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## Modern structural chemistry

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A century ago the structural theory of organic chemistry was developed. Frankland in 1852 suggested that an atom of an element has a definite capacity for combining with atoms of other elements - a definite valence. Six years later Kekulé and Couper, independently, introduced the idea of valence bonds between atoms, including bonds between two carbon atoms, and suggested that carbon is quadrivalent. In 1861 Butlerov, making use for the first time of the term "chemical structure", stated clearly that the properties of a compound are determined by its molecular structure, and reflect the way in which atoms are bonded to one another in the molecules of the compound. The development of the structure theory of organic chemistry then progressed rapidly, and this theory has been of inestimable value in aiding organic chemists to interpret their experimental results and to plan new experiments.

A most important early addition to organic structure theory was made by the first Nobel Laureate in Chemistry, Van 't Hoff, who in 1874 recognized that the optical activity of carbon compounds can be explained by the postulate that the four-valence bonds of the carbon atom are directed in space toward the corners of a tetrahedron.

The structure theory of inorganic chemistry may be said to have been born only fifty years ago, when Werner, Nobel Laureate in Chemistry in 1913, found that the chemical composition and properties of complex inorganic substances could be explained by assuming that metal atoms often coordinate about themselves a number of atoms different from their valence, usually four atoms at the corners either of a tetrahedron or of a square coplanar with the central atom, or six atoms at the corners of an octahedron. His ideas about the geometry of inorganic complexes were completely verified twenty years later, through the application of the technique of X-ray diffraction.

After the discovery of the electron many efforts were made to develop an electronic theory of the chemical bond. A great contribution was made in 1916 by Gilbert Newton Lewis, who proposed that the chemical bond,

such as the single bond between two carbon atoms or a carbon atom and a hydrogen atom represented by a line in the customary structural formula for ethane, consists of a pair of electrons held jointly by the two atoms that are bonded together. Lewis also suggested that atoms tend to assume the electronic configuration of a noble gas, through the sharing of electrons with other atoms or through electron transfer, and that the eight outermost electrons in an atom with a noble-gas electronic structure are arranged tetrahedrally in pairs about the atom. Applications of the theory and additional contributions were made by many chemists, including Irving Langmuir and Nevil Vincent Sidgwick.

After the discovery of quantum mechanics in 1925 it became evident that the quantum mechanical equations constitute a reliable basis for the theory of molecular structure. It also soon became evident that these equations, such as the Schrödinger wave equation, cannot be solved rigorously for any but the simplest molecules. The development of the theory of molecular structure and the nature of the chemical bond during the past twenty-five years has been in considerable part empirical - based upon the facts of chemistry - but with the interpretation of these facts greatly influenced by quantum mechanical principles and concepts.

The solution of the wave equation for the hydrogen molecule-ion by Ø. Burrau (*Kgl. Danske Videnskab. Selskab, Mat. Fys. Medd.*, 7, (1927) 14) completely clarified the question of the nature of the one-electron bond in this molecule-ion. Two illuminating quantum mechanical discussions of the shared-electron-pair bond in the hydrogen molecule were then simultaneously published, one by Heitler and London (*Z. Physik*, 44 (1927) 455), and the other by E. U. Condon (*Proc. Natl. Acad. Sci. U.S.*, 13 (1927) 466). In the approximate solution of the wave equation for the hydrogen molecule by Heitler and London a wave function is used that requires the two electrons to be separated, each being close to one of the two nuclei. The treatment by Condon permits the electrons to be distributed between the two nuclei independently of one another, each occupying a wave function similar to Burrau's function for the hydrogen molecule-ion. Condon's treatment is the prototype of the molecular-orbital treatment that has been extensively applied in the discussion of aromatic and conjugated molecules, and Heitler and London's treatment is the prototype of the valence-bond method. When the effort is made to refine the two treatments they tend to become identical.

These early applications of quantum mechanics to the problem of the nature of the chemical bond made it evident that in general a covalent bond,

involving the sharing of a pair of electrons between two atoms, can be formed if two electrons are available (their spins must be opposed, in order that the bond be formed), and if each atom has available a stable electronic orbital for occupancy by the electrons.

The equivalence of the four bonds formed by a carbon atom, which had become a part of chemical theory, was not at first easily reconciled with the quantum mechanical description of the carbon atom as having one  $2s$  orbital and three  $2p$  orbitals in its outer shell. The solution to this difficulty was obtained when it was recognized that as a result of the resonance phenomenon of quantum mechanics a tetrahedral arrangement of the four bonds of the carbon atom is achieved'. The carbon atom can be described as having four equivalent tetrahedral bond orbitals, which are hybrids of the  $s$  and  $p$  orbitals. Further study of this problem led to the discovery of many sets of hybrid bond orbitals, which could be correlated with bond angles, magnetic moments, and other molecular properties<sup>2</sup>. In particular it was found that  $sp^3$ ,  $dsp^2$ , and  $d^2sp^3$  hybrid orbitals correspond respectively to the tetrahedral, square planar, and octahedral configurations of inorganic complexes that had been discovered by Werner. Conclusions as to the utilization of atomic orbitals in bond formation can be drawn from experimental values of magnetic moments. For example, the theory of the  $dsp^2$  square complexes of bivalent nickel, palladium, and platinum requires that these substances be diamagnetic. The square complexes of bivalent palladium and platinum had been recognized by Werner and their structure verified by Dickinson (*J. Am. Chem. Soc.*, 44 (1922) 2404); but the assignment of the square configuration to the complexes of nickel which are diamagnetic had not been made until the development of the new theory.

Further detailed information about the chemical bond resulted from a consideration of the energy of single bonds in relation to the relative electronegativity of the bonded atoms<sup>3</sup>. It was found that the elements can be assigned electronegativity values such as to permit the rough prediction of the heats of formation of compounds to which chemical structures involving only single bonds are conventionally assigned, and that many of the properties of substances can be discussed in a simple way with the use of the electronegativity values of the elements.

The idea that the properties of many organic compounds, especially the aromatic compounds, cannot be simply correlated with a single valence-bond structure, but require the assignment of a somewhat more complex electronic structure, was developed during the period 1923 to 1926 by a

number of chemists, including Lowry, Lapworth, Robinson, and Ingold in England, Lucas in the United States, and Arndt and Eistert in Germany. It was recognized that the properties of aromatic and conjugated molecules can be described by the use of two or more valence-bond structures, as reflected in the names, the theory of mesomerism and the theory of intermediate states, proposed for the new chemical theory. In 1931 Slater, E. Hückel, and others recognized that these theories can be given a quantum mechanical interpretation: an approximate wave function for a molecule of this sort can be set up as the sum of wave functions representing the hypothetical structures corresponding to the individual valence-bond structures. The molecule can then be described as having a structure that is a hybrid of the individual valence-bond structures, or as resonating among these structures, and the theory itself is now usually called the resonance theory of chemical structure. Very many quantitative calculations, approximate solutions of the wave equation, for aromatic and conjugated molecules have been made, with results that are in general in good agreement with experiment. Perhaps more important than the quantitative calculations is the possibility of prediction by simple chemical arguments. For example, the amide group, an important structural feature of proteins, can be described as resonating between two structures, one with the double bond between the carbon atom and the oxygen atom, and the other with the double bond between the carbon atom and the nitrogen atom<sup>4</sup>:



General arguments about the stability of alternative structures indicate that the structure with the double bond between carbon and oxygen should contribute somewhat more to the normal state of the amide group than the other structure; experience with other substances and acquaintance with the results of quantum mechanical calculations suggest the ratio 60% : 40% for the respective contributions of these structures. A 40% contribution of the structure with the double bond between the carbon atom and the nitrogen atom would confer upon this bond the property of planarity of the group of six atoms; the resistance to deformation from the planar configuration would be expected to be 40% as great as for a molecule such as ethylene, containing a pure double bond, and it can be calculated that rotation of one end by 3° relative to the other end would introduce a strain energy of 100 cal/mole. The estimate of 40% double-bond character for the C-N bond

is supported by the experimental value of the bond length, 1.32 Å, interpreted with the aid of the empirical relation between double-bond character and interatomic distance<sup>5</sup>. Knowledge of the structure of amides and also of the amino acids, provided by the theory of resonance and verified by extensive careful experimental studies made by R. B. Corey and his co-workers, has been of much value in the determination of the structure of proteins.

In the description of the theory of resonance in chemistry there has been a perhaps unnecessarily strong emphasis on its arbitrary character. It is true, of course, that a description of the benzene molecule can be given, in quantum mechanical language, without any reference to the two Kekulé structures, in which double bonds and single bonds alternate in the ring. An approximate wave function for the benzene molecule may be formulated by adding together two functions, representing the two Kekulé structures, and adding other terms, to make the wave function approximate the true wave function for the molecule more closely, or it may be constructed without explicit introduction of the wave functions representing the two Kekulé structures. It might be possible to develop an alternative simple way of discussing the structure of the amide group, for example, that would have permitted chemists to predict its properties, such as planarity; but in fact no simple way of discussing this group other than the way given above, involving resonance between two valence-bond structures, has been discovered, and it seems likely that the discussion of complex molecules in terms of resonance among two or more valence-bond structures will continue in the future to be useful to chemists, as it has been during the past twenty years.

The convenience and usefulness of the concept of resonance in the discussion of chemical problems are so great as to make the disadvantage of the element of arbitrariness of little significance. Also, it must not be forgotten that the element of arbitrariness occurs in essentially the same way in the simple structure theory of organic chemistry as in the theory of resonance - there is the same use of idealized, hypothetical structural elements. In the resonance discussion of the benzene molecule the two Kekulé structures have to be described as hypothetical: it is not possible to synthesize molecules with one or the other of the two Kekulé structures. In the same way, however, the concept of the carbon-carbon single bond is an idealization. The benzene molecule has its own structure, which cannot be exactly composed of structural elements from other molecules. The propane molecule also has its own structure, which cannot be composed of structural elements from other

molecules - it is not possible to isolate a portion of the propane molecule, involving parts of two carbon atoms and perhaps two electrons in between them, and say that this portion of the propane molecule is the carbon-carbon single bond, identical with a portion of the ethane molecule. The description of the propane molecule as involving carbon-carbon single bonds and carbon-hydrogen single bonds is arbitrary; the concepts themselves are idealizations, in the same way as the concept of the Kekulé structures that are described as contributing to the normal state of the benzene molecule. Chemists have found that the simple structure theory of organic chemistry and also the resonance theory are valuable, despite their use of idealizations and their arbitrary character.

Other extensions of the theory of the chemical bond made in recent years involve the concept of fractional bonds. Twenty-five years ago it was discovered that a simple theory of complex crystals with largely ionic structures, such as the silicate minerals, can be developed on the basis of the assumption that each cation or metal atom divides its charge or valence equally among the anions that are coordinated about it<sup>6</sup>. For example, in a crystal of topaz,  $\text{Al}_2\text{SiO}_5\text{F}_2$ , each silicon atom is surrounded by a tetrahedron of four oxygen atoms, and each aluminum atom is surrounded by an octahedron of four oxygen atoms and two fluorine atoms. The valence of silicon, 4, is assumed to be divided among four bonds, which then have the bond number 1 - they are single bonds. The valence of aluminum, 3, is divided among six bonds, each of which is a half bond. A stable structure results when the atoms are arranged in such a way that each anion, oxygen or fluorine, forms bonds equal to its valence. In topaz each oxygen atom forms one single bond with silicon and two half bonds with aluminum, whereas each fluorine atom forms only two half bonds with aluminum. The distribution of the valences hence then corresponds to the bivalence of oxygen and the univalence of fluorine. It was pointed out by W. L. Bragg that if the metal atoms are idealized as cations ( $\text{Si}^{++++}$  and  $\text{Al}^{+++}$ ) and the oxygen and fluorine atoms as anions ( $\text{O}^-$  and  $\text{F}^-$ ), this distribution corresponds to having the shortest possible lines of force between the cations and the anions - the lines of force need to reach only from a cation to an immediately adjacent anion, which forms part of its coordination polyhedron. Occasionally ionic crystals are found in which there are small deviations from this requirement, but only rarely are the deviations larger than one quarter of a valence unit.

Another application of the concept of fractional valence bonds has been made in the field of metals and alloys. In the usual quantum mechanical

discussion of metals, initiated by W. Pauli (*Z. Physik*, 41 (1927) 81) and Sommerfeld (*Naturwiss.*, 15 (1927) 825), the assumption was made that only a small number of electrons contribute significantly to the binding together of the metal atoms. For example, it was customary to assume that only one electron, occupying a  $4s$  orbital, is significantly involved in the copper-copper bonds in the metal copper. Sixteen years ago an analysis of the magnetic properties of the transition metals was made that indicated that the number of bonding electrons in the transition metals is much larger, of the order of magnitude of six<sup>7</sup>. Iron, for example, can be described as having six valence electrons, which occupy hybrid  $d^2sp^2$  orbitals. The six bonds, corresponding to these six valence electrons, resonate among the fourteen positions connecting an iron atom with its fourteen nearest neighbors. The bonds to the eight nearest neighbors have bond number approximately  $\frac{5}{8}$ , and those to the six slightly more distant neighbors have bond number  $\frac{1}{6}$ . In gamma iron, where each atom is surrounded by twelve equally distant neighbors, the bonds are half bonds. The concept that the structure of metals and intermetallic compounds can be described in terms of valence bonds that resonate among alternative positions, aided by an extra orbital on most or all of the atoms (the metallic orbital), has been found of value in the discussion of the properties of these substances<sup>8</sup>. The resonating-bond theory of metals is supported especially strongly by the consideration of interatomic distances in metals and intermetallic compound<sup>9</sup>.

The iron atom has eight electrons outside of the argon shell of eighteen. Six of these electrons are assumed, in the resonating-valence-bond theory, to be valence electrons, and the remaining two are atomic electrons, occupying  $3d$  orbitals, and contributing two Bohr magnetons to the magnetic moment of the atom. A theory of the ferromagnetism of iron has recently been developed<sup>10</sup>, in which, as suggested by Zener (*Phys. Rev.*, 81 (1951) 440), the interaction producing the Weiss field in the ferromagnetic metal is an interaction of the spin moments of the atomic electrons and uncoupled spins of some of the valence electrons. It has been found possible to use spectroscopic energy values to predict the number of uncoupled valence electrons, and hence the saturation magnetic moment for iron: the calculation leads to 0.26 uncoupled valence electrons per atom, and saturation magnetic moment 2.26 Bohr magnetons, which might be subject to correction by two or three percent because of the contribution of orbital moment. The experimental value is 2.22. A calculated value of the Curie temperature in rough agreement with experiment is also obtained.

The valence theory of metals and intermetallic compounds is still in a rather unsatisfactory state. It is not yet possible to make predictions about the composition and properties of intermetallic compounds with even a small fraction of the assurance with which they can be made about organic compounds and ordinary inorganic compounds. We may, however, hope that there will be significant progress in the attack on this problem during the next few years.

Let us now return to the subject of the structural chemistry of organic substances, especially the complex substances that occur in living organisms, such as proteins. Recent work in this field<sup>11</sup> has shown the value of the use of structural arguments that go beyond those of the classical structure theory of organic chemistry. The interatomic distances and bond angles in the polypeptide chains of proteins are precisely known, the bond distances to within about 0.02 Å and the bond angles to within about 2°. It is known that the amide groups must retain their planarity; the atoms are expected not to deviate from the planar configuration by more than perhaps 0.05 Å. There is rotational freedom about the single bonds connecting the alpha carbon atom with the adjacent amide carbon and nitrogen atoms, but there are restrictions on the configurations of the polypeptide chain that can be achieved by rotations about these bonds: atoms of different parts of the chain must not approach one another so closely as to introduce large steric repulsion, and in general the N-H and O atoms of different amide groups must be so located relative to one another as to permit the formation of hydrogen bonds, with N-H... O distance equal to  $2.79 \pm 0.10$  Å and with the oxygen atom not far from the N-H axis. These requirements are stringent ones. Their application to a proposed hydrogen-bonded structure of a polypeptide chain cannot in general be made by the simple method of drawing a structural formula; instead, extensive numerical calculations must be carried out, or a model must be constructed. For the more complex structures, such as those that are now under consideration for the polypeptide chains of collagen and gelatin, the analytical treatment is so complex as to resist successful execution, and only the model method can be used. In order that the principles of modern structural chemistry may be applied with the power that their reliability justifies, molecular models must be constructed with great accuracy. For example, molecular models on the scale  $2.5 \text{ cm} = 1 \text{ Å}$  have to be made with a precision better than 0.01 cm.

We may, I believe, anticipate that the chemist of the future who is interested in the structure of proteins, nucleic acids, polysaccharides, and other

complex substances with high molecular weight will come to rely upon a new structural chemistry, involving precise geometrical relationships among the atoms in the molecules and the rigorous application of the new structural principles, and that great progress will be made, through this technique, in the attack, by chemical methods, on the problems of biology and medicine.

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