longrightarrow C_6H_5\cdot CO\cdot \underset{\displaystyle CH_2\cdot C_6H_5}{\underset{|}{C}}H\cdot N(CH_3)_2+H_2O+NaBr.$$

The rearrangement may be written in the generalized form

$$R\cdot CH_2\cdot \overset{\oplus}{N}R'(CH_3)_2 \longrightarrow R\cdot CHR'\cdot N(CH_3)_2,$$

and it has been observed in quaternary ammonium salts where R = acetyl, benzoyl, substituted benzoyl (electron-attractive substituents *decreasing* its speed), phenyl, or vinyl, and R′ = benzyl, substituted benzyl (electron-attractive substituents now *increasing* its speed), α-phenylethyl, benzhydryl, 9-fluorenyl or phenacyl. The dimethylammonium radical may also be replaced by piperidinium. The change appears to be unimolecular, and, since they failed to detect any exchange of groups between two different quaternary ammonium salts, the authors consider it to be *intra*molecular. The mechanism suggested is

$$R\cdot CH_2\cdot \overset{\oplus}{N}R'(CH_3)_2 \longrightarrow R\cdot \overset{\ominus}{C}H\cdot \overset{\oplus}{N}R'(CH_3)_2$$

$$\longrightarrow \left.\begin{array}{c} R\cdot CH{=}\overset{\oplus}{N}(CH_3)_2 \\ R'^{\ominus} \end{array}\right\} \longrightarrow R\cdot CHR'\cdot N(CH_3)_2,$$

where, however, the benzyl or other anion is never actually free. This scheme is in harmony with the observed effects of substituents.

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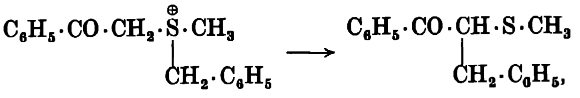
[54] Stevens *et al.*, *J.C.S.* 1928, 3193; 1930, 2107, 2119; 1932, 55, 1926, 1932.

The analogous reaction has been observed in a sulphonium compound,

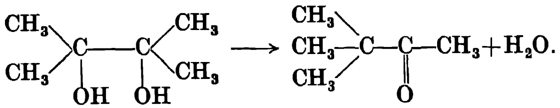


$$C_6H_5\cdot CO\cdot CH_2\cdot\underset{CH_2\cdot C_6H_5}{\overset{\oplus}{S}}\cdot CH_3 \longrightarrow C_6H_5\cdot CO\cdot\underset{CH_2\cdot C_6H_5}{CH}\cdot S\cdot CH_3,$$

but not in an oxonium compound.[55]

The Pinacon-Pinacolin and Allied Transformations

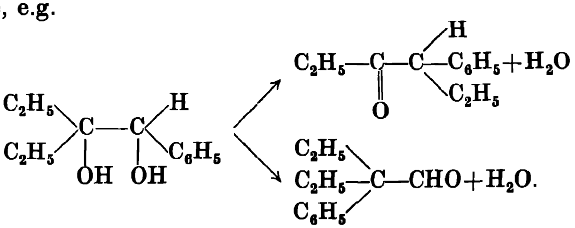
The conversion of tetramethylethylene glycol (pinacon) to methyl *tert*-butyl ketone (pinacolin), first observed by Fittig,[56] involves the loss of a molecule of water accompanied by the transference of a methyl group from one carbon atom to the next:



Other tertiary glycols behave similarly. In unsymmetrical compounds the nature of the product (or products) will depend upon the 'orientation' of the elimination of hydrogen and hydroxyl (governed by the relative capacities of the attached groups for electron-release), and also upon the ease with which the different groups can migrate from one carbon to the other.[57] Secondary glycols give aldehydes, as exemplified by the conversion of hydrobenzoin to diphenylacetaldehyde,

$$C_6H_5\cdot CH(OH)\cdot CH(OH)\cdot C_6H_5 \longrightarrow (C_6H_5)_2\cdot CH\cdot CHO+H_2O.$$

If one secondary and one tertiary alcoholic group is present, two types of rearrangement are possible, the semipinacolinic and semihydrobenzoinic changes, which lead respectively to a ketone and an aldehyde, e.g.



All these transformations occur in the presence of *acids*. A similar

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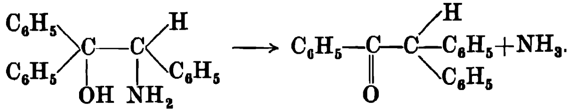
[55] Thomson and Stevens, *J.C.S.* 1932, 69.

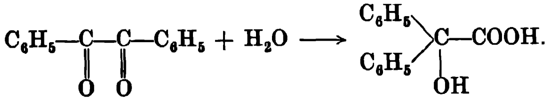
[56] *Annalen*, 1860, **114**, 56.

[57] Ingold, *Ann. Reports*, 1928, **25**, 133; Bennett and Chapman, ibid. 1930, **27**, 114; Kon, ibid. 1933, **30**, 181. See also Baker, *Tautomerism*, ch. xiv.

migration, with elimination of ammonia, takes place when αβ-amino-alcohols react with nitrous acid (pinacolic deamination),[58] e.g.

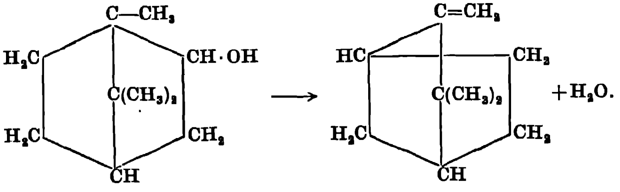


The transformation of benzil to benzilic acid is also comparable; this involves the *addition* of water, and requires the presence of *alkali*,

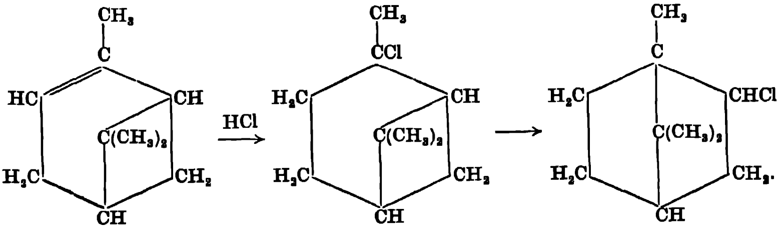


The first step here is probably the attack of hydroxyl ion upon carbonyl carbon,[59] whereas in the other instances the hydrogen ion attacks the hydroxyl or amino group.

The Wagner-Meerwein Rearrangement, which is familiar in terpene chemistry, and which may or may not involve the elimination of water or hydrogen chloride, is essentially a 'pinacolic' change. Well-known examples are the conversion of borneol to camphene (water removed), and of pinene hydrochloride, which is stable only below 0°, to bornyl chloride (no elimination).



(Borneol) (Camphene)



(Pinene) (Pinene hydrochloride) (Bornyl chloride)

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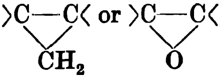
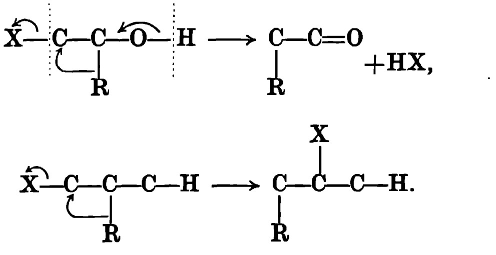
[58] McKenzie *et al.*, *J.C.S.* 1924, **125**, 2105, and later.

[59] Ingold and Shoppee, ibid. 1928, 371. Compare the Hofmann, Lossen, and Curtius Degradations (this chapter, p. 146), and the alkaline hydrolysis of esters (Chap. VIII, p. 110).

The fact that elimination of water or halogen acid does not occur in cases such as the latter is attributed by Ingold to the difficulty with which hydrogen ionizes from carbon, as contrasted with its ready ionization from oxygen.[60]

The earliest mechanisms suggested for the representation of these changes assumed elimination of water with the formation of a *cyclo*propane or ethylene oxide ring,  $>C-C<$ (CH_2) or $>C-C<$ (O), which then ruptured to give the product of the change.[61] Such a view is not supported by the experimental evidence, however, and, moreover, is not likely to be applicable to cases where there is no elimination.[62] Other suggestions have involved the operation of 'partial valencies',[63] the rearrangement of a molecule having free valencies,[64] or preliminary ionization followed by rearrangement of the cation.[65] The problem is one of great difficulty, and the clearest representation of the pinacon-pinacolin and allied rearrangements is that put forward by Ingold.[60] It is evident that, in order to preserve the octets of the atoms concerned, electronic transferences of the type indicated below must occur *simultaneously*. The first scheme represents the pinacon change (X = OH), where ionization of hydrogen is relatively easy, and elimination of water occurs; in the second, exemplified by the rearrangement of pinene hydrochloride to bornyl chloride (X = Cl), there is no elimination owing to the difficulty of the ionization of hydrogen.



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[60] Ref. 57.

[61] Erlenmeyer Sr., *Ber.* 1881, **14**, 322; Erlenmeyer Jr., *Annalen*, 1901, **316**, 84; Ruzicka and Liebl, *Helv. Chim. Act.* 1923, **6**, 267.

[62] For a critical discussion of these theories, see Henrich, *Theories of Organic Chemistry*, trans. by Johnson and Hahn (John Wiley & Sons, New York, 1922), p. 530. Also Ingold, *Ann. Reports*, 1924, **21**, 96.

[63] Robinson, *Mem. Manchester Phil. Soc.* 1920, **64**, No. 4.

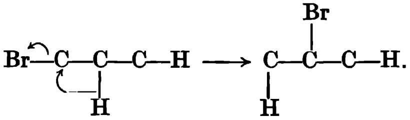
[64] Tiffeneau, *Compt. rend.* 1906, **143**, 684.

[65] Meerwein and Wortmann, *Annalen*, 1924, **435**, 190.

The well-known rearrangements of alkyl groups under the influence of aluminium chloride (e.g. *n*-propyl → *iso*propyl, *iso*butyl → *tert*-butyl), which frequently lead to difficulties in Friedel-Crafts preparations, may be represented by the latter scheme (R = H). Thus, the change of *n*-propyl bromide to *iso*propyl bromide,

$$\mathrm{Br{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3 \longrightarrow CH_3{\cdot}CHBr{\cdot}CH_3},$$

becomes



$$\mathrm{Br{-}C{-}\underset{H}{C}{-}C{-}H \longrightarrow \underset{H}{C}{-}\overset{Br}{C}{-}C{-}H.}$$

XI

THE FACTORS DETERMINING REACTION VELOCITY[1]

THE simplest possible view of the manner in which two substances A and B interact would be to suppose that a chemical change occurs every time a molecule of A comes into collision with a molecule of B, but such a conception is rendered untenable by the results of kinetic studies. Thus, the velocities of bimolecular reactions in the gaseous phase are smaller by many powers of ten than the number of collisions as calculated from the kinetic theory,[2] and this leads inevitably to the conclusion that the collisions which actually produce chemical change form only a very small proportion of the total number occurring. It would appear, therefore, that only those molecules which are in some exceptional state can enter into reaction, a view which receives confirmation from the fact that *unimolecular* reactions can proceed at measurable speeds. Again, the temperature coefficients of chemical reactions are of far greater magnitude than can be accounted for on the basis of the increased speeds of the molecules, and it may further be concluded, therefore, that the attainment of the exceptional state is strongly favoured by increasing temperature, the reactive molecules being those of high energy content.

This view was first expressed by Arrhenius in 1889.[3] He found that the variation of reaction velocity with temperature could be represented by an expression of the form $\log k = B-A/T$, where T is the absolute temperature and A and B are constants for the particular reaction under consideration. Writing $A = E/R$, where R is the gas constant, the equation becomes $\log k = B-E/RT$, or $d\log k/dT = E/RT^2$. This expression shows an obvious resemblance to the van't Hoff Isochore, which represents the effect of temperature upon the *equilibrium* constant of a balanced reaction, and Arrhenius postulated an equilibrium between 'active' and 'normal' molecules,

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[1] See Hinshelwood, *Kinetics of Chemical Change in Gaseous Systems* (Oxford University Press, 3rd edition, 1933).

[2] For example, the velocity of decomposition of hydrogen iodide, $2HI \rightarrow H_2+I_2$, is of the order 10^{17} mols. per litre per sec. (Bodenstein, *Z. physikal. Chem.* 1899, **29**, 295), while the number of collisions is of the order 10^{34}.

[3] *Z. physikal. Chem.* 1889, **4**, 226.

of which the former alone were capable of reaction. E is termed the 'critical increment of energy' or 'energy of activation', and is identified with the energy absorbed in the formation of an active molecule from a normal molecule; it can be determined experimentally from the slope of the straight line obtained by plotting $\log k$ against $1/T$.

A notable advance was made by W. C. McC. Lewis when, in 1918, he calculated the absolute velocities of some gaseous bimolecular reactions on the basis of the concept of activation.[4] The Arrhenius equation may be written in the form

$$k = \alpha e^{-E/RT}, \tag{1}$$

where the exponential term, according to the Maxwell-Boltzmann Distribution Law, gives the fraction of the molecules which have energy E in excess of the average energy of all the molecules. Lewis therefore assumed that

$$\text{no. of effective collisions} = (\text{total no. of collisions}) \times e^{-E/RT},$$

and proceeded to calculate the velocities of the decomposition of hydrogen iodide and the union of hydrogen and iodine; E was determined from the temperature coefficients found by Bodenstein, and the number of collisions from the formula based on the kinetic theory. The values so obtained were in very good agreement with the experimental results, and a similar agreement has been found in a considerable number of other instances. Indeed, for the majority of homogeneous[5] *gaseous* bimolecular reactions which have been investigated, the non-exponential term of the Arrhenius equation is given, to a high degree of approximation, by the collision frequency Z as calculated from the kinetic theory, i.e. $k = Ze^{-E/RT}$.

Of all the conditions upon which the occurrence of a chemical reaction may depend, therefore, the most important is the possession by the colliding molecules of a quantity of energy which is not less than the energy of activation for the particular process concerned; for gaseous bimolecular reactions, 'the general coherence of the results would seem to justify the statement that an activating collision is not merely a necessary but very often a sufficient condition for chemical transformation'.[6] For reactions which proceed with

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[4] *J.C.S.* 1918, **113**, 471.

[5] i.e. occurring uniformly throughout the gas, and not specifically at the walls of the containing vessel.

[6] Hinshelwood, *Kinetics*, p. 126.

measurable speeds at temperatures within the range of experiment, the value of E varies between 15,000 and 60,000 calories. Of recent years a number of homogeneous *unimolecular* gaseous reactions have been discovered, mainly by Hinshelwood and his collaborators; the conception of activation by collision is applicable here also, provided it be assumed that a period of time elapses between the collision and the moment of chemical transformation.[7]

The Inner Mechanism of a Chemical Change.[8] The energy of a molecule has a minimum value when the nuclei are at certain 'equilibrium' distances apart; when they vibrate, the distances are sometimes smaller and sometimes greater than this. A diatomic molecule provides the simplest case, of course. If, starting from their equilibrium positions, the nuclei of such a molecule approach each other, they will oppose a rapidly increasing force which resists compression, and the energy of the molecule rises; if, on the other hand, they move away from each other, work is done in separating them, and the energy again increases, at first rapidly and then more slowly as the forces between them become weaker. With increasing distance, therefore, the energy approaches a constant limiting value, at which complete dissociation occurs. These energy variations are shown in Fig. 10; O represents the equilibrium position, and the height d is a measure of the energy of dissociation of the molecule.[9] The values of the energies of activation of chemical reactions indicate, however, that they do not proceed by way of complete

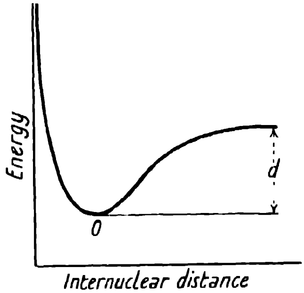

FIG. 10.

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[7] See Hinshelwood, *Kinetics*, chap. v. The reactions include the decomposition of nitrogen pentoxide, of acetone, of propionic aldehyde, and of certain ethers. The present view was first expressed by Lindemann, *Trans. Faraday Soc.* 1922, **17**, 598.

[8] See Polanyi, *Atomic Reactions* (Williams and Norgate, London, 1932), chap. i.

[9] The rupture of a linkage occurring as represented in Fig. 10 is termed an 'adiabatic' process, i.e. one in which no change in electronic energy occurs. If the compound is raised to a higher electronic level, its potential energy curve lies above that shown, the minimum energy point usually being to the right of O. Dissociation is frequently observed in electronic band spectra. The absorption of a light quantum of sufficiently high frequency raises the electronic level to a point at which the amplitude of vibration is great enough to cause dissociation, one of the atoms being in an electronically activated state; the spectrum now becomes continuous. See Hinshelwood, *Kinetics*, p. 139.

dissociation; thus, the energy of activation for the thermal decomposition of hydrogen iodide is 44,000 calories, whereas dissociation into hydrogen and iodine atoms would require about 70,000 calories.[10]

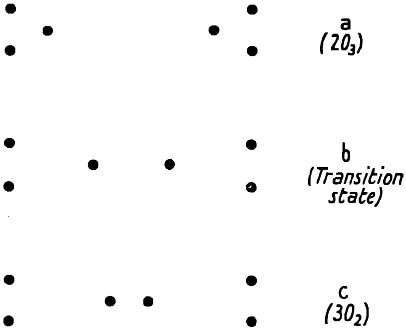

FIG. 11.

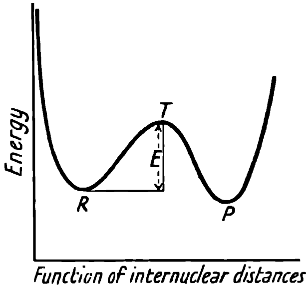

FIG. 12.

A very illuminating picture of the inner mechanism of chemical change has been given by Polanyi, taking the change $2O_3 \rightleftarrows 3O_2$ as an illustration.[11] Two ozone molecules may be represented as in Fig. 11 (*a*); there are bonds linking the nuclei of each molecule, and 'gaps' separating the molecules. In order to rearrange these two ozone molecules into three oxygen molecules, two bonds of each must be stretched, and ultimately be replaced by gaps, the final state being as in Fig. 11 (*c*). Half-way between (*a*) and (*c*) there must be a condition in which the differences between bonds and gaps disappear; this is represented by Fig. 11 (*b*) and is known as the 'transition state' (or 'critical complex'[12]). Since the stretching of the bonds involves the expenditure of work, the transition state is associated with a relatively high energy content. In passing from (*a*) to (*b*) the energy of the system rises, and when the products are formed from the transition state, i.e. as (*b*) passes into (*c*), it falls again. These energy changes are shown diagrammatically in Fig. 12. The minima (*R* and *P*) represent the normal or unexcited states of the reactants and the products respectively, and the crest of the curve (*T*)

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[10] The decomposition of hydrogen iodide by light, in common with many other photochemical processes, occurs by dissociation of a single molecule, HI → H+I. See Hinshelwood, *Kinetics*, p. 136.

[11] *J.C.S.* 1937, 629.

[12] Compare Brönsted, *Z. physikal. Chem.* 1922, **102**, 169.

represents the transition state. The reactants and the products are thus separated by an 'energy barrier' the height of which gives the energy of activation.

A simple substitution reaction, $XY+Z = XZ+Y$, may be visualized in a similar way.[13] Reference has already been made to

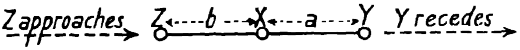

FIG. 13.

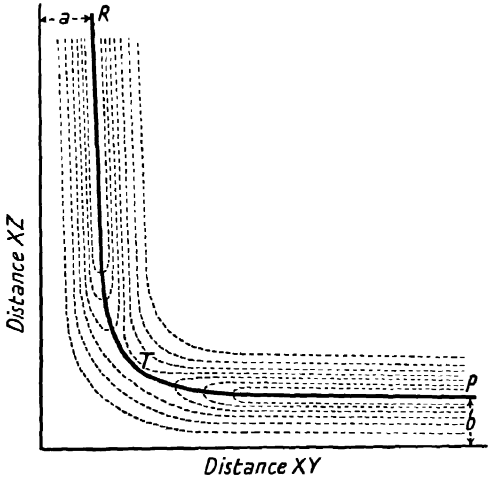

FIG. 14.

London's view, according to which the approach of Z and the removal of Y proceed simultaneously.[14] He has further shown that Z will approach along the line of the axis of XY, as illustrated in Fig. 13. Eyring and Polanyi adopt a three-dimensional representation, in which the co-ordinates are the energy of the system containing X, Y, and Z, and the internuclear distances XY and YZ. This is conveniently depicted on a 'contour diagram' constructed by drawing lines of constant energy upon the plot of XY against XZ, as shown in Fig. 14. The dotted lines are the 'energy contours', their altitude increasing in three directions from the minima at R and P. R therefore lies at the bottom of a 'valley', which is flanked on either

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[13] Eyring and Polanyi, *Z. physikal. Chem.* 1931, **12**, 279. Again the process is assumed to be 'adiabatic'.

[14] Chap. IV, p. 54.

side by 'energy hills' and which runs upwards to an 'energy pass' at T, while a similar 'valley' descends to P. When Z is at a great distance from XY, the nuclear separation of X and Y is represented by a, and the energy of the system has its minimum value. As Z approaches (i.e. XZ decreasing), the distance XY increases, slowly at first, and then more rapidly as shown by the line RT. At the same time the energy increases, and the system ascends the 'valley' RT to the 'pass' at T, where it is in its transition state. There is here no distinction between the relationship of X to Y and to Z. As Z approaches still nearer to X, however, Y continues to recede, and the system now descends the valley TP until, at P, XZ has the value b, the normal internuclear separation for the molecule XZ, and Y is outside the sphere of action. The pass at T represents the energy barrier between XY and XZ, and its height is a measure of the energy of activation for the process $XY+Z = XZ+Y$. A simple physical picture of chemical changes is provided when they are looked at from this point of view.

Reactions in Solution. The simple collision theory has proved highly successful when applied to gaseous reactions, but attempts to extend the same conceptions to reactions in the liquid phase or in solution are at once met with the difficulty arising from lack of knowledge of the conditions existing in the liquid state. No complete interpretation of the effect of the solvent upon reaction velocity has as yet been reached;[15] it is difficult, moreover, to estimate the extent to which the kinetic theory may be employed in solution, and further complications may arise owing to solvation phenomena, energy transfers due to collisions of solute with solvent molecules, ionization phenomena, and other causes.[16]

The earliest comparisons of experimentally determined velocities in solution with those calculated on the basis of the simple collision theory (by the method of Lewis) indicated a large divergence.[17] Nevertheless, a comprehensive survey of the available data by Moelwyn-Hughes revealed the fact that of 181 bimolecular reactions which had been studied in solution with reasonable accuracy, more

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[15] This is sometimes very great. Thus Menschutkin (*Z. physikal. Chem.* 1890, **6**, 41) found the combination of ethyl iodide with triethylamine to be nearly a thousand times as fast in benzyl alcohol as in hexane. Attempts to correlate such effects with physical properties of the solvent are summarized by Moelwyn-Hughes, ref. 18, p. 117.

[16] See Hinshelwood, *Kinetics*, p. 230.

[17] Christiansen, *Z. physikal. Chem.* 1924, **113**, 35; Norrish and Smith, *J.C.S.* 1928, 129.

than 40 per cent. had velocities of the same order of magnitude as those calculated.[18] Further, the decomposition of nitrogen pentoxide, the conversion of *d*-pinene to dipentene (unimolecular reactions), and the decomposition of chlorine monoxide (bimolecular) were found to have approximately the same rates and energies of activation in the gas phase and in certain solvents.[19] Since it was improbable that in a bimolecular process, such as the decomposition of chlorine monoxide, there could be an accurate neutralization of opposing factors which would leave both the velocity and the energy of activation unchanged, it was concluded that the collision frequency of molecules in dilute solution is not very different from that in a gas at the same concentration. A demonstration of the similarity of the two for certain diene syntheses (1:4-additions to conjugated olefinic systems) has recently been given by Wassermann.[20]

The velocity coefficient of a reaction may therefore be expressed, with a good degree of approximation, by the general formula

$$k = PZe^{-E/RT}, \qquad (2)$$

where E is the energy of activation, Z is the collision frequency, and P is a probability factor which expresses the proportion of the collisions between sufficiently energized molecules which actually lead to the formation of the products of reaction. For the majority of bimolecular reactions in the gaseous phase, P is not far from unity,[21] indicating that activation is not only a necessary but also a sufficient condition for reaction. The investigation of bimolecular reactions in solution, on the other hand, has given values of P which cover the whole range from unity to 10^{-8}.

An alternative treatment of reaction velocities approaches the problem from the standpoint of thermodynamics; this is the 'Transition State Method', employed by Polanyi, Eyring, and others.[22] The collision term PZ is here replaced by the thermodynamic probability of the transition state. Hinshelwood compares the two methods of approach in the following words:

'The transition state method and the kinetic method of treating reaction velocity problems are very much more similar than they might appear at

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[18] *Kinetics of Reactions in Solution* (Oxford University Press, 1933), chap. iv.

[19] Eyring and Daniels, *J. Amer. Chem. Soc.* 1930, **52**, 1472; Smith, ibid. 1927, **49**, 43; Moelwyn-Hughes and Hinshelwood, *Proc. Roy. Soc.* 1931, **131**, A, 177.

[20] *J.C.S.* 1936, 1028. The value of P for these reactions is about 10^{-6}.

[21] See p. 155.

[22] Eyring, *J. Chem. Physics*, 1935, **3**, 107; Evans and Polanyi, *Trans. Faraday Soc.* 1935, **31**, 875; Polanyi, ref. 11.

first sight. Neither can be said to stand in opposition to the other. The thermodynamic method frequently has the advantage of a greater formal elegance of its equations and a greater generality. On the other hand, this quality is accompanied by the corresponding defect that the magnitudes operated with are often quite inaccessible to experimental control, and further, that the plausibility of certain assumptions cast in a mathematical form is less easy to assess at its face value than it would be with the corresponding assumptions of the alternative method.'[23]

'It seems, then, that the collision theory is not really at a fundamental disadvantage, if, as a matter of taste, we prefer to approach the problem in that way.'[24]

The kinetic method has the definite advantage that it provides a simple physical picture of the reaction, and it is therefore adopted here.

Hinshelwood and Winkler enumerate a number of factors which may operate to reduce the probability factor P below unity, and also some factors which may tend to increase P.[25] For a reaction $A+B \rightarrow$ products, taking place in solution, the velocity may be less than that predicted by the kinetic theory for any or all of the following reasons:

(*a*) The colliding molecules must be so oriented that the reactive groups are brought within each other's sphere of influence.

(*b*) The bond to be broken must be sufficiently near the extreme of its amplitude of vibration for rupture to occur (that is, it must be sufficiently weakened).

(*c*) Access to the reactive centre may be impeded by the neighbouring groups, a collision being effective only when these groups are at that point of their oscillation which opens a sufficiently wide angle for the approach of the reagent.

(*d*) A favourable orientation of solvent molecules may be necessary. Thus if the colliding molecules, as a result of the fulfilment of the necessary energy, phase, and orientation conditions, have actually 'got to grips' and formed the transition complex, the intervention of the molecules of the solvent may be necessary for the consummation of the reaction.[26]

As an extension of (*d*), it seems reasonable to suggest that a somewhat similar condition must be fulfilled in catalysed reactions such

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[23] *J.C.S.* 1937, 635.

[24] Hinshelwood and Winkler, ref. 25, p. 373.

[25] *J.C.S.* 1936, 371.

[26] Perhaps to remove energy from the complex; Hinshelwood, *Trans. Faraday Soc.* 1936, **32**, 970.

as esterification and hydrolysis. These changes may be formulated in general

$$A+\text{Catalyst} \longrightarrow (A\cdot\text{Catalyst}) \xrightarrow{B} \text{Products}+\text{Catalyst},$$

as exemplified by an esterification reaction

$$\mathrm{R\cdot COOH+H^{\oplus} \longrightarrow (R\cdot COOH\cdot H^{\oplus}) \xrightarrow{R'OH} R\cdot COOR'+H_2O+H^{\oplus}}.$$

($A\cdot$Catalyst) here represents the energized complex. If at the instant of the formation of this complex a molecule of B is suitably placed, the reaction will proceed to completion; otherwise the system will revert to the original state ($A+$Catalyst), and a collision between reagent and catalyst, in spite of the fulfilment of all the conditions necessary for the production of the *complex*, will not result in the formation of the *products*.[27]

The unfavourable effect of these factors will, however, be lessened by some or all of the following:

(*a*) Simplicity of the reacting molecules.

(*b*) A lengthened duration of collision, the extreme case of which is the formation of a definite addition complex.

(*c*) Ionic charges on the reacting molecules; it is worthy of note that reactions which proceed at normal rates in solution ($P = 1$) usually involve an ion.

(*d*) Specific kinds of energy transfer, which will cause the substances to behave as simpler structures.

The combination of factors such as those listed above would account for values of P extending from unity to 10^{-8}.

The Influence of Substituents. Since the velocity of a chemical change can be represented by the formula $k = PZe^{-E/RT}$, and the collision frequency Z varies but little from one reaction to another (it is always about $2{\cdot}8\times10^{11}$), it is evident that the marked effects of constitutional changes such as the introduction of highly polar substituents may be due to differences in E, in P, or in both. For three reactions of nuclear-substituted benzene derivatives it has been shown that the influence of the substituents upon the velocity (groups in the *o*-position being excluded) is to be ascribed almost entirely to changes in the energy of activation. The examples for

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[27] Compare Evans, Morgan, and Watson, *J.C.S.* 1935, 1171. It seems not improbable that in all reactions catalysed by acids and bases the P factor depends very largely upon the fulfilment or otherwise of the conditions necessary for the transformation of the complex to the products. Cf. Chap. IX, p. 130.

which this has been demonstrated are (I) the chlorination of phenolic ethers,[28] (II) the benzoylation of anilines,[29] and (III) the alkaline hydrolysis of benzoic esters.[30]

From the equation $k = PZe^{-E/RT}$ it follows that

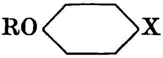
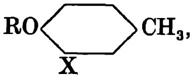
$$\log_e k = \log_e P + \log_e Z - E/RT,$$

or, since changes in Z may be ignored, $\log_e k = \text{const.} + \log_e P - E/RT$. For a definite value of P, therefore,

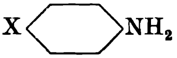
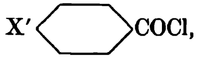
$$\log_e k = \text{const.} - E/RT \qquad (3)$$

and the plot of E against $\log_e k$ for any given temperature is a straight line having the slope $-RT$ (or $-2{\cdot}303RT$ if $\log_{10} k$ is plotted).[31] Figs. 15, 16, and 17 show this plot for the three reactions referred to above; in each case the energies of activation for a series of nuclear-substituted derivatives were determined from the temperature coefficients of the velocities, and in the figures these values are plotted against the logarithms of the velocity coefficients for one temperature. The straight lines have the theoretical slope $-2{\cdot}303RT$.

The reactions concerned are:

I. Chlorination of  and ,

where R = methyl, ethyl, *n*-propyl, *iso*propyl, or *n*-butyl
and X = NO_2, Cl, or Br.

II. Reaction of  with ,

where X and X′ = H, CH_3, Cl, or NO_2.

III. Alkaline hydrolysis of (*m* or *p*) $X{\cdot}C_6H_4{\cdot}COOC_2H_5$,
where X = H, NH_2, OCH_3, CH_3, Hal, or NO_2.

The order of magnitude of the factor P is 10^{-5} for reaction I, 10^{-7} for reaction II, and 10^{-2} for reaction III. The figures make it clear that in reaction I the points show a very definite tendency to fall around the theoretical line, while in reactions II and III this tendency is still more marked and all the points (excepting those for the *o*-substituted esters in Fig. 17) approximate very closely to the line.

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[28] Bradfield and B. Jones, *J.C.S.* 1928, 1006, 3073; Bradfield, W. O. Jones, and Spencer, ibid. 1931, 2907; Bradfield, *Chem. and Ind.* 1932, **51**, 254.

[29] Williams and Hinshelwood, *J.C.S.* 1934, 1079.

[30] Ingold and Nathan, ibid. 1936, 222. The *o*- and *m*-substituted esters have more recently been investigated by Evans, Gordon, and Watson (ibid. 1937, 1430).

[31] The value of P determines the *position* of the line; this is the principle adopted by Hinshelwood and Winkler (see ref. 25) in their diagram illustrating the distribution of P values over a range extending from unity to 10^{-8}.

It is clear, therefore, that the electronic displacements caused by substituents in the *m*- and *p*-positions have a very marked influence upon the energy of activation, but only a small effect (if any) upon the probability factor P. The approximate constancy of P is not observed, however, for substituents in the *o*-position.

The results of Bradfield and Jones have shown further that the groups contribute independently and additively to the energy of activation, which may therefore be represented as the sum of a series of terms,

$$E = E_0+e_1+e_2+\dots,$$

where E_0 is the value relating to the unsubstituted compound, and e_1, e_2, etc., are the contributions (which may be either positive or negative) due to the substituents.

It is probably safe to conclude that, for a given chemical process, the factor P retains a very nearly constant value when the reacting substances are *similarly constituted* compounds in which the variable group is *separated from the point of reaction* by a system (e.g. the benzene nucleus) which transmits the electronic displacements set up by the substituents. Under these conditions the effect of the substituent consists essentially in a change in the energy of activation. Even when the variable group is relatively *near* to the point of reaction (and local disturbances may contribute to the total effect), the changes in velocity are often to be ascribed very largely to changes in E. This has been shown in Hinshelwood and Legard's investigation of the kinetics of 15 esterification reactions involving six different acids (acetic, benzoic, *o*-nitrobenzoic, diphenylacetic, 2:4:6-trimethylbenzoic, and trichloroacetic) and four alcohols (methyl, benzyl, *iso*propyl, and *tert*-butyl), and in Winkler and Hinshelwood's study of twelve reactions of alkyl halides (methyl, ethyl, *n*-propyl, and *iso*propyl) with tertiary bases (trimethylamine, triethylamine, pyridine, and quinoline). The differences in velocity are still due to a great extent to changes in E, but the P factor also varies appreciably.[32] On the other hand, the retardation of the alkaline hydrolysis of benzoic esters by groups in the *o*-position is to be ascribed to a decrease of about a power of ten in P (see Fig. 17).[33]

Hughes, Ingold, and Shapiro have pointed out that caution should be exercised before significance is attached to *small* differences in the values of E and P, since the accuracy with which these quantities

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[32] *J.C.S.* 1935, 587, 1147.

[33] See further Chap. XII, p. 210.

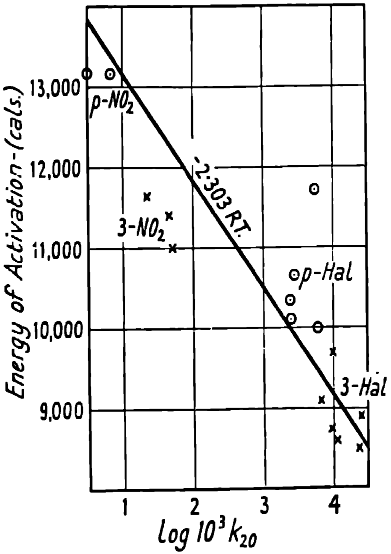
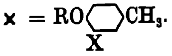


Fig. 15. Reaction I. Chlorination of phenolic ethers (Bradfield and Jones).

⊙ = RO⬡X.



× = RO⬡CH₃.
X

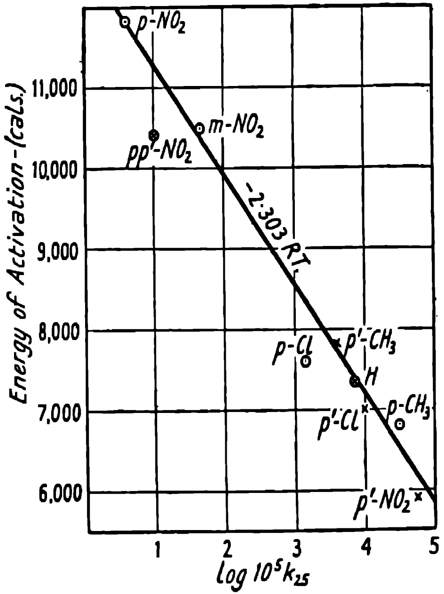


Fig. 16. Reaction II. Benzoylation of anilines (Williams and Hinshelwood).

⊙ = Substituent in amine.

× = Substituent in acid chloride.

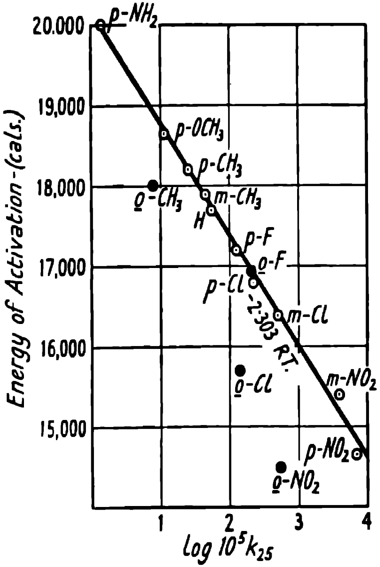


Fig. 17. Reaction III. Alkaline hydrolysis of substituted ethyl benzoates (Ingold and Nathan; Evans, Gordon, and Watson).

can be determined is subject to some uncertainty.[34] Thus, in certain reactions there are indications of an appreciable variation with temperature of both the E and P terms in the Arrhenius equation. La Mer and Miller find, for example, that in the dealdolization of diacetone alcohol E increases by nearly 1,400 calories when the temperature is raised from 5° to 32·5°, and then decreases by 500 calories on a further rise of temperature to 45°; P shows a parallel variation.[35] Similar phenomena have been observed in certain other reactions, although, as La Mer says, 'the temperature variation of E is frequently within the limits of experimental error'; it must be pointed out, indeed, that large variations may be due to some change in the mechanism of the reaction. The conclusion drawn by Ingold and his collaborators is that 'this does not mean that it is useless to examine the dependence of changes of rate with structure and solvent on changes in the Arrhenius parameters; but it does mean that the results should be interpreted with reserve unless the differences are large'. This condition is satisfied in the examples quoted above, where E varies over a range of several thousand calories.

Relationships between Energies of Activation and Dipole Moments. It appears from the foregoing that the changes in reactivity which result from the introduction of substituents into the nucleus of an aromatic compound (*ortho*-positions being excluded) are to be traced almost entirely to changes in the energy of activation. Since the influence of the substituents is of a polar character,[36] it is logical to seek for some quantitative relationship between the values of E for a given reaction (e.g. the hydrolysis of a series of benzoic esters, $X \cdot C_6H_4 \cdot COOC_2H_5$) and the dipole moments of the appropriate substituted benzenes ($X \cdot C_6H_5$). The existence of such a relationship is rendered the more probable by the fact, referred to in Chapter III, that a connexion has been traced between the logarithms of the dissociation constants of substituted carboxylic acids (the variations of which are a measure of changes in the free energy of ionization) and the dipole moments of the corresponding substituted methanes

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[34] *J.C.S.* 1936, 228. For this reason Ingold and Nathan (ref. 30) do not consider that any significance can be attached to the variations in P (from 0·15 to 0·3) found by Evans, Morgan, and Watson (*J.C.S.* 1935, 1167) in the bromination of a series of nuclear-substituted acetophenones, although these variations are capable of a simple interpretation.

[35] *J. Amer. Chem. Soc.* 1935, **57**, 2674. This is, of course, a case where the variations are unusually large.

[36] See Chap. V.

or benzenes. Thus, the dissociation constants of a series of acetic, benzoic, or phenylacetic acids can be represented by the formula $\log K = \log K_0 - C(\mu + a\mu^2)$, where K and K_0 refer to the substituted and unsubstituted acids respectively, C and a are constants, and μ is given its conventional sign. The saturated aliphatic acids conform to this equation accurately, and *m*-substituted aromatic acids in general depart from it but little; substituents in the *p*-position, however, lead to very considerable divergences owing to complicating factors. A similar relationship for *o*-substituted acids is not to be anticipated of course, for their dissociation constants are governed largely by factors which are quite distinct from the polar characters of the group.[33]

A connexion between dipole moments and energies of activation for the reactions of *m*-substituted aromatic compounds is therefore not unlikely; *p*-substituted compounds, however, would be expected to show divergence from such a relationship.[37] Unfortunately, suitable data for testing these expectations are scanty. A satisfactory examination of the position demands a knowledge of the energies of activation for a considerable number of reactions of whole series of nuclear-substituted benzene derivatives. While a large volume of work has been carried out upon the reaction velocities of aromatic compounds, the measurements have usually been restricted to one temperature, and energies of activation are therefore not known. If data of this type are to be used, it is necessary to assume that the substituents change only the energy of activation. Equation (3) (p. 163) is then applicable, viz. $\log k = \text{const.} - E/RT$; i.e. the variations in $\log k$ may be taken as a measure of the changes in E, and a connexion between $\log k$ and μ may be sought. As a rule, the assumption that E alone changes is probably not far from the truth when *m*- or *p*-substituted compounds are under consideration (see above), but there still remains the difficulty that, in most cases, insufficient members of a given series have been studied. For example, investigations have often been limited to *p*-substituted compounds.

The energies of activation for the acid-catalysed prototropy of a whole series of *m*-substituted acetophenones are given by the expression $E = E_0 - 429(\mu + 0{\cdot}125\mu^2)$, where E and E_0 refer to the substituted and unsubstituted compounds respectively, and divergences

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[37] Quantitative relationships between dipole moments and reaction velocities or dissociation constants of acids were first sought by Waters (*Phil. Mag.* 1929, **8**, 436).

for the *p*-compounds are found as in the case of benzoic acids;[38] owing to the relatively small differences in E, however, this system does not provide a good test case. A similar equation appears to be applicable to the benzoylation of anilines, but the known values here refer almost entirely to *p*-substituted compounds.[29] A fairly comprehensive set of data has now become available, however, for the alkaline hydrolysis of substituted ethyl benzoates.[30] It has been pointed out that in both these reactions the changes in velocity are due almost exclusively to changes in E. In Fig. 18 the energies of activation for the hydrolysis of a number of *m*- and *p*-substituted benzoic esters are plotted against the dipole moments of the appropriate substituted benzenes.[39] The curve is represented by the equation $E = E_0 + 1030(\mu + 0{\cdot}11\mu^2)$. The sign outside the bracket is here *positive* because the reaction is of Type B; electron-attractive substituents (for which μ is conventionally written with a negative sign) decrease the energy of activation for the attack of hydroxyl ion (a nucleophilic reagent). On the other hand, for the acid-catalysed prototropy of substituted acetophenones the sign outside the bracket

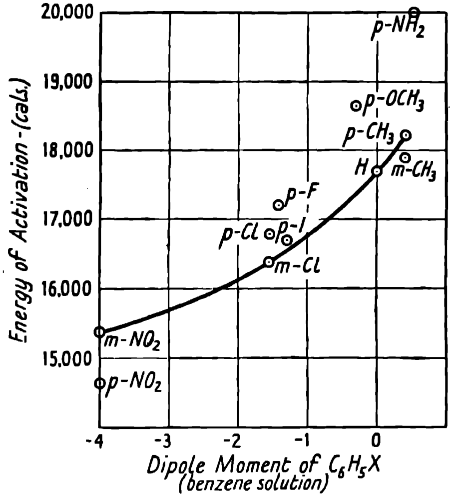

FIG. 18. Alkaline hydrolysis of benzoic esters $X \cdot C_6H_4 \cdot COOC_2H_5$. Relationship between energies of activation and dipole moments.

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[38] Evans, Morgan, and Watson, *J.C.S.* 1935, 1167, 1174.

[39] The 'effective moments' for $-OCH_3$ and $-NH_2$ are taken as $\mu \cos\theta$ (θ = valency angle of oxygen or nitrogen); see p. 43 (footnote).

is *negative* because this reaction is of Type A; the energy of activation for the attack of an acid catalyst (electrophilic reagent) is decreased by an electron-repulsive group (μ positive). An inspection of Fig. 18 makes it clear that the *m*-substituted esters in general conform with the relationship, while groups in the *p*-position show the usual divergence. In a number of cases where the available data refer to one temperature only, there is a similar relationship between μ and $-\log k$ (which is an approximate measure of E in the absence of variations in other factors).[40]

Although, therefore, further data are necessary in order to carry out a comprehensive test, it may be suggested with some degree of confidence that, in the absence of complicating factors, the influence of substituent groups upon energies of activation[41] may be represented by the general equation

$$E = E_0 \pm C(\mu + a\mu^2). \tag{4}$$

It is satisfactory, moreover, that the deviations from this relationship (and those from the analogous equation referring to the dissociation constants of acids) can be interpreted on the basis of the electronic theory which was considered in Chapter V. The difference between the dipole moment of an aromatic compound C_6H_5X and that of its aliphatic analogue may be regarded as a measure of the mesomeric effect of the group X in the former. Bennett and Glasstone's analysis of the moments of *p*-substituted anilines, phenols, and phenolic ethers has shown, however, that the magnitude of the mesomeric effect of a group is not constant in different systems;[42] for example, the mesomeric effect of $—OCH_3$ is no doubt greater in *p*-anisic acid than in anisole, and that of $—NO_2$ is greater in *p*-nitrobenzoic acid than in nitrobenzene. Further, time-variable (electromeric) effects may operate in *p*-substituted compounds. These additional factors account for the divergences found when groups such as NH_2, OCH_3, NO_2, or Halogen are present in the *p*-position. The mesomeric and electromeric effects cannot be transmitted from the *m*-position, however, and when two groups are placed *meta* with respect to each other it is not likely that either will modify appreciably the extent to which the other causes displace-

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[40] Nathan and Watson, *J.C.S.* 1933, 1248; *Nature*, 1934, **133**, 379. Evans, Morgan, and Watson, ref. 38.

[41] Compare Waters, *J.C.S.* 1933, 1551; *Nature*, 1934, **134**, 178.

[42] Chap. II, p. 31. Compare Chap. III, p. 43.

ments of the nuclear electrons.[43] Methyl stands apart from the other groups in that *p*-CH_3 usually conforms to the relationship more closely than *m*-CH_3 does. The moment of toluene, however, arises largely from electromeric displacements in the nucleus,[44] whereas those of nitrobenzene or chlorobenzene are due mainly to the intrinsic electron-attractive character of the substituent itself. A considerable proportion of the effect which is measured in the moment of toluene does not therefore operate from the *m*-position, and *m*-CH_3 behaves in accordance with a smaller moment, while *p*-CH_3 has the effect anticipated.

On the whole, the divergences from the quantitative relationships cannot be regarded as surprising. Reaction velocities may be influenced by a large number of factors, and the experimental observations show perhaps more regularities than might have been predicted from purely theoretical considerations.[45]

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[43] The 'mesomeric' effect of halogen differs from that of groups such as methoxyl (see Chap. V, p. 79), and it may perhaps be influenced by the change in the polarizability of the nucleus which results from the presence of a second group; this may account for some relatively small irregularities of *m*-halogen.

[44] See Chap. V, p. 73.

[45] Brief reference may be made to two other observed relationships: (1) Dippy (*Nature*, 1937, **139**, 591; cf. *J.C.S.* 1937, 1012) finds that, for *m*-substituted benzoic and phenylacetic acids, the plot of K against μ is linear. This is peculiar to these systems; it does not follow from the logarithmic relationship, but may be connected with the particular values of the coefficients C and a. (2) The plot of the values of $\log k$ against $\log K$ for the corresponding acids is sometimes approximately linear (Hammett, *J. Amer. Chem. Soc.* 1933, **55**, 4079; *Chem. Reviews*, 1935, **17**, 125; Burkhardt *et al.*, *J.C.S.* 1936, 20). This does not follow mathematically from the dipole moment relationships (see Dippy and Watson, *J.C.S.* 1936, 436), but is not unexpected for processes such as ester hydrolysis, where the influence of the substituent in the ester is likely to be consistently proportional to its influence in the acid.

XII

A REVIEW OF SOME STEREOCHEMICAL PROBLEMS

THE existence of two kinds of quartz crystals, which had opposite effects upon a beam of polarized light, was observed by Biot in 1815; the optical activity was dependent upon the arrangement of the *molecules* in the crystal, and was absent in other forms of silica. Some thirty to forty years later Pasteur discovered *l*-tartaric acid, which differed from the ordinary (*d*-) acid in crystalline form and gave, *when in solution*, an equal and opposite rotation of the plane of polarization. The optical isomerism was here to be ascribed to different spacial configurations of the *atoms* within the molecule, and Pasteur pointed out that the relationship of the *d*- and *l*-acids must be that of object to mirror-image, the optically inactive racemic acid being composed of equal proportions of the active isomerides. He also devised the three well-known methods for the resolution of racemic substances into their optically active forms. Somewhat later (1873) Wislicenus, on the basis of his researches on the lactic acids, also emphasized the necessity for postulating different arrangements of the atoms in space. Then in 1874 van't Hoff and Le Bel published their theories of stereoisomerism almost simultaneously. They pointed out that all organic compounds which were known to exhibit optical activity in the liquid state or in solution contained at least one carbon atom linked to four different atoms or groups, and they regarded this feature as being responsible for the dissymmetry of the molecule and hence for the existence of two forms which were non-superimposable and related to each other as object to mirror-image. Van't Hoff supposed the four groups to be situated at the angular points of a tetrahedron with the carbon atom at the centre; this explained the disappearance of the stereoisomerism when two of the groups became identical.

The van't Hoff - Le Bel theory being accepted, it was a simple matter to predict the number of isomerides which should be formed by a compound containing a given number of 'asymmetric' carbon atoms, and among the most brilliant applications of the theory was Fischer's determination (1894) of the configurations of the sugars, including the sixteen possible hexoses. The further discoveries of mutarotation and of the α- and β-methylglucosides have led to the modern ring formulae. The conception of the tetrahedral carbon atom was also adopted by Baeyer in his Strain Theory (1885) and by Wislicenus in his interpretation of the geometrical isomerism of olefinic compounds (1887).

A new stage was reached when, in 1899, Pope and Peachey discovered an instance of optical activity with nitrogen as the centre of asymmetry, and the classical methods of stereochemistry have led to the recognition of the tetrahedral configuration for a number of elements other than carbon. Such a disposition of valencies appears to be usual, though not invariable, for elements exhibiting a covalence of four or less, while the octahedral configuration first established by Werner in 1911 for certain cobalt complexes is universal, as far as is known, for six-covalent elements.

Perhaps the most striking advance of the present century, however, is the application of physical methods to the elucidation of stereochemical problems; like other branches of theoretical organic chemistry, stereochemistry has profited in no small degree from the development of these new methods of attack. Sir William Pope has described the position as follows:[1]

> 'Just as a fresh outburst of expansion followed on the van't Hoff-Le Bel theory of the asymmetric carbon atom in 1874 and a further era of progress commenced in the early 90's, so we are again witnessing the opening of a new epoch in the evolution of stereochemistry. The classical stereochemistry based on Pasteur's work will continue to expand, but it is becoming merged in a larger stereochemistry which embraces all chemical substances whether optically active or not. The rapid expansion of modern physics during recent years has provided novel and powerful methods for determining the arrangement of the atoms, and indeed of the components of the atoms, in solid, liquid, and even gaseous substances.'

Thus the tetrahedral configuration of the valencies of carbon was confirmed by one of the earliest triumphs of the Bragg X-ray method, viz. the elucidation of the structure of the diamond crystal, and numerous other results have subsequently been obtained by the same procedure. Dipole moments and band spectra have also played their part in the development of this branch of chemistry. Meanwhile, the classical methods have yielded valuable results, as instanced by the discovery of optical activity due to restricted rota-

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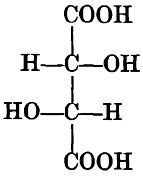
[1] 'Forty Years of Stereochemistry', Messel Memorial Lecture, *J. Soc. Chem. Ind.* 1932, **51**, 229 T.

tion, the preparation of optically active allene derivatives, and the resolution of numerous compounds having elements other than carbon as the centre of dissymmetry. Some of these advances will be considered in the sequel.

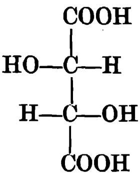
1. *Dissymmetry of Carbon Compounds*

Optical isomerism is possible only if the molecule is dissymmetric in such a way that it is not identical with its mirror-image. It need not, however, be completely devoid of geometrical symmetry; the necessary condition is fulfilled provided that it has no *plane* or *centre* of symmetry. The absence of an *axis* of symmetry is not necessary.[2] For example, *d*-, *l*-, and *meso*-tartaric acids may be represented by the following projection formulae:



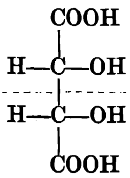
$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{COOH}\end{array}$$

(active)



$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{COOH}\end{array}$$

(active)



$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{COOH}\end{array}$$

(meso)

and it is evident that the inactive *meso* form has a plane of symmetry (indicated by the dotted line) whereas the active forms have not; they have an axis of symmetry, however.

The actual condition for optical activity is, therefore, the absence of certain elements of symmetry, and not the presence of an 'asymmetric' carbon atom; such an atom provides a special, though admittedly the most common, case of dissymmetry.[3] Van't Hoff actually predicted the possibility of optical activity in certain cases

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[2] Pope, loc. cit., p. 232 T. The terms here employed are defined most simply as follows. A *plane of symmetry* is an imaginary plane dividing the structure into two parts, one of which is the mirror-image of the other. A *centre of symmetry* is a point such that all lines drawn through it meet corresponding points of the structure at equal distances on either side. An *axis of symmetry* is an imaginary line such that, if the structure be rotated about it through 360°, it is coincident with itself at least twice.

[3] The discovery of the heavy isotope of hydrogen (deuterium, D) naturally led to speculations regarding the possibility of optical activity in compounds of the type CHDRR′. Several attempts to observe such activity were unsuccessful, until Clemo and McQuillen (*J.C.S.* 1936, 808) claimed the resolution of α-pentadeuterophenylbenzylamine, $C_6H_5 \cdot CH(C_6D_5)NH_2$. The hexadeuterobenzene from which this compound was prepared appears to have had a low freezing-point, however, and it cannot be concluded with certainty that the optical activity was due to the difference between hydrogen and deuterium (Turner, *Ann. Reports*, 1936, **33**, 228).

where there is no 'asymmetric' carbon atom as usually understood. The compounds to which he referred were allene derivatives having the general formula ${}^{a}_{b}\!>\!C{=}C{=}C\!<^{c}_{d}$. It is universally recognized that groups may rotate freely about a single bond but that such rotation is prevented by a double bond. The olefinic linkages in substituted allenes thus endow the molecule with a certain rigidity, and the tetrahedral disposition of the carbon valencies causes the groups attached to the terminal atoms to lie in different planes (see Fig. 19; this is best understood by the use of a model, however). If now these groups are all different, or even if only those linked to the same carbon are different as in ${}^{a}_{b}\!>\!C{=}C{=}C\!<^{a}_{b}$, the *molecule as a whole* is dissymmetric; it is non-superimposable upon its mirror image. Up to 1935 all attempts to demonstrate optical activity in allene derivatives were unsuccessful. Similar characters are possessed, however, by compounds in which either one or both double bonds are replaced by rings as in

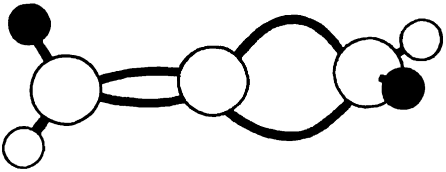
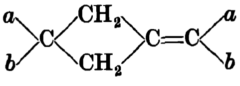
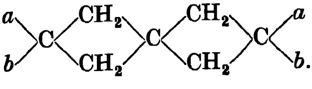


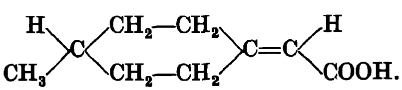
FIG. 19. Diagram of allene derivative: ${}^{a}_{b}\!>\!C{=}C{=}C\!<^{a}_{b}.$



or



An instance of optical activity in a compound of the former type was found when Perkin, Pope, and Wallach prepared and resolved 1-methyl*cyclo*hexylidene-4-acetic acid,[4]



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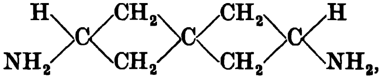
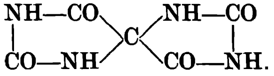
[4] *J.C.S.* 1909, **95**, 1789.

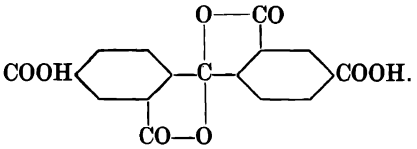
Cases of the latter type were provided later, as exemplified by Janson and Pope's resolution[5] of the diamine



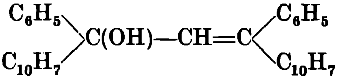
and a modification of this type of stereoisomerism was found when Pope and Whitworth resolved *spiro*-5:5-dihydantoin,[6]



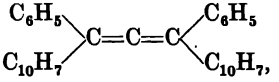
Another example of optical isomerism in the absence of an 'asymmetric' carbon atom had meanwhile been observed by Mills and Nodder[7] who resolved the compound



Then, in 1935, sixty years after van't Hoff's prediction of the dissymmetry of allene derivatives, the preparation of the optically active forms of one of these compounds was achieved by Maitland and Mills.[8] In the method which ultimately proved successful they employed 'asymmetric catalysis'. The alcohol



was prepared and dehydrated in benzene solution in presence of optically active camphorsulphonic acid; by using the *d*- and *l*-acids in turn the corresponding active forms of diphenyldinaphthylallene,



were obtained.[9] The correctness of van't Hoff's prediction was thus

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[5] *Chem. and Ind.* 1932, **51**, 316.

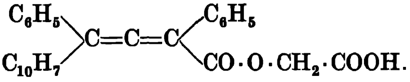
[6] *Proc. Roy. Soc.* 1931, **134** A, 357.

[7] *J.C.S.* 1921, **119**, 2094.

[8] *Nature*, 1935, **135**, 994; *J.C.S.* 1936, 987.

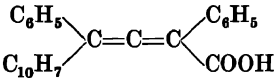
[9] Maitland and Mills suggest the intermediate formation of the alcohol camphorsulphonates. The alcohol (which contains an 'asymmetric' carbon atom) was a mixture of equal parts of *d*- and *l*-forms, and optically active compounds are known to react with such forms at unequal speeds.

demonstrated. Shortly after the announcement of Maitland and Mills's result, Kohler, Walker, and Tishler reported the resolution, by fractional crystallization of its brucine salts, of a similar compound,[10] viz.



$$\begin{array}{l}C_6H_5 \\ C_{10}H_7\end{array}\!\!>\!C{=}C{=}C\!<\!\!\begin{array}{l}C_6H_5 \\ CO\cdot O\cdot CH_2\cdot COOH.\end{array}$$

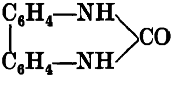
This is actually the carboxymethyl ester of the acid



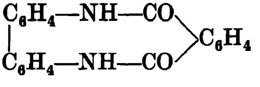
$$\begin{array}{l}C_6H_5 \\ C_{10}H_7\end{array}\!\!>\!C{=}C{=}C\!<\!\!\begin{array}{l}C_6H_5 \\ COOH\end{array}$$

which Lapworth and Wechsler had prepared in 1910, but failed to resolve.[11] The attack on one of the most interesting of the outstanding problems of classical stereochemistry has thus been brought to a successful conclusion.

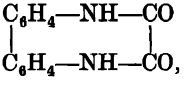
The optical activity of allene derivatives depends upon the dissymmetry of the molecule as a whole, and not upon the presence of an 'asymmetric' carbon atom; it is made possible by the lack of free rotation about the carbon to carbon double bonds. An analogous case is found in derivatives of diphenyl and certain other compounds, where the rotation about a *single* bond is restricted by the presence of substituents in suitable positions.[12] The reported existence of cyclic derivatives of benzidine (4:4′-diaminodiphenyl[13]), e.g.



$$\begin{array}{l}C_6H_4—NH \\ | \\ C_6H_4—NH\end{array}\!\!>\!CO$$



$$\begin{array}{l}C_6H_4—NH—CO \\ | \\ C_6H_4—NH—CO\end{array}\!\!>\!C_6H_4$$



$$\begin{array}{lr}C_6H_4—NH—CO \\ | \qquad\qquad\quad | \\ C_6H_4—NH—CO,\end{array}$$

had led Kaufler to the conclusion, in 1907, that the amino-groups must be closer together than would be the case if the usually accepted formula (I) for diphenyl were correct.[14] Accordingly, he suggested a folded structure (II) which was later found to provide a possible

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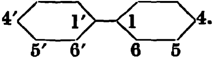
[10] *J. Amer. Chem. Soc.* 1935, **57**, 1743.

[11] *J.C.S.* 1910, **97**, 38.

[12] For an excellent summary and full bibliography see Adams and Yuan, *Chem. Reviews*, 1933, **12**, 261.

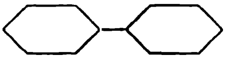
[13] The positions in diphenyl are numbered as follows:



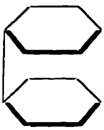
[14] *Annalen*, 1907, **351**, 151; *Ber.* 1907, **40**, 3250. In the above representation of the Kaufler structure the rings are perpendicular to the plane of the paper, and the thick lines indicate the near sides.

explanation of supposed cases of stereoisomerism among diphenyl derivatives.[15]

I

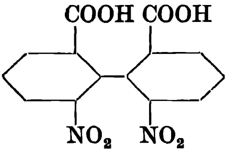


II

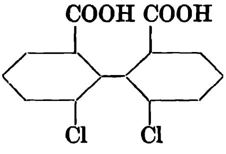


In 1926, however, a systematic re-examination of the subject, principally by Turner and his collaborators, led to the complete collapse of the evidence upon which the Kaufler formula was based.[16] Practically all the relevant experimental observations were proved to be erroneous; in no case were the amino-groups of benzidine combined in a ring, and the reputed stereoisomerides were structurally distinct (e.g. of the two supposed 3:3′-dinitrobenzidines one was actually the 2:3′-dinitro compound). Further, 4:4′-dinitro- and -dichloro-diphenyls were both shown to have zero dipole moment,[17] a result which was possible only if the two nuclei were coaxial. The original formula for diphenyl (I) was thus re-established.

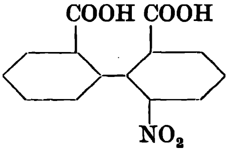
The Kaufler formula being discredited, it was now possible to give a rational interpretation to an observation which had been made originally by Christie and Kenner in 1922.[18] They had succeeded in resolving 6:6′-dinitrodiphenic acid (III) into optically active forms, and by 1926 the resolution of five other substituted diphenyls had been achieved, e.g. IV and V.



III



IV



V

In all these compounds at least three substituents were situated in *ortho*-positions with respect to the junction of the nuclei, and compounds with less than three substituents so placed resisted resolution. Since the nuclei are known to have a common axis, dis-

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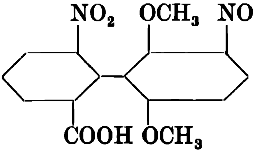
[15] Cain *et al.*, *J.C.S.* 1912, **101**, 2298, and later. Kenner and Stubbings, ibid. 1921, **119**, 593.

[16] Ibid. 1926, 2476, and other papers 1926–8; Christie and Kenner, ibid., 1926, 470, 671.

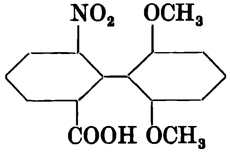
[17] Williams and Weissberger, *J. Amer. Chem. Soc.* 1928, **50**, 2332.

[18] *J.C.S.* 1922, **121**, 614.

symmetry is possible only if they lie in different planes; this was pointed out by Christie and Kenner.[18] Moreover, *both* rings must be substituted unsymmetrically, as demonstrated experimentally by Adams and his co-workers, who have found, for example, that while VI is resolvable VII is not.[19]

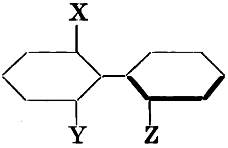


VI

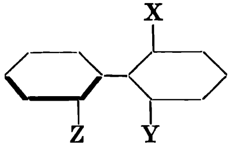


VII

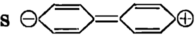
If these conditions are fulfilled, non-superimposable mirror-image forms such as VIII and IX (where the nucleus containing the substituent Z is not in the plane of the paper) can exist.



VIII



IX

If free rotation is possible about the bond joining the nuclei, however, the molecule will be able to take up a uniplanar configuration, and there will be no dissymmetry. According to the modern conception of resonance, the freedom of rotation of the nuclei is reduced both in diphenyl itself and in its derivatives by the participation in the resonance state of structures such as , for the central bond will have, to some extent, the characters of an olefinic linkage. This will tend, however, to hold the nuclei in one plane.[20] Clearly, dissymmetry will be made possible only by the operation of some factor which maintains a non-coplanar configuration. Such a factor was postulated in 1926 by Turner and Le Fèvre,[21] by Bell and Kenyon,[22] and by Mills.[23] Since optical activity had been observed only when at least three substituents were placed *ortho* to the junction of the nuclei, the dissymmetry was clearly connected with substituents in these positions; it is not to be expected, indeed, that groups otherwise placed could exert the necessary influence.

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[19] See ref. 12, p. 293.

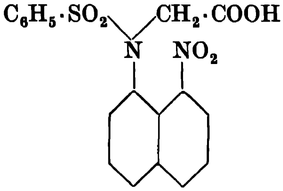
[20] Sutton, *Trans. Faraday Soc.* 1934, **30**, 791.

[21] *Chem. and Ind.* 1926, **45**, 831.

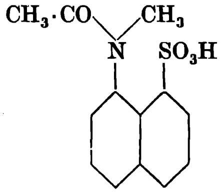
[22] Ibid., p. 864.

[23] Ibid., pp. 883, 905.

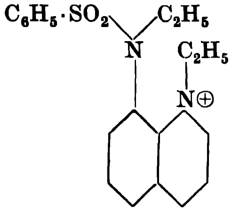
The stereoisomerism of diphenyls is therefore ascribed to the effect of *ortho*-substituents in preventing the nuclei from becoming coplanar; their rotation is restricted in such a way as to render this particular configuration impossible. In confirmation of this view Mills and his collaborators have observed similar phenomena in quite different systems;[24] they have resolved *peri*-naphthalene derivatives such as X and X *a*, the quinolinium ion XI, and finally the benzene derivative XI *a*.



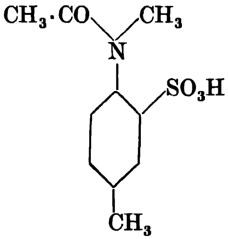
X



X *a*



XI



XI *a*

The un-nitrated analogue of X, the tertiary base corresponding to XI, and the acid having —COOH in place of —SO_3H in XI *a* are not resolvable, and the optical activity must depend upon the restriction of the rotation of the disubstituted amino-group —NRR′ about the bond linking it to the nucleus. Adams and his co-workers have also resolved certain suitably substituted heterocyclic nitrogen compounds.[25] The observations made in the diphenyl series are not, therefore, peculiar to this system, and hence require for their interpretation a theory, such as that outlined above, which is applicable in any system where the groups are suitably placed.

The manner in which groups give rise to this effect is not, as yet, perfectly clear, since their influence might arise from their polar

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[24] *J.C.S.* 1928, 1291; 1932, 2209; 1937, 274.

[25] See ref. 12, p. 317.

characters or from their volumes. Mills has suggested that a sufficient interpretation is provided by postulating mere mechanical obstruction, dependent solely upon the bulk of the groups, and models constructed to scale show that groups can interfere in this way and prevent the nuclei from becoming coplanar. This is obvious from Fig. 20 (reproduced from Mills's original contribution in *Chemistry and Industry*), which represents 6-chloro-diphenic acid; the carboxyl attached to the lower nucleus cannot pass either the chlorine (large shaded circle) or the carboxyl linked to the upper ring, and hence the nuclei can rotate only through a small arc *which does not include the uniplanar position*. Evidence obtained subsequently by Adams, Turner, and their collaborators is in harmony with this Obstacle Theory of Mills.[26] Thus, certain diphenyls having *four* substituents in *ortho*-positions are not resolvable, e.g. XII, XIII, and XIV.

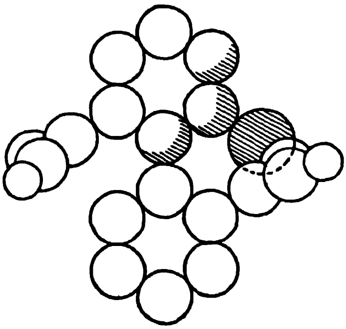
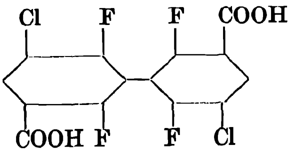
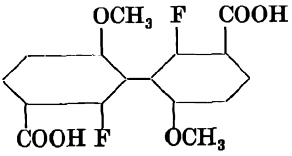


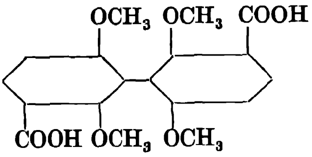
FIG. 20. 6-Chlorodiphenic acid. (Reproduced from Mills, *Chem. and Ind.* 1926, **45**, 883.)



XII



XIII



XIV

Apparently the fluorine and methoxyl substituents (both of which have small diameters) are not sufficiently large to interfere with the rotation of the nuclei. Then, there is a steady gradation in the ease with which substituted diphenyls pass into their inactive forms, and the observed sequence agrees quite well with the order of sizes of

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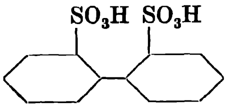
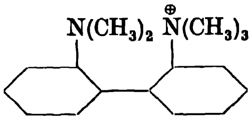
[26] See ref. 12, pp. 296 ff.

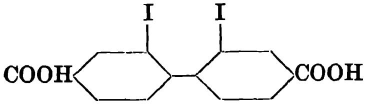
the groups; for example, when two *o*-substituents in one ring remain constant and one group is introduced into an *o*-position in the other ring, the order of effectiveness in stabilizing the active form is Br > CH_3 > Cl > NO_2 > COOH > OCH_3 > F. The effect of bulk is emphasized by the demonstration that, when the groups are sufficiently large to collide with the hydrogen of the other ring, *two* *o*-substituents can give rise to optical activity as in XV, XVI, XVII, and XVIII.



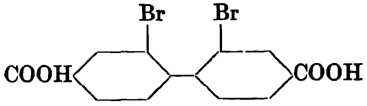
XV[27]



XVI[28]

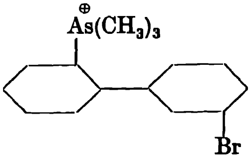


XVII[29]

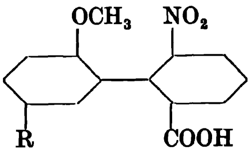


XVIII[30]

Finally, Lesslie and Turner have been able to realize optical activity in a diphenyl derivative containing only *one* *o*-substituent;[31] this was achieved by the preparation and resolution of the ion XIX. The $\overset{\oplus}{A}s(CH_3)_3$ group appears therefore to be sufficiently bulky to cause restriction of rotation when both *o*-positions of the other nucleus are occupied by hydrogen.



XIX



XX

Notwithstanding all this evidence of the importance of the sizes of the *o*-substituents, however, the stereoisomerism is influenced, to some extent at least, by other factors. Thus Yuan and Adams have observed a definite influence of groups in positions other than those *o*- to the junction of the nuclei; in a series of compounds of

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[27] Lesslie and Turner, *J.C.S.* 1932, 2394.

[28] Shaw and Turner, ibid. 1933, 135.

[29] Searle and Adams, *J. Amer. Chem. Soc.* 1933, **55**, 1649.

[30] Idem, ibid. 1934, **56**, 2112.

[31] *J.C.S.* 1933, 1588.

the general formula XX the stability of the active form was dependent upon the nature of R.[32] The position of R is also a factor determining the stability.[33] While, therefore, the experimental evidence leads to the conclusion that the *bulk* of the substituents in *o*-positions is mainly responsible for the optical activity of diphenyl derivatives, the intervention of other factors cannot be entirely neglected.

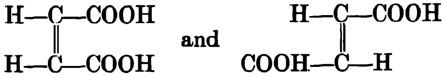
2. *The Configurations of Geometrical Isomerides*

As a result of the absence of free rotation about an olefinic linkage, the groups attached to a pair of doubly bound carbon atoms occupy fixed positions relatively to one another. The presence of four different groups does not lead to optical activity, however, and this is in harmony with van't Hoff's tetrahedral theory, according to which the groups lie in one plane and do not therefore give rise to molecular dissymmetry. But in cases where the groups attached to each carbon atom are different, *cis* and *trans* isomerides (geometrical isomerides) exist, having the relationship represented, in accordance with the views of Wislicenus (1887), as follows:

$$\begin{array}{ccc} a\text{—}C\text{—}b & \qquad & a\text{—}C\text{—}b \\ \| & & \| \\ a\text{—}C\text{—}b & & b\text{—}C\text{—}a \end{array}$$

cis *trans*

The most widely studied example is, of course, that of maleic and fumaric acids (hence the terms maleinoid and fumaroid). Their preparation from malic acid, and the products of reduction, oxidation, and addition indicate the same structural formula for each, viz. $\text{COOH—CH}{=}\text{CH—COOH}$. They are optically inactive, and they differ in solubility, melting-point, and other properties which are identical in *d* and *l* optical isomerides. Their formulae are written



$$\begin{array}{ccc} \text{H—C—COOH} & \qquad & \text{H—C—COOH} \\ \| & \text{and} & \| \\ \text{H—C—COOH} & & \text{COOH—C—H} \end{array}$$

Geometrical isomerism is also observed in a large number of cyclic compounds where the ring confers the necessary rigidity upon the molecule, e.g. the hexahydroterephthalic acids

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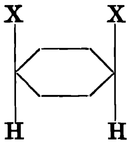
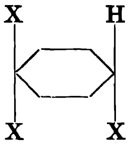
[32] *J. Amer. Chem. Soc.* 1932, **54**, 4434.

[33] Chien and Adams, ibid. 1934, **56**, 1787.

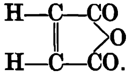


and

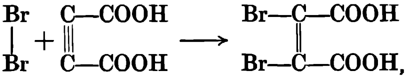


(the ring is here to be visualized as in a plane at right angles to the paper). Certain of these cyclic compounds are dissymmetric structures, and some have been resolved.

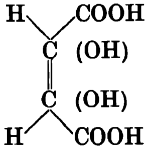
In the case of maleic and fumaric acids the former is given the *cis* configuration on account of its ability to form an anhydride

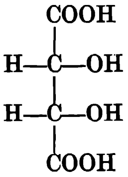


Wislicenus attempted to devise other methods for the determination of the configurations of geometrical isomerides. These were based upon the expectation of *cis* addition and elimination of groups, but Michael[34] has shown that they are of no value. Thus, acetylene dicarboxylic acid which, according to the views of Wislicenus, should add bromine to give dibromomaleic acid,



actually gives dibromofumaric in major quantity, and halogen acid is eliminated far more easily from chloro- and bromo-fumaric acids than from their *cis*-isomerides. The production of *meso*tartaric and racemic acids by oxidation of maleic and fumaric acids respectively is in harmony with the postulate of *cis*-addition, e.g.





but bromine gives the reverse (*trans*-addition). A survey of available data, indeed, leads to the conclusion that *trans* addition or elimination is the rule and not the exception.[35] The formation or fission of cyclic structures provides the only chemical method by which the

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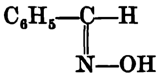
[34] *J. pr. Chem.* 1892, **46**, 210; 1895, **52**, 307.

[35] See Frankland, *J.C.S.* 1912, **101**, 673.

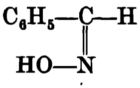
configurations of geometrical isomerides can be determined with any degree of certainty. In some cases information has been obtained by the application of physical methods. Thus for a *s*-dihalogenoethylene the *cis* form should have a considerable dipole moment while the *trans* form should be non-polar, and the experiments of Errera have actually given results in accordance with this view.[36] The distances between the chlorine atoms in *cis* and *trans* dichloroethylenes provide similar evidence.[37]

Comparable with the stereoisomerism of ethylene derivatives is that of compounds containing the C=N or N=N linking. The existence of isomerism among unsymmetrical oximes (e.g. three benzildioximes, two benzilmonoximes,[38] two oximes of benzaldehyde[39]) was given a satisfactory interpretation by Hantzsch and Werner, who supposed that the three valencies of nitrogen were not in the same plane, and that the compounds were geometrical isomerides,[40] e.g.



$$\begin{array}{l} C_6H_5\text{—}C\text{—}H \\ \qquad \| \\ \qquad N\text{—}OH \end{array}$$

syn



$$\begin{array}{r} C_6H_5\text{—}C\text{—}H \\ \| \quad\; \\ HO\text{—}N \quad\; \end{array}$$

anti

The isomerides differ in much the same way as do *cis* and *trans* ethylene derivatives, and only the stereochemical interpretation can account for the absence of isomerism in symmetrical oximes (CRR=NOH where R groups are identical) and for certain instances of optical activity which have been observed.[41] The same view is applicable to the isomerism of hydrazones and related compounds, and of the diazotates,[42] and although criticized adversely at times[43] it has received general acceptance.

Hantzsch's methods of determining the configurations of isomeric oximes resembled those which Wislicenus attempted to apply to the analogous olefinic compounds; they depended upon the assumption of *cis*-interaction.[44] In the case of the aldoximes *one* isomeride

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[36] *Compt. rend.* 1926, **182**, 1623.

[37] Debye, *Physikal. Z.* 1930, **31**, 419.

[38] V. Meyer and Auwers, *Ber.* 1888, **21**, 784, 3510; 1889, **22**, 705.

[39] Beckmann, ibid. 1889, **22**, 429, 1531.

[40] Ibid. 1890, **23**, 11. The earlier view of Meyer and Auwers, which postulated lack of rotation about a carbon to carbon single linkage, proved untenable.

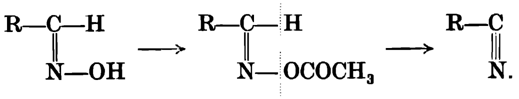
[41] Mills *et al.*, *J.C.S.* 1910, **97**, 1866; 1923, **123**, 312.

[42] Hantzsch, *Ber.* 1894, **27**, 1702. See Cain, *The Chemistry of the Diazo-compounds*, Second Edition (Edward Arnold and Co., 1920).

[43] e.g. Atack, *J.C.S.* 1921, **119**, 1175.

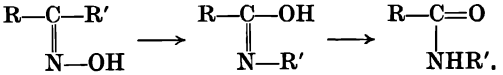
[44] *Ber.* 1891, **24**, 13.

readily gives a nitrile on acetylation and subsequent removal of acetic acid by alkali, and this was assumed to have the *syn* configuration (H and OH adjacent), i.e.



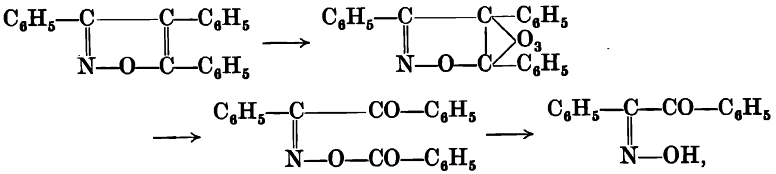
$$\begin{array}{l}R-C-H\\ \quad\;\|\\ \quad\;N-OH\end{array} \longrightarrow \begin{array}{l}R-C-H\\ \quad\;\|\\ \quad\;N-OCOCH_3\end{array} \longrightarrow \begin{array}{l}R-C\\ \quad\;|||\\ \quad\;N.\end{array}$$

The ketoximes were distinguished by the products of the Beckmann Transformation,[45] a *cis* interchange of groups being postulated, i.e.

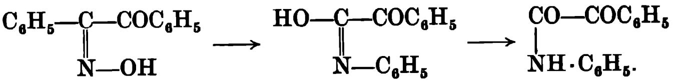


$$\begin{array}{l}R-C-R'\\ \quad\;\|\\ \quad\;N-OH\end{array} \longrightarrow \begin{array}{l}R-C-OH\\ \quad\;\|\\ \quad\;N-R'\end{array} \longrightarrow \begin{array}{l}R-C{=}O\\ \quad\;|\\ \quad\;NHR'.\end{array}$$

The theory of preferential *cis* interaction was rendered doubtful by the discovery of *trans* addition and elimination in olefinic compounds (see above), but nevertheless the configurations assigned by Hantzsch to the oximes were not seriously challenged for thirty years. Then, in 1921, Meisenheimer prepared and decomposed the ozonide of triphenylisoxazole and obtained the benzoyl derivative of a benzil monoxime which on hydrolysis yielded the oxime.[46] It was necessary to suppose that these changes occurred as follows:



and the configuration of the benzil monoxime was thus determined by a ring-fission method. The Beckmann Transformation of the same oxime, however, gave benzoylformanilide which could be produced only by a *trans*-interchange,



$$\begin{array}{l}C_6H_5-C-COC_6H_5\\ \qquad\quad\|\\ \qquad\quad N-OH\end{array} \longrightarrow \begin{array}{l}HO-C-COC_6H_5\\ \qquad\|\\ \qquad N-C_6H_5\end{array} \longrightarrow \begin{array}{l}CO-COC_6H_5\\ |\\ NH\cdot C_6H_5.\end{array}$$

Processes of ring formation led to a similar conclusion. For example, one of the isomeric 2-halogen-5-nitrobenzophenoneoximes, on treatment with alkali, readily eliminated halogen acid forming an

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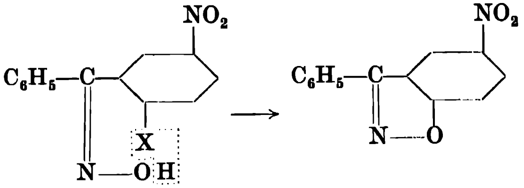
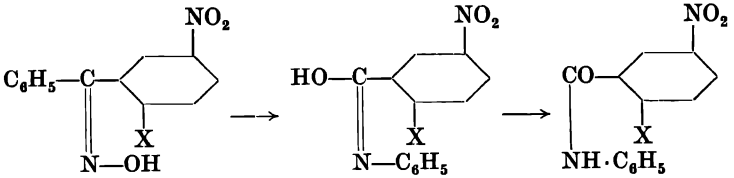
[45] See Chap. X, p. 139.

[46] *Ber*. 1921, **54**, 3206.

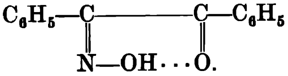
isoxazole ring; the proximity of the halogen-substituted nucleus to the hydroxyl group was thus indicated:



The Beckmann Transformation, however, gave the following:

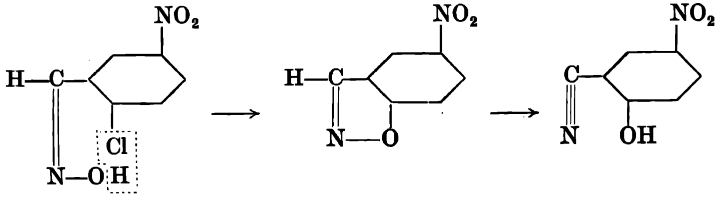


Trans-interchange had again occurred, and these and similar results provided a strong argument for the inversion of the Hantzsch configurations of ketoximes.[47] Moreover, Meisenheimer's revised configurations for the benzil monoximes were confirmed by their properties, which indicated a chelate ring[48] in the isomeride where the hydroxyl was nearer to carbonyl oxygen,[49] i.e.



$$\begin{array}{l} C_6H_5\text{—}C\text{————}C\text{—}C_6H_5 \\ \qquad\;\; \| \qquad\qquad\; \| \\ \qquad\;\; N\text{—}OH\cdots O. \end{array}$$

Meanwhile, the necessity for a similar inversion of aldoxime configurations was suggested by Beckmann[50] and by Auwers,[51] and rendered highly probable by the observations of Brady and Bishop.[52] These workers prepared two isomeric 2-chloro-5-nitrobenzaldoximes, and found that one of these gave ring closure with ease:



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[47] Meisenheimer *et al.*, *Ber.* 1924, **57**, 289; *Annalen*, 1926, **446**, 205.

[48] See p. 201.

[49] Taylor and Ewbank, *J.C.S.* 1926, 2818. On 'two-covalent' hydrogen see p. 202.

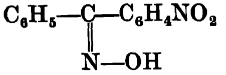
[50] *Ber.* 1923, **56**, 341.

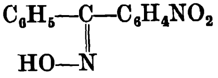
[51] Ibid. 1924, **57**, 446.

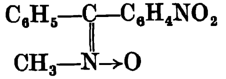
[52] *J.C.S.* 1925, **127**, 1357.

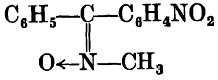
This was therefore the *anti*-aldoxime. It was, however, the isomeride which Hantzsch, on the basis of ready elimination of acetic acid from its acetyl derivative, would have designated the *syn* compound. The conclusion was therefore drawn that *trans* interaction occurs in the aldoximes, and that here also the formulae arrived at by the Hantzsch method must be inverted.[53]

Confirmation of this view has been obtained by Taylor and Sutton[54] from measurements of the dipole moments of oxime-ethers (the oximes themselves were unsuitable for examination owing to association). The two oximes of *p*-nitrobenzophenone having the formulae I and II give the *N*-ethers I*a* and II*a*.

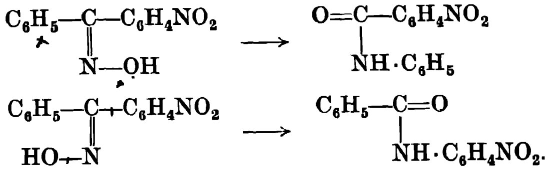
I

$$\begin{array}{c} C_6H_5-C-C_6H_4NO_2 \\ \| \\ \quad N-OH \end{array}$$

II

$$\begin{array}{c} C_6H_5-C-C_6H_4NO_2 \\ \| \\ HO-N \quad \end{array}$$

I*a*

$$\begin{array}{c} C_6H_5-C-C_6H_4NO_2 \\ \| \\ CH_3-N\rightarrow O \end{array}$$

II*a*

$$\begin{array}{c} C_6H_5-C-C_6H_4NO_2 \\ \| \\ O\leftarrow N-CH_3 \end{array}$$

Two dipolar groups, $\overset{\oplus}{N}\left\langle\begin{matrix}O\\O\end{matrix}\right\}^{\ominus}$ and $\overset{\oplus}{N}-\overset{\ominus}{O}$, are present in each, and these groups no doubt give rise to moments of about the same magnitude. In I*a* the moments will co-operate to give a large resultant value, while in II*a* they are in opposite directions and will oppose each other. The experimentally determined moments of the isomeric ethers were 6·60 and 1·09, and definite evidence of the structures of the ethers and hence of the corresponding oximes was thus found. The products of the Beckmann Transformation of the same oximes are as follows:


I.
$$\begin{array}{c} C_6H_5-C-C_6H_4NO_2 \\ \| \\ \quad N-OH \end{array} \longrightarrow \begin{array}{c} O=C-C_6H_4NO_2 \\ | \\ NH\cdot C_6H_5 \end{array}$$

II.
$$\begin{array}{c} C_6H_5-C-C_6H_4NO_2 \\ \| \\ HO-N \quad \end{array} \longrightarrow \begin{array}{c} C_6H_5-C=O \\ | \\ NH\cdot C_6H_4NO_2. \end{array}$$

Trans exchange of groups therefore occurs.

For aldoximes, where isomeric *N*-ethers have not been obtained, evidence was forthcoming from a comparison of the dipole moments of *O*-ethers with those of the corresponding ethers of ketoximes. The

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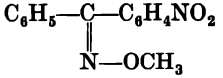
[53] See also Brady, ibid. 1931, 105.

[54] Ibid. 1931, 2190; 1933, 63.

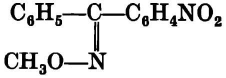
O-methyl ethers of *p*-nitrobenzophenoneoxime and their dipole moments are as follows (I *b* and II *b*):

I *b*



$$\begin{array}{c}\mathrm{C_6H_5\text{—}C\text{—}C_6H_4NO_2}\\ \|\\ \mathrm{N\text{—}OCH_3}\end{array}$$

$\mu = 3{\cdot}75$



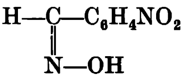
$$\begin{array}{c}\mathrm{C_6H_5\text{—}C\text{—}C_6H_4NO_2}\\ \|\\ \mathrm{CH_3O\text{—}N}\end{array}$$

II *b*

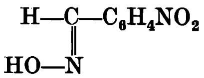
$\mu = 4{\cdot}25$

The corresponding *p*-nitrobenzaldoximes and their *O*-ethers are represented by the formulae III, IV, III *b*, and IV *b*:

III (*anti*)



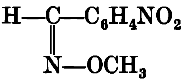
$$\begin{array}{c}\mathrm{H\text{—}C\text{—}C_6H_4NO_2}\\ \|\\ \mathrm{N\text{—}OH}\end{array}$$



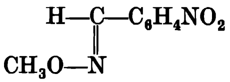
$$\begin{array}{c}\mathrm{H\text{—}C\text{—}C_6H_4NO_2}\\ \|\\ \mathrm{HO\text{—}N}\end{array}$$

IV (*syn*)

III *b*



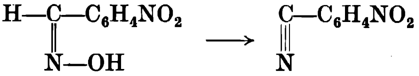
$$\begin{array}{c}\mathrm{H\text{—}C\text{—}C_6H_4NO_2}\\ \|\\ \mathrm{N\text{—}OCH_3}\end{array}$$



$$\begin{array}{c}\mathrm{H\text{—}C\text{—}C_6H_4NO_2}\\ \|\\ \mathrm{CH_3O\text{—}N}\end{array}$$

IV *b*

The dipole moments found for these ethers were 3·4 and 3·9 respectively, and by analogy with the ketoxime derivatives (I *b* and II *b*) the aldoxime giving the *O*-ether of larger moment was assigned the *syn* configuration IV. The isomeric (*anti*) aldoxime, however, is the one easily converted to a nitrile, and this reaction therefore occurs as follows:



$$\begin{array}{c}\mathrm{H\text{—}C\text{—}C_6H_4NO_2}\\ \|\\ \mathrm{N\text{—}OH}\end{array} \longrightarrow \begin{array}{c}\mathrm{C\text{—}C_6H_4NO_2}\\ \|\!|\\ \mathrm{N}\end{array}$$

Trans elimination was thus demonstrated again, and the evidence in favour of the inversion of the Hantzsch configurations, both for ketoximes and for aldoximes, seems to be overwhelming.

3. *Stereochemistry of Elements other than Carbon*[55]

The distinction between covalent and electrovalent linkages makes it clear that, while four groups in an ammonium salt are bound to nitrogen by directed valencies, the fifth occupies no fixed position; from the stereochemical point of view, therefore, only the four covalently bound groups enter into consideration. The tetrahedral disposition of these groups was suggested by van't Hoff, and as early as 1891 Le Bel claimed to have observed a feeble optical activity in a solution of methyl-ethyl-propyl-*iso*butyl-ammonium chloride which had been submitted to the action of penicillium glaucum (Pasteur's biochemical method of resolution). The definite resolution

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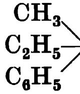
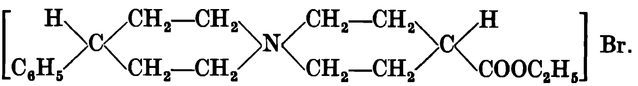
[55] See Sidgwick, *The Electronic Theory of Valency* (Oxford University Press, 1927), chap. xiii; *The Covalent Link in Chemistry* (Cornell University Press, 1933), chap. vi.

of an ammonium salt was first achieved in 1899 by Pope and Peachey who obtained the optical isomerides of a phenyl-benzyl-allyl-methyl-ammonium salt,[56] and a considerable number of similar resolutions were carried out subsequently by H. O. Jones, Wedekind, and others. These were followed by Meisenheimer's separation of methyl-ethyl-aniline oxide,  $\begin{matrix} CH_3 \\ C_2H_5 \\ C_6H_5 \end{matrix}\!\!> N \rightarrow O$, into its active components,[57] and the tetrahedral configuration of the valencies of four-covalent nitrogen was finally demonstrated by Mills and Warren,[58] who resolved a spirocyclic ammonium salt of the formula



Other configurations were definitely excluded by the dissymmetry of this compound. The resolution of compounds containing four-covalent phosphorus or arsenic (e.g. methyl-ethyl-phenyl-phosphine oxide) has also been accomplished.[59] If the valencies of nitrogen, phosphorus, and arsenic retain their relative positions in compounds where these elements are three-covalent, these should also have dissymmetric molecules when the three attached groups are different; no example of optical activity has been found, however. Nevertheless, the chemistry of the oximes indicates a non-coplanar configuration for the valencies of doubly-linked three-covalent nitrogen (see preceding section), and the dipole moment and infra-red spectrum of ammonia, and the moments of phosphine, arsine, and the trichlorides of phosphorus, arsenic, and antimony lead to the conclusion that the three hydrogens or chlorines occupy three angular points of a tetrahedron with the nitrogen or other atom at the apex. This conclusion is supported by the known facts regarding other elements in the three-covalent state (see below).

Of the elements of the carbon group, silicon and tin have both been shown to give rise to optical activity when linked to four different groups; some thirty years ago Kipping resolved certain silico-ethers and silicanes having an 'asymmetric' silicon atom,[60] while

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[56] *J.C.S.* 1899, **75**, 1127.

[57] *Ber.* 1908, **41**, 3966.

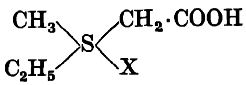
[58] *J.C.S.* 1925, **127**, 2507. Compare Mills *et al.*, ibid. 1927, 2613.

[59] Meisenheimer, and Lichtenstadt, *Ber.* 1911, **44**, 356; Mills and Raper, *J.C.S.* 1925, **127**, 2479.

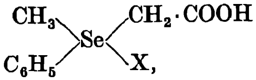
[60] *J.C.S.* 1907, **91**, 209, 717; 1908, **93**, 457.

Pope and Peachey had previously followed up their successful resolution of four-covalent nitrogen compounds by the observation of optical activity in methyl-ethyl-propyl-tin iodide.[61] The tetrahedral configuration of the valencies of the elements in this group has been confirmed by X-ray measurements on compounds such as the tetrahalides and tetraphenyls.[62]

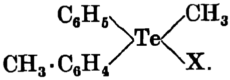
The tetrahedral disposition of the valencies of four-covalent oxygen was demonstrated by Bragg and Morgan;[63] an X-ray study of basic beryllium acetate, $Be_4O(O \cdot COCH_3)_6$, showed that the oxygen atom is situated at the centre of a tetrahedron with the beryllium atoms at the corners and the acetate groups spanning the edges. In *divalent* oxygen the valencies retain their directions to a greater or less extent, as shown by the 'triangular' configuration of water.[64] The stereochemistry of the remaining elements of the oxygen subgroup has been studied by classical methods. For example, Pope and his collaborators[65] have resolved compounds of the type



and



where X is the anion of a strong acid. A doubt existed in the case of tellurium, owing to the reported preparation of geometrical isomerides (which would indicate a uniplanar structure), but this element fell into line with the others when Drew proved that such geometrical isomerides did not exist,[66] and Lowry and Gilbert[67] were able to detect optical activity in a compound



An interesting feature of these observations was the fact that one of the four groups attached to the sulphur, selenium, or tellurium atom is ionizable, and the same remark probably applies to Pope and Peachey's trialkyl stannic iodide. All these compounds are actually of the type [Mabc]X; as in the case of trivalent nitrogen, therefore, it appears that *three* of the groups occupying the corners

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[61] *Proc. Chem. Soc.* 1900, **16**, 42, 116.

[62] e.g. Dickinson, *J. Amer. Chem. Soc.* 1923, **45**, 958; George, *Proc. Roy. Soc.* 1927, **113** A, 585.

[63] *Proc. Roy. Soc.* 1923, **104** A, 437.

[64] See p. 29.

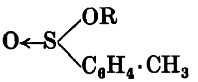
[65] Pope and Peachey, *J.C.S.* 1900, **77**, 1072; Pope and Neville, ibid., 1902, **81**, 1552. Compare Smiles, ibid. 1900, **77**, 1174.

[66] Ibid. 1929, 560.

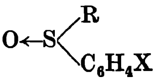
[67] Ibid., p. 2867.

of a tetrahedron remain in their positions in the absence of a fourth.[68] The most convincing demonstration of the correctness of this conclusion was provided by the resolution of sulphinic esters (I), sulphoxides (II), and a sulphonylimine (III) by Kenyon and Phillips:[69]

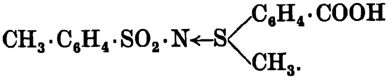
I



II

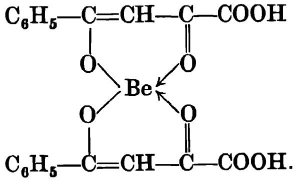


III



In addition to giving information regarding the arrangement of the groups around the central atom, this work also demonstrated the presence of a co-ordinate linkage, for dissymmetry would be impossible if the sulphur atom were doubly linked to oxygen or nitrogen.

Results obtained by the classical methods of stereochemistry also indicate a tetrahedral configuration of valencies for boron and beryllium; in both cases optical activity was detected in co-ordination compounds, such as the beryllium derivative of benzoylpyruvic acid:[70]



A similar result was claimed for the corresponding compounds of copper and zinc, but in the case of copper the correctness of the observation is now open to doubt (see later). The crystal structures of a number of ions have also indicated a tetrahedral disposition of the valencies of the central atom; for example, permanganates, perchlorates, pervanadates, and the ions $Zn(CN)_4''$, $Cu(CN)_4''$, and $Hg(CN)_4''$. We are thus led inevitably to the conclusion that a tetrahedral disposition of four covalencies is to be regarded as the rule (certain definite exceptions are dealt with below), and that the directions are maintained to a very large extent when less than four groups are linked to an atom which can be four-covalent. Two double bonds, or a triple and a single link, as in CO_2, CS_2, C_2H_2, and HCN, of necessity give a rectilinear molecule.

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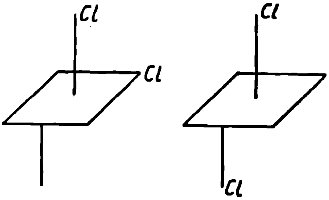
[68] On a case of optical activity possibly due to three-covalent carbon, see Sidgwick, *Covalent Link*, p. 216.

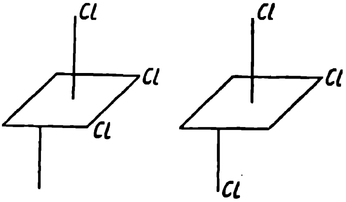
[69] *J.C.S.* 1925, **127**, 2552; 1926, 2079; 1927, 188.

[70] Mills and Gotts, ibid. 1926, 3121.

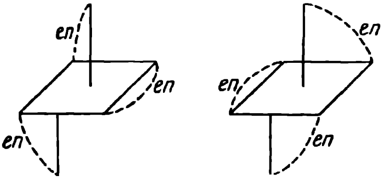
Six-Covalent Elements. The arrangement of six groups at the angular points of an octahedron was first demonstrated by Werner,[71] and no exception has been found; so far as we know, the valencies of a six-covalent element are always disposed octahedrally. Werner's conclusion was based on the preparation of geometrical isomerides of co-ordination compounds such as $[Cl_2Co(NH_3)_4]Cl$ and $[Cl_3Co(NH_3)_3]$, which could be represented



and



(NH_3 groups are here situated at the corners of the octahedron not occupied by chlorine atoms, and the metallic atom is at the centre of the solid figure). Elegant confirmation was obtained by the optical resolution of certain ethylenediamine complexes,[72] e.g. $[Co(NH_2 \cdot CH_2 \cdot CH_2 \cdot NH_2)_3]Cl_3$, where the mirror-images may be written



Subsequent work by Werner and others has led to the resolution of compounds with the following elements in the six-covalent state: chromium, iron, nickel, ruthenium, rhodium, iridium, platinum, arsenic, and aluminium.[73] Crystal structure determinations have confirmed the octahedral configuration in every case so far examined.

The available evidence, therefore, provides no exception to the generalization that *six* covalencies are directed from the centre of an octahedron to its angular points, while there are sufficient examples

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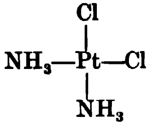
[71] *New Ideas on Inorganic Chemistry* (Longmans, 1911).

[72] *Ber.* 1911, **44**, 1887, and later. Ethylenediamine is a 'chelate' group, having a donor atom at each end; it therefore satisfies two valencies of the central atom. Dipyridyl, $NC_5H_4 \cdot C_5H_4N$, is similar.

[73] For references see Sidgwick, ref. 55. A supposed case of six-covalent copper has been disproved (*J.C.S.* 1934, 1783).

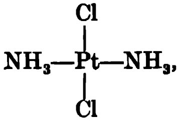
of the tetrahedral disposition of *four* covalencies to justify the conclusion that such a configuration is the most usual.

Planar Configuration of Four Covalencies.[74] As early as 1893 Werner suggested that the valencies of four-covalent platinum lie in one plane.[75] This view made it possible to explain the existence of isomeric ammines of the type $[Cl_2Pt(NH_3)_2]$, which he represented as *cis* and *trans* stereoisomerides,



$$\begin{array}{c} Cl \\ | \\ NH_3-Pt-Cl \\ | \\ NH_3 \end{array}$$

and



$$\begin{array}{c} Cl \\ | \\ NH_3-Pt-NH_3, \\ | \\ Cl \end{array}$$

where the four groups lie in one plane with the platinum atom. The earlier observations of supposed isomerides among derivatives of four-covalent palladium were disproved,[76] but there is now a considerable body of evidence which shows that four groups covalently linked to platinum, palladium, or nickel are frequently coplanar.

(i) The existence of geometrical isomerism has been demonstrated conclusively; examples are found in the isomeric nickel derivatives of methyl-benzyl, methyl-*n*-propyl, and methyl-*n*-butyl glyoximes,[77] and the diglycine derivatives of palladium and platinum,

$$Pd(NH_2 \cdot CH_2 \cdot COO)_2 \quad \text{and} \quad Pt(NH_2 \cdot CH_2 \cdot COO)_2.^{78}$$

(ii) Morgan and Burstall have isolated a red crystalline salt [Pt(trpy)Cl]Cl, where trpy = 2:2′:2″-tripyridyl, in which a tetrahedral structure is impossible,[79] and Mills and Quibell have observed optical activity in certain substituted derivatives of $[Pt(en)_2]Cl_2$ which could not be dissymmetric if the platinum valencies were disposed tetrahedrally.[80]

(iii) In 1931 the possibility of a planar configuration of covalencies in the transitional elements was deduced by Pauling from wave-mechanical considerations.[81] On the basis of the Heitler-London theory of valency, he finds that the *normal* arrangement of six covalencies is octahedral and that of four covalencies tetrahedral. In the latter case the electrons which form the covalent bonds are

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[74] For an excellent summary, see Wardlaw, *Ann. Reports*, 1933, **30**, 106; 1934, **31**, 116; 1935, **32**, 160; 1936, **33**, 157.

[75] Ref. 71. Compare Hantzsch, *Ber.* 1926, **59**, 2761.

[76] Drew, Wardlaw, *et al.*, *J.C.S.* 1932, 1895; 1933, 1294.

[77] Sugden, ibid. 1932, 246; 1935, 621.

[78] Wardlaw, Cox, *et al.*, ibid. 1934, 1012.

[79] Ibid. 1934, 1498.

[80] Ibid. 1935, 839.

[81] *J. Amer. Chem. Soc.* 1931, **53**, 1367.

usually those of the incomplete outermost group, and they belong only to the *s* and *p* sub-groups;[82] in the transitional elements, however, the electrons of the large group next to the outermost may take part in the process. These belong to the *s*, *p*, and *d* sub-groups, and Pauling arrives at the conclusion that a planar configuration is possible if *d* electrons take part in the formation of covalencies. Moreover, since the *d* electrons are mainly responsible for the paramagnetism of these atoms, this will be decreased if they are shared; hence the criterion of a planar configuration of valencies will be a reduced or zero paramagnetism in the resulting compound. Nickel, for example, which is paramagnetic in its simple salts, should become diamagnetic in its planar four-covalent compounds, and this is actually found to be the case; Sugden has shown that the nickel derivatives of dialkylglyoximes are diamagnetic.[77] The magnetic evidence relating to platinum and palladium is not so significant, for *all* compounds of these elements, both simple and complex, are diamagnetic. Diamagnetism does not persist throughout the compounds of four-covalent nickel, however; a number are paramagnetic, and if Pauling's argument be correct the valencies of four-covalent nickel are not always planar.

(iv) Definite evidence of the planar configuration of four-covalent nickel, palladium, and platinum has been obtained by X-ray measurements. In 1922 Dickinson examined potassium platino- and pallado-chlorides, K_2PtCl_4 and K_2PdCl_4, and concluded from his results that the four chlorine atoms are in one plane with the platinum or palladium atom, whereas analogous compounds of zinc, cadmium, and mercury [e.g. $K_2Zn(CN)_4$] show a tetrahedral arrangement.[83] Wardlaw, Cox, and their co-workers, in a series of X-ray investigations from 1932 onwards, have demonstrated a planar configuration in no less than fourteen derivatives of four-covalent platinum, palladium, and nickel,[84] viz. $[Pt(NH_3)_4]Cl_2$, $[Pd(NH_3)_4]Cl_2$, Magnus's green salt $[Pt(NH_3)_4][PtCl_4]$, $[Pt(en)_2]Cl_2$, $[Pd(en)_2]Cl_2$, $Pt(Me_2S)_2Cl_2$, $Pd(Me_2S)_2Cl_2$, the diglycine derivatives of palladium and platinum, the nickel and palladium derivatives of salicylaldoxime (the nickel compound being diamagnetic), and the dithio-oxalates of all three elements. The results of a chemical and X-ray examination of

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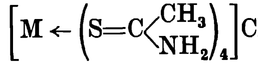
[82] These terms are explained on p. 13. Magnetic phenomena are considered briefly on p. 85.

[83] *J. Amer. Chem. Soc.* 1922, 44, 744, 2404.

[84] *J.C.S.* 1932, 1912, 2527; 1933, 1089; 1934, 182, 1012; 1935, 459, 1475.

$Pd(NH_3)_2Cl_2$ by Mann and his collaborators[85] are also in harmony with the same view. In nickel carbonyl and the quadrivalent platinum compound $Pt(CH_3)_3Cl$, however, the valencies of the metallic atom are arranged tetrahedrally.[86] It is evident that a planar configuration of valencies is frequent but not invariable in four-covalent nickel, palladium, and platinum.

Wardlaw, Cox, and their collaborators have recently shown by the X-ray method that four-covalent copper, silver, and gold (the neighbours in series of Ni, Pd, and Pt) also have their valencies disposed in one plane in certain of their compounds.[87] Such a configuration has been demonstrated for the *cupric* derivatives of salicylaldoxime and of certain β-diketones, for dipyridinocupric chloride $CuCl_2(py)_2$, for the cupric and argentic derivatives of picolinic acid, and for potassium auribromide. $CuCl_2 \cdot 2H_2O$ is also planar.[88] On the other hand, *cuprous* and *argentous* compounds are tetrahedral. This has been shown for potassium cuprocyanide and for certain derivatives of cuprous and argentous chlorides having the formula  $\left[\mathrm{M} \leftarrow \left(\mathrm{S{=}C}\!<\!\begin{matrix}\mathrm{CH_3}\\ \mathrm{NH_2}\end{matrix}\right)_4\right]\mathrm{Cl}$, while Mann and his co-workers[89] have also demonstrated a tetrahedral arrangement of the copper valencies in $[(C_2H_5)_3As{\rightarrow}CuI]_4$ and the corresponding phosphorus derivative, both of which have four-covalent *cuprous* copper. It is clear, therefore, that the valencies of copper, silver, and gold, like those of nickel, palladium, and platinum, may have either a planar or a tetrahedral disposition, and it would appear (as suggested by Wardlaw and Cox) that the 'principal valency' (in the Werner sense) of the metallic atom determines the arrangement in any particular compound. This view is confirmed by the recent observation[90] that the four covalencies of tin and lead have a planar distribution in the double halides M_2SnX_4 (co-ordination compounds of $SnCl_2$), potassium plumbo-oxalate, di-thiourea lead chloride, lead salicylate, and the lead derivative of benzoylacetone (in all of which lead has the 'principal' valency 2). This contrasts with the tetrahedral configuration in stannic compounds and in lead tetraphenyl.[91] It is evident that a planar disposition of four covalencies is not con-

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[85] Ibid. 1935, 1642.

[86] Brockway and Cross, *J. Chem. Physics*, 1935, **3**, 828; Cox and Webster, *Z. Krist.* 1935, **90**, 561.

[87] *J.C.S.* 1935, 731; 1936, 129, 775, 1635.

[88] Harker, *Z. Krist.* 1936, **93**, 136.

[89] Ibid. 1936, 1503.

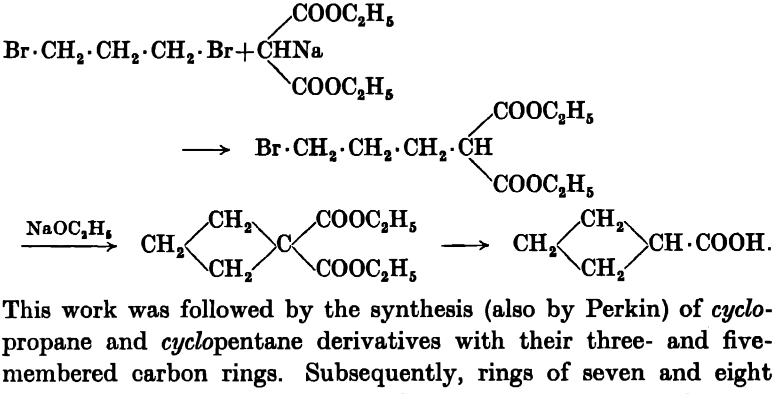
[90] Cox, Shorter, and Wardlaw, *Nature*, 1937, **139**, 71.

[91] See p. 190.

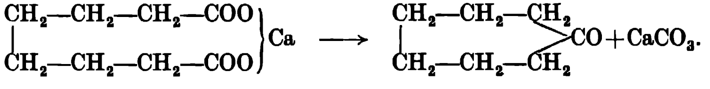
fined to elements standing in the middle of the long periods (transitional elements), and Pauling's deduction from wave-mechanics does not therefore provide a complete explanation.

4. *Formation and Stability of Rings*

An exceedingly clear and interesting account of the early investigations leading to the synthesis of carbon rings having less than six atoms is to be found in the late Professor W. H. Perkin's Pedler Lecture of 1929.[92] Prior to 1883 only the six-membered rings of benzene and *cyclo*hexane were known,[93] but in that year Perkin succeeded in preparing *cyclo*butane carboxylic acid (four-membered ring) by the following series of reactions:



This work was followed by the synthesis (also by Perkin) of *cyclo*propane and *cyclo*pentane derivatives with their three- and five-membered carbon rings. Subsequently, rings of seven and eight carbon atoms were obtained, as, for example, in the synthesis of *cyclo*heptanone or *cyclo*octanone by heating the calcium salts of the appropriate $\alpha\omega$-dicarboxylic acids, e.g.



From 1926 onwards Ruzicka and his collaborators have made a striking advance in the chemistry of carbocyclic compounds by the preparation of ketones and hydrocarbons having rings of carbon atoms up to 34 in number.[94] Finding that a 25 per cent. yield of

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[92] *J.C.S.* 1929, 1347.

[93] Impure specimens of *cyclo*propane and of *cyclo*butane-1 : 3-dicarboxylic acid had actually been prepared, but not recognized, some one or two years earlier; see ref. 92.

[94] For summaries of this work and full references to original papers see *Ann. Reports*, 1926, **23**, 112; 1928, **25**, 111; 1930, **27**, 151; 1934, **31**, 146. Also Ruzicka, *Chem. and Ind.* 1935, **54**, 2,

*cyclo*octanone could be obtained by heating thorium azelate, whereas the calcium salt gave only 5 per cent., they heated the thorium and yttrium salts of the longer chain $\alpha\omega$-dicarboxylic acids, and thus succeeded in synthesizing ketones with rings containing from 9 to 34 carbon atoms, with the exception of those of 25, 27, 31, and 33 members. In most cases reduction by the Clemmensen method gave the corresponding *cyclo*paraffins. When once formed these rings were found to be exceedingly stable, and in fact rings of 15 and 17 carbon atoms are now known to occur naturally in the animal products muscone and civetone.

The Strain Theory. According to the famous Strain Theory of Baeyer, put forward in 1885 and based upon the van't Hoff tetrahedral model,[95] rings of five and six carbon atoms should be more stable than those having a larger or smaller number. If the valencies of carbon are directed towards the angular points of a *regular* tetrahedron, they will make angles of 109° 28′ with one another (the 'tetrahedral angle'), and Baeyer considered that any distortion of these directions owing to the inclusion of the atoms in a ring would lead to a condition of strain and therefore to decreased stability. This was regarded as being manifested both in the difficulty with which the ring was formed and in the ease with which it was ruptured. Since the distortion is least in five- and six-membered rings, these should constitute the most stable carbocyclic systems. The theory received strong confirmation when, only four months after its publication, Perkin reported the great stability of the *cyclo*pentane ring.[96] Since a large number of other atoms are now known to have tetrahedrally directed valencies, the extension of Baeyer's theory to include the ready formation of compounds such as succinic and glutaric anhydrides and the γ- and δ-lactones is obvious. The peculiar stability of the aromatic nucleus is, of course, ascribed to other causes.[97]

In actual fact van't Hoff did not postulate a *regular* tetrahedron except in cases where the four groups linked to the carbon atom are identical,[98] and the inequality of the valence angles in other compounds has been emphasized by Thorpe and Ingold in their 'Valency Deflexion Hypothesis'. Ingold[99] quotes various instances of the

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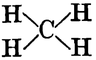
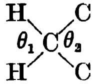
[95] *Ber.* 1885, **18**, 2278.

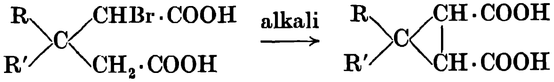
[96] Ibid., p. 3246.

[97] See Chap. V.

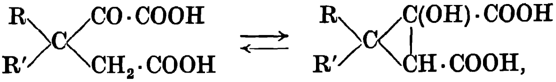
[98] The reader is referred to a passage quoted by Sidgwick in *The Covalent Link*, p. 201.

[99] *J.C.S.* 1921, **119**, 305.

inadequacy of the simple Baeyer theory to account for the relative stabilities of ring systems, e.g. the heats of formation of *cyclo*-paraffin derivatives which indicate a minimum of stability at *cyclo*-butane, the difficulty frequently experienced in the synthesis of the four-membered as compared with the three-membered carbon ring, and the retardation of the hydrolysis of glutaric anhydride by alkyl substituents. It is concluded that the Baeyer theory must be modified in accordance with the probability that the 'tetrahedral angle' of 109° 28′ is found only when the carbon atom is linked to groups of equal size. Thus in  the valence angles will be 109° 28′, but in  θ_1 will be less and θ_2 greater than this, on account of the larger volume of the carbon atoms than of the hydrogen atoms. Thorpe and Ingold do not claim that the chemical characters of a compound are related in any *quantitative* manner with the valence angles calculated on the basis of the molecular volumes of the attached groups; the hypothesis is essentially of a *qualitative nature*,[100] and as such is supported by a considerable number of experimental observations.[101] Thus in the substituted glutaric acid systems



and



when the groups R and R′ are varied, the facility of *cyclo*propane ring formation is in the order predicted by the hypothesis, e.g. $(C_2H_5)_2 > (CH_3)_2 > (CH_3)H > H_2$; the values of the primary and secondary dissociation constants of β-alkylglutaric acids are also in agreement.[102]

Similar variations in valency angles are indicated by dipole moments and other physical data. Thus the angle between the oxygen valencies in water, deduced from spectroscopic measure-

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[100] Ingold and Thorpe, *J.C.S.* 1928, 1318.

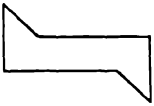
[101] Papers by Thorpe, Ingold, *et al.*, ibid. 1921 onwards.

[102] Spiers and Thorpe, ibid. 1925, **127**, 538.

ments, is about 105°, whereas the value is appreciably greater in dimethyl ether and greater still in diphenyl ether.[103] It is clear, moreover, that polar influences will operate in many cases as well as bulk effects,[104] and the Baeyer Theory of Strain must be regarded as no more than a rough approximation. It is nevertheless a useful guide provided that its limitations are recognized.

The Sachse-Mohr Theory of Strainless Rings. The stability of Ruzicka's large carbon rings is obviously incapable of interpretation on any hypothesis which regards the atoms as lying in one plane, an assumption which is made, of course, both in the original theory of Baeyer and in its modified form as elaborated by Thorpe and Ingold. As early as 1890, however, Sachse pointed out that in a ring of more than five atoms, where the strain is outward (i.e. the angles between the valencies are larger than the natural tetrahedral angle), a complete release of strain may be brought about by the buckling of the ends.[105] The smallest ring in which this can occur is that of *cyclo*hexane, where there are two possible strainless forms; these are generally referred to as the 'boat' and 'chair' structures, and they may be represented

and



Derivatives of *cyclo*hexane have not, however, been found to exhibit the isomerism which such a theory predicts. Moreover, the properties of glutaric acid derivatives in which two valencies of the β-carbon atom are enclosed in a *cyclo*hexane ring appear, for the most part, to be in harmony with the view that this ring is a plane hexagon with strain.[106] The apparently strained character of the *cyclo*hexane ring may be due to oscillation between the strainless (multiplanar) forms,[107] since there is definite evidence that, given conditions under which such oscillation is impossible, the isomerism

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[103] See Glasstone, *Ann. Reports*, 1935, **32**, 126.

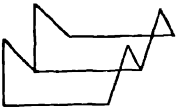
[104] Compare Gane and Ingold, *J.C.S.* 1929, 1691.

[105] *Ber.* 1890, **23**, 1363.

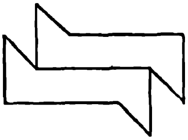
[106] Thorpe *et al.* The evidence is summarized in Professor Thorpe's Presidential Address to the Chemical Society, *J.C.S.* 1931, 1020. See also, however, Desai, ibid. 1932, 1047; Ives, Linstead, and Riley, ibid., p. 1093.

[107] Baker and Ingold, ibid. 1923, **123**, 122; 1925, **127**, 1678.

predicted by the Sachse theory does actually exist. As a deduction from this theory, Mohr pointed out that the fusion of two buckled *cyclo*hexane rings to give decahydronaphthalene could take place in two ways,[108] as follows:



and



Here again, therefore, two stereoisomerides are predicted, and in this case their isolation has been achieved. The first step was the preparation of two hexahydrohomophthalic anhydrides by Hückel, who followed up this success by isolating, from the two known decahydro-β-naphthols, two different ketones and two decahydronaphthalenes.[109] Other similar pairs of stereoisomerides are known, as, for example, the isomeric cholane derivatives dihydrocholesterol and coprosterol. Rao has shown further that the effect of the decahydronaphthalene system when linked to the β-carbon atom of glutaric acid indicates that it is strainless.[110] There is little doubt, therefore, that the *cyclo*hexane ring, when locked by the junction of another ring at *ortho*-positions, is multiplanar and strainless, and the application of the Sachse-Mohr theory accounts for the stability of the large carbon rings prepared by Ruzicka; the strain is released by their multiplanar configurations.

The ease with which these rings are formed is not dependent upon their stability ('strain factor') alone, however. In spite of their 'strainless' character they are synthesized with difficulty and in small yields, and Ruzicka ascribes this to a 'distance factor', i.e. the distance in the original straight chain compound between the atoms which are linked to form the ring. This is illustrated in Fig. 21, where *a* represents the distance factor which would result in a steadily decreasing yield as the number of carbon atoms increases, and *b* represents the strain factor which would lead to an increasing yield up to five atoms, and thereafter remain constant since the larger rings are strainless. The combination of *a* and *b* gives a curve

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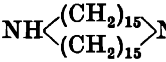
[108] *J. pr. Chem.* 1918, **98**, 315.
[109] See *Ann. Reports*, 1924, **21**, 92.
[110] *J.C.S.* 1930, 1162. Compare Kandiah, ibid. 1931, 922.

such as *c*, which indicates the relative yields actually obtained under similar conditions.

Large rings containing nitrogen or oxygen in addition to carbon have recently been prepared,[111] e.g.  $NH\left\langle\begin{matrix}(CH_2)_{15}\\(CH_2)_{15}\end{matrix}\right\rangle NH$, and no doubt their stability is due to a multiplanar configuration. The phthalocyanines, recently discovered by Linstead and his collaborators,[112] with rings of eight carbon and eight nitrogen atoms, resemble aromatic compounds, however. The sixteen-membered ring, containing six double bonds, is *uniplanar* as shown by X-ray examination. The porphyrins are similar, four nitrogens of the phthalocyanine ring being replaced by four carbon atoms. The stability of these rings must therefore be interpreted along the lines now accepted for aromatic compounds.

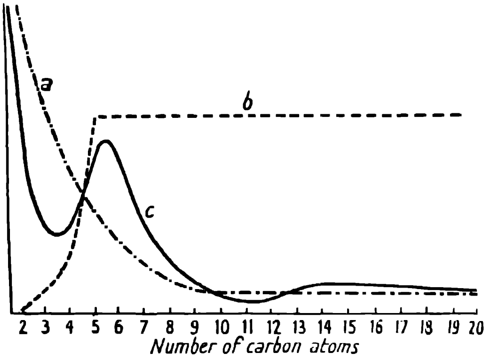
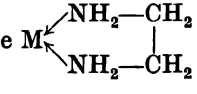


FIG. 21. Factors influencing ring-formation.
(Reproduced from Ruzicka, *Chem. and Ind.* 1935, **54**, 6.)

Chelate Rings.[113] The term 'chelate' (from the 'chela' or great claw of crustaceans) was introduced by Sir Gilbert Morgan to describe groups which can form two links with a metal in a co-ordination complex thus producing a ring.[114] Well-known examples are ethylenediamine which gives rings of the type  $M\left\langle\begin{matrix}NH_2-CH_2\\ \qquad\;\; |\\ NH_2-CH_2\end{matrix}\right.$ as

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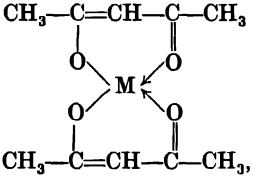
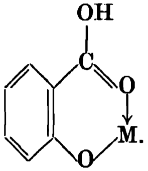
[111] See Drew, *Ann. Reports*, 1934, **31**, 146.
[112] *J.C.S.* 1934, 1016, and following papers; *Ann. Reports*, 1935, **32**, 359.
[113] See Sidgwick, *The Electronic Theory of Valency*, chap. xiv.
[114] *J.C.S.* 1920, **117**, 1457.

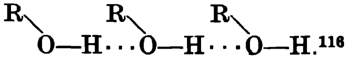
in $[\mathrm{Co(en)_3}]\mathrm{Cl_3}$, the acetylacetone radical in metallic derivatives such as



and the salicylic acid residue in



The inclusion of the metal in a complex is indicated by the fact that it does not separate as kation, or by the absence of salt-like characters in the compound. A notable feature of these cyclic systems is the frequent occurrence of six-membered 'chelate' rings with two conjugated double linkages. Assuming the regular tetrahedral model (as in the simple Baeyer theory which, as pointed out above, may be accepted as a rough guide in predicting the stability of ring systems), the angle between the valencies of a saturated carbon atom is 109° 28′, while that between a single and a double bond, $\mathrm{C}{<}^{\mathrm{C}}_{\mathrm{C}}$, is 125° 16′; a calculation made on this basis leads to the result that a six-membered ring with two double linkages has no strain and should therefore be very stable. The predominance of chelate rings of this particular type is not surprising, therefore, while the presence of *conjugated* double linkages will lead to a further increase of stability owing to resonance.[115]

Sidgwick and his co-workers have demonstrated the existence of similar ring systems having hydrogen in place of the metallic atom; an atom which has unshared electrons acts as donor, and hydrogen as acceptor. The conception of 'co-ordinated' hydrogen is necessary in order to account for phenomena such as the existence of the acid fluorides with the ion $[\mathrm{F\cdots H—F}]^{\ominus}$, the polymerization of hydrogen fluoride molecules $\mathrm{H—F\cdots H—F}$, and the association of hydroxylic liquids  $\overset{\mathrm{R}\diagdown}{\mathrm{O}}\mathrm{—H\cdots}\overset{\mathrm{R}\diagdown}{\mathrm{O}}\mathrm{—H\cdots}\overset{\mathrm{R}\diagdown}{\mathrm{O}}\mathrm{—H}$.[116] It was first

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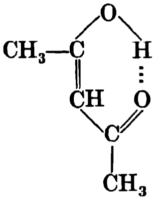
[115] See Chap. V.

[116] Sidgwick, *Electronic Theory of Valency*, p. 72.

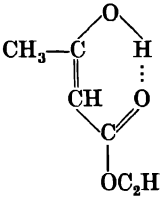
suggested by Latimer and Rodebush,[117] in connexion with molecular association and the lack of basic strength exhibited by ammonia.[118] On theoretical grounds, however, hydrogen cannot form a four-electron valence group of the usual type, for the Pauli Principle would thereby be violated.[119] This difficulty is overcome by ascribing the 'hydrogen bond' to resonance,[120] the unperturbed structures having hydrogen attached to one or the other of the atoms which it joins together, i.e. [X—H Y] and [X H—Y]. The resonance state will have a lower energy content than either of these, and hence will be stable.

The presence of a 'hydrogen bond' in numerous organic compounds is indicated by consideration of their physical properties.[121] Thus if the hydrogen of a hydroxyl group forms a 'bond' of the type described above, as in —O—H···O⟨, the characters which depend upon this group will be suppressed. For example, the solubility of the compound in hydrocarbons will be increased and its solubility in hydroxylic liquids such as water will be decreased; also, since the hydrogen is already acting as 'acceptor' atom, molecular association will be inhibited and an increased volatility will result. On these grounds a hydrogen bond is indicated in the monoenols of β-diketones (e.g. acetylacetone) and β-ketonic esters (e.g. ethyl acetoacetate) when their solubilities and boiling-points are compared with those of their ketonic isomerides, and in certain *o*-substituted phenols by a comparison with the corresponding *m*- and *p*-substituted compounds. The enols of acetylacetone and ethyl acetoacetate, *o*-nitrophenol, and salicylic aldehyde are therefore written as in I, II, III, and IV below:

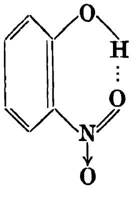
I



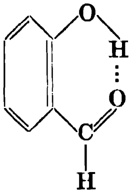
II



III



IV



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[117] *J. Amer. Chem. Soc.* 1920, **42**, 1431.

[118] On strengths of ammonium bases, see Sidgwick, *Electronic Theory of Valency*, p. 97.

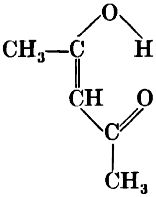
[119] See p. 13.

[120] Sidgwick, *Ann. Reports*, 1933, **30**, 112; 1934, **31**, 40.

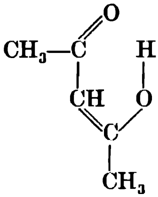
[121] Sidgwick and Callow, *J.C.S.* 1924, **125**, 527. Sidgwick, ibid. 1925, **127**, 907; *Electronic Theory of Valency*, p. 147.

The formation of the hydrogen bond is rendered possible by the relative positions of the oxygen atoms which are thereby linked in a six-membered chelate ring with two double bonds; a similar process does not occur in the isomeric *m*- and *p*-substituted phenols, for example. The resonance is assisted, moreover, by the electronic redistribution which is permitted by the conjugated double linkages, the unperturbed structures being of the type represented in I*a* and I*b* (for acetylacetone) and IV*a* and IV*b* (for salicylic aldehyde):

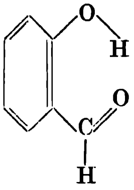
I *a*



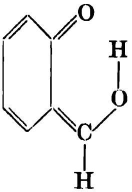
I *b*



IV *a*

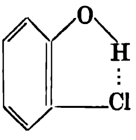


IV *b*

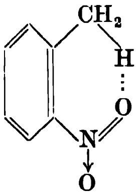


Certain other *o*-substituted phenols in which the formation of a six-membered ring is not possible also differ very appreciably in volatility and solubility from their *m*- and *p*-isomerides, although not to the same extent as those referred to above. The formation of a five-membered ring is here postulated by Sidgwick and Callow, who represent *o*-chlorophenol as in V (below).

V

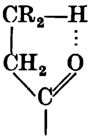


VI

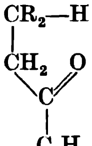


It is evident that such chelation depends upon the presence of an electron donating atom (e.g. carbonyl oxygen); moreover, the atoms to be linked through hydrogen must be so placed that ring closure is possible without undue strain. This latter condition is apparently fulfilled best in the six-membered ring with two double linkages and less completely in the five-membered ring, for in the latter case chelation occurs to a smaller extent than in the former. The physical properties of *o*-cresol and other *o*-alkyl substituted phenols give no indication of chelation. There are two reasons for this: (*a*) the difficulty of removal of a proton from its combination with carbon to take part in a process which is virtually an ionization, and (*b*) the fact that hydroxyl is predominantly electron accepting rather than donating. A neighbouring group of a powerfully electron-attractive character might, however, loosen the hydrogen of an alkyl group sufficiently to permit the formation of such a 'bond' with a suitably placed electron donor. Sidgwick and Callow[122] suggest that this may occur in *o*-nitrotoluene (VI), and it has more recently been postulated by D. P. Evans in order to interpret his observations of the prototropy of side-chain alkylated acetophenones.[123] Evans finds that the energy of activation of the acid-catalysed prototropy of propiophenone, $CH_3 \cdot CH_2 \cdot CO \cdot C_6H_5$, is some 2,000 calories higher than that of the corresponding reaction in the case of acetophenone, $H \cdot CH_2 \cdot CO \cdot C_6H_5$, whereas no additional effect is caused by further lengthening of the chain. This is explained by supposing that chelation occurs between the β-hydrogen and carbonyl oxygen, as in VII. The electron-attractive character of carbonyl probably renders this hydrogen sufficiently mobile to permit resonance between the structures VII *a* and VII *b*.

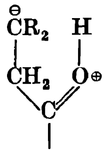
VII



VII *a*



VII *b*



The resulting depression of electron availability at the carbonyl oxygen will operate against the attack of the acid catalyst, thus giving rise to the observed increase in the energy of activation. Evans quotes other observations which may be interpreted by postulating the 'co-ordination' of the hydrogen of an alkyl group.

5. *The* 'Ortho-*Effect*'

The 'abnormal' physical properties of *o*-substituted phenols, ascribed by Sidgwick to chelation, form one example of the frequent and marked differences between benzene derivatives having groups

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[122] Loc. cit., p. 538.

[123] *J.C.S.* 1936, 785.

in *o*-positions with respect to each other and the isomeric compounds where the groups are not so placed. It does not appear possible to ascribe this '*ortho*-effect' to the same cause in every instance, but whatever be its nature in individual cases it is clear that the relative positions of the groups in *o*-substituted compounds make possible the operation of some factor which is absent in the isomeric derivatives. The *ortho*-effect is frequently made evident by a singular depression of chemical reactivity, and the earliest recorded example appears to be found in Hofmann's observation (1872) that certain dialkylanilines with two substituents in *ortho*-positions refused to form quaternary salts when treated with alkyl halides under ordinary conditions;[124] this reaction is also retarded by *one ortho*-substituent.[125] A similar effect was observed, at quite an early date, in many other reactions, such as the hydrolysis of aromatic nitriles and acid amides[126] and the formation of oximes and phenylhydrazones by quinones and aromatic ketones.[127] A series of investigations by Victor Meyer, Sudborough, and their collaborators, from 1894 onwards, revealed a multitude of facts regarding the esterification of di-*ortho*-substituted benzoic acids, and the hydrolysis of their esters, chlorides, amides, and nitriles.[128] The acids gave no ester when their alcoholic solutions were either saturated with hydrogen chloride at 0° or treated by the Fischer-Speier method; even when the boiling solutions were saturated with hydrogen chloride for long periods of time the esterification was either not detectable (when the two groups in *o*-positions were NO_2, Cl, Br, or I) or very slight (with alkyl groups, OH or F). Moreover, the esters and other derivatives of these acids were unusually stable to hydrolytic reagents. The retardation of esterification and hydrolysis by *one ortho*-substituent has also been demonstrated.[129] Again, a single *ortho*-substituent inhibits almost completely the esterification of an aromatic nitrile by alcohol and hydrogen chloride.[130]

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[124] *Ber.* 1872, **5**, 704. Compare Fischer and Windaus, ibid. 1900, **33**, 345, 1967.

[125] See e.g. Thomas, *J.C.S.* 1913, **103**, 594.

[126] Merz and Weith, *Ber.* 1883, **16**, 2886; Hofmann, ibid. 1884, **17**, 1915; Jacobsen, ibid. 1889, **22**, 1219; Claus *et al.*, *Annalen*, 1891, **265**, 364, and later papers.

[127] Kohrmann, *Ber.* 1888, **21**, 3315, and later; Hantzsch, ibid. 1890, **23**, 2773; V. Meyer, ibid. 1896, **29**, 835.

[128] See summary and full references given by Lloyd and Sudborough, *J.C.S.* 1899, **75**, 580. For a summary of the literature on the *ortho*-effect see Cohen, *Organic Chemistry*, Fifth Edition (Edward Arnold & Co., 1928), vol. i, chap. v.

[129] Goldschmidt, *Ber.* 1895, **28**, 3218; Kellas, *Z. physikal. Chem.* 1897, **24**, 221; Kindler, *Annalen*, 1928, **464**, 278.

[130] Pfeiffer *et al.*, ibid. **467**, 158.

The reactivity of a group in an *aliphatic* compound may also be greatly depressed by the presence of neighbouring substituents as shown, for example, by the order of velocities

$$CH_3{\cdot}COOH > CH_2X{\cdot}COOH > CHX_2{\cdot}COOH > CX_3{\cdot}COOH$$

for the esterification of *all* series of substituted acetic acids independent of the nature of X,[131] and by the different rates of esterification of *cis* and *trans* substituted acrylic acids.[132]

The strengths of aromatic acids and bases are also profoundly influenced by substituents in the *o*-position, and analogies are found in phenomena such as the greater strength of *allo*cinnamic than of cinnamic acid. All *o*-substituted benzoic acids are stronger than benzoic acid itself, and often very considerably stronger than their *m*- and *p*-isomerides. This is illustrated by the following thermodynamic dissociation constants.[133]

10^5K *for substituted Benzoic Acids*

Benzoic acid = 6·27

	OH	OCH_3	CH_3	F	Cl	Br	I	NO_2	OC_6H_5
o-	105·0	8·06	12·35	54·1	114·0	140·0	137·0	671·0	29·7
m-	8·3	8·17	5·35	13·65	14·8	15·4	14·1	32·1	11·2
p-	2·9	3·38	4·24	7·22	10·5	10·7	. .	37·6	3·00

Very few values for di-*ortho*-substituted benzoic acids are available, but in at least two cases (2:6-dihydroxy and 2:6-dinitro) the presence of a second *o*-substituent leads to a further large increase in the dissociation constant. Groups in the *o*-position *decrease* the strengths of anilines, sometimes very greatly,[134] and confer increased stability upon benzaldehyde cyanohydrins.[135]

Victor Meyer attributed the *ortho*-effect to steric hindrance. This view was based upon the observation that the influence of a group in the *ortho*-position appears to be dependent upon its size (as measured, according to Meyer, by the sum of the weights of the atoms present) rather than upon its chemical characters; for example, *o*-F is not comparable with the other halogens. Meyer also pointed out that no *ortho*-effect is observed if the reacting group is separated

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[131] Sudborough and Lloyd, *J.C.S.* 1899, **75**, 467.

[132] Sudborough *et al.*, ibid. 1898, **73**, 81; 1905, **87**, 1840.

[133] Dippy *et al.*, ibid. 1934, 1888; 1935, 343; 1936, 644; 1937, 1426. Branch and Yabroff, *J. Amer. Chem. Soc.* 1934, **56**, 2568.

[134] See, for example, Farmer and Warth, *J.C.S.* 1904, **85**, 1726.

[135] Lapworth and Manske, ibid. 1928, 2533.

from the nucleus by one or more carbons atoms; this is evident, for example, in the dissociation constants and esterification velocities of *o*-substituted phenylacetic and cinnamic acids and in the velocities of hydrolysis of their esters.[136] Flürscheim applied Meyer's view to the interpretation of the strengths of *o*-substituted acids by supposing that the steric hindrance opposed the recombination of the ions but not their dissociation.[137] There is, however, no simple relationship, even of a qualitative nature, between the relative effects of groups in the *o*-position and their weights or volumes (for example, NO_2 is usually more effective than Br or I in spite of its smaller size). While, therefore, steric retardation may frequently be an important factor (compare also the restricted rotation in *o*-substituted diphenyls and analogous compounds), the problem of the *ortho*-effect is one of great complexity, and the observations cannot be explained completely in terms of a purely geometrical effect.[138]

It is significant that in all cases where the *ortho*-effect has been observed to operate powerfully, the reacting group contains an atom which is known to be a powerful electron donor, e.g. COR, COOR, NR_2. Olivier finds, for example, that while the hydrolysis of *benzoyl* chloride is very greatly retarded by two bromine atoms in *ortho*-positions, that of *benzyl* chloride is not; taking the velocity of hydrolysis of the unsubstituted compound as unity in each case, those of 2 : 6- and 3 : 5-dibromo*benzoyl* chlorides are 0·0112 and 13·5, and those of the corresponding *benzyl* chlorides are 0·12 and 0·07 respectively.[139] The *ortho*-effect is never detected, indeed, in the reactions of substituted benzyl chlorides,[140] nor is it evident in the dissociation constants of the phenylboric acids, $X \cdot C_6H_4 \cdot B(OH)_2$.[141] Moreover, *o*-substituted phenols are not more strongly acidic than their *m*- and *p*-isomerides, nor are they appreciably less reactive;[142] it may be noted that hydroxyl is predominantly an electron-acceptor (through its hydrogen atom), and that the hydrogen bond in the formulae written by Sidgwick and Callow would not be expected to have much

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[136] Meyer and Sudborough, *Ber.* 1894, **27**, 1580; Kindler, ref. 129; Dippy *et al.*, ref. 133.

[137] *J.C.S.* 1909, **95**, 725.

[138] Compare Davis, ibid. 1900, **77**, 33; Kindler, ref. 129.

[139] *Rec. trav. chim.* 1929, **48**, 227.

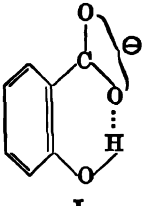
[140] See, e.g., Olivier, ibid. 1930, **49**, 697; Bennett and Jones, *J.C.S.* 1935, 1815.

[141] Branch *et al.*, *J. Amer. Chem. Soc.* 1934, **56**, 937, 1850, 1865.

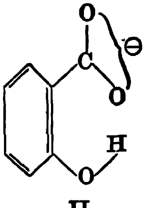
[142] e.g. Boyd *et al.*, *J.C.S.* 1914, **105**, 2117; 1915, **107**, 1538; 1919, **115**, 1239; Burkhardt *et al.*, ibid. 1936, 17. The influences recorded by Davis (ref. 138) in the reactions of alcohols with 1-substituted β-naphthols are probably inductive effects.

influence upon the dissociation of the phenol or upon the electron-availability of the oxygen.

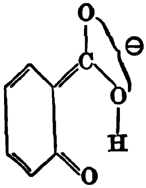
This apparent connexion of the *ortho*-effect with electron-donating atoms leads at once to the suspicion that it may have its origin in a chelation process. The high dissociation constant of salicylic acid (as contrasted with that of *o*-methoxybenzoic acid) has, in fact, been interpreted by Branch and Yabroff as due to the formation of a hydrogen bond between the hydroxyl and carboxyl groups;[143] this is, of course, an obvious extension of the views of Sidgwick and Callow. The positions of the atoms in salicylic acid are particularly favourable for the occurrence of such a process since it leads to a six-membered chelate ring with two conjugated double linkages. It may be suggested further that the chelation will occur in the anion to a far greater extent than in the undissociated acid, and that the high dissociation constant therefore arises almost entirely from the decreased electron-availability of the oxygen atoms in the ion $R\cdot COO^{\ominus}$;[144] the reassociation is inhibited, a conclusion reached by Flürscheim on different grounds. The anion of salicylic acid is probably to be represented, therefore, by I, which is a resonance state between the structures II and III. W. Baker points out the



I



II



III

probability that the further large increase in strength found in 2:6-dihydroxybenzoic acid ($K = 5\times10^{-2}$) is due to the formation of hydrogen bonds by *both* oxygen atoms of carboxyl[145] (which are, of course, actually equivalent).

In view of the possibility (mentioned in the preceding section) that the hydrogen atom of an alkyl group may form a 'bond' with an electron-donating atom, it is no great step to suggest that the

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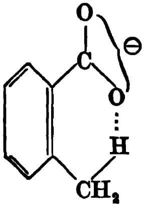
[143] Ref. 133.

[144] If the effect occurs almost entirely in the *anion*, it is not surprising that no *ortho*-effect is observed in reactions such as those studied by Norris and Strain (*J. Amer. Chem. Soc.* 1935, **57**, 187) and by Hammett and Pfluger (ibid. 1933, **55**, 4079).

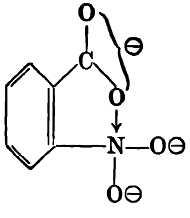
[145] *Nature*, 1936, **137**, 236.

relatively high dissociation constant of *o*-toluic acid is to be attributed to a similar cause, in accordance with formula IV for the anion. Then, in the anions of *o*-nitro- and the *o*-halogeno-benzoic acids (excluding *o*-F), an oxygen of carboxyl may act as electron donor in the formation of a co-ordinate linkage of the ordinary type. Chlorine, bromine, and iodine can increase their valence groups beyond eight electrons (e.g. in ClF_3[146]), and Bennett and Willis, in their formulation of the additive products of nitro-compounds with amines and hydrocarbons, ascribe electron *acceptor* properties to the nitrogen atom of the nitro-group.[147] Structures V and VI are therefore suggested for the anions of *o*-nitro- and *o*-chloro-benzoic acids. At the same time steric hindrance of the Victor Meyer type may also play a part, and may be the principal factor contributing to the relatively high dissociation constants of *o*-phenoxy- and *o*-phenylbenzoic acids where the substituent groups are very bulky; chelation cannot account, moreover, for the strength of *o*-*tert*-butylbenzoic acid ($10^5K = 35$).[148] The absence of an *ortho*-effect in *o*-methoxybenzoic acid, and in the *o*-substituted phenylacetic and cinnamic acids, is in harmony with the fact that the positions of the atoms are here unsuitable for the formation of a hydrogen bond.

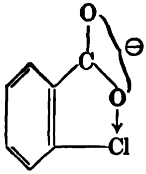
IV



V



VI



Kinetic studies of the acid-catalysed esterification of *o*-substituted acids and of the alkaline hydrolysis of their esters have led to results which support the above interpretation of the *ortho*-effect. In the esterification process[149] substituents in the *ortho*-position *increase* the energy of activation, and also, to some extent, the P factor of the equation $k = PZe^{-E/RT}$; in alkaline hydrolysis, on the other

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[146] Ruff *et al.*, *Z. anorg. Chem.* 1930, **190**, 270; 1932, **207**, 46.

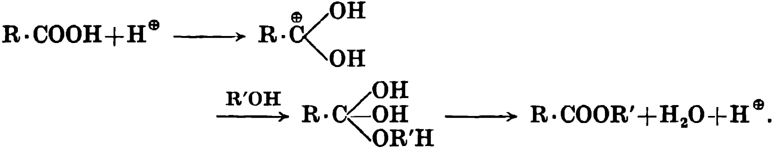
[147] *J.C.S.* 1929, 256.

[148] Shoesmith and Mackie, ibid. 1936, 300.

[149] Hinshelwood and Legard, *J.C.S.* 1935, 587, 1588. The same applies to the methyl groups in trimethylacetic acid.

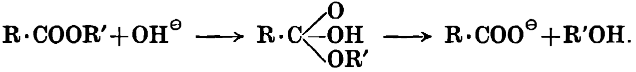
hand, the energies of activation tend to be slightly *lower* than the value for the unsubstituted compound, and the *P* factor is *decreased* very considerably.[150] The processes concerned may be written as follows:[151]

Esterification



$$R\cdot COOH + H^{\oplus} \longrightarrow R\cdot\overset{\oplus}{C}\begin{matrix}\diagup OH\\ \diagdown OH\end{matrix} \xrightarrow{R'OH} R\cdot C\begin{matrix}\diagup OH\\ -OH\\ \diagdown OR'H\end{matrix} \longrightarrow R\cdot COOR' + H_2O + H^{\oplus}.$$

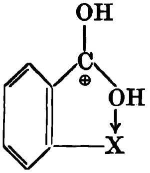
Alkaline Hydrolysis



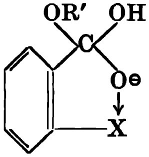
$$R\cdot COOR' + OH^{\ominus} \longrightarrow R\cdot C\begin{matrix}\diagup \overset{\ominus}{O}\\ -OH\\ \diagdown OR'\end{matrix} \longrightarrow R\cdot COO^{\ominus} + R'OH.$$

The formation of the transition complex involves the electromeric change $>C\overset{\curvearrowright}{=}O$, and when this change occurs the electrons move into higher energy levels and therefore become more reactive. Although, therefore, there is probably but little chelation in the un-ionized acid or ester (see above), the electrons of the oxygen are likely to react with a suitably placed acceptor *simultaneously* with the attack of the catalyst. The resulting decrease in the electron-availability of the oxygen will lead to a high energy of activation when, as in esterification or acid-catalysed prototropy,[152] the reaction is with an acid catalyst, but in alkaline hydrolysis, where a basic catalyst is added at carbon, there will be no such effect; the electromeric change may, indeed, be somewhat facilitated, in accordance with the rather low value of *E*. The complex will then have a structure such as VII (for esterification) or VIII (for hydrolysis). The effect

VII



VIII



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[150] Evans, Gordon, and Watson (*J.C.S.* 1937, 1430); see Fig. 17, p. 165. Newling and Hinshelwood (*J.C.S.* 1936, 1357) have obtained similar results for the alkaline hydrolysis of ethyl *iso*butyrate.

[151] See pp. 53 and 130.

[152] See p. 205.

of the chelation is a drift of electrons away from the carbon of carboxyl, and the subsequent change in the esterification reaction, viz. the addition of R′OH, will thereby be facilitated, whereas the elimination of —OR′ in hydrolysis will be rendered more difficult. If, therefore, as suggested in Chapter XI,[153] the *P* factor depends very largely in these cases upon the probability that the transition complex, when once formed, will break down to give the products, the effect of *o*-substituents upon this factor is explained.

The behaviour of ethyl *o*-fluorobenzoate on alkaline hydrolysis is in complete harmony with an interpretation of this type. The values of *E* and *P* are almost the same as those found for the isomeric *p*-substituted ester.[154] The formation of a co-ordinate bond is here impossible since fluorine cannot expand its valence group, and this enforced absence of chelation is accompanied by the complete non-existence of all the criteria of the *ortho*-effect.

It seems quite probable, therefore, that chelation is one of the factors to which the *ortho*-effect is to be traced. There are also other factors, and the complete solution of the problem—and we may hope that a complete solution will some day be found—must await the results of further experimental investigation.

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[153] See p. 162.

[154] Evans, Gordon, and Watson, ref. 150.

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