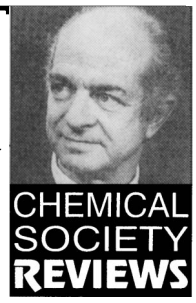
The science and humanism of Linus Pauling (1901–1994)



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The versatile and outstanding contributions of Linus Pauling to the chemical sciences, including the biomedical consequences of radioactive fallout, were recognised by the award of two Nobel Prizes (1954 and 1963). Pauling's contributions in historical context are discussed under five headings: X-ray crystallography and theoretical chemistry; the nature of the chemical bond; biological chemistry; global fallout; and molecular medicine.

The award of two Nobel Prizes, the first for chemistry at Stockholm in 1954 and the second for peace at Oslo in 1963, measures the eminence of Linus Pauling as a scientist and as a world citiizen. Festschrifts honoured his sixty-fifth,[1] eightieth,[2] and ninetieth birthday,[3] with autobiographical contributions by Pauling himself in two of these, and in the *Annual Review of Physical Chemistry* series (1965). Pauling was interviewed many times on his scientific and social concerns, and a selection of his replies and his occasional writings has appeared recently,[4] as well as a collection of tributes to him to the *Journal of Chemical Education* (No. 1, 1996). Substantial biographies of Pauling are available, one by a philosopher,[5] a second co-authored by a sociologist and a psychologist,[6] and another, the most comprehensive, balanced, and informed of the three, by a medical writer turned academic administrator.[7] The second biography curiously concludes with eight interpretations from expert psychologists of the replies Pauling had given to Rorschach ink-blot tests in the 1960s, when his biochemical view of mental disorders was at odds with standard psycho-analytical thinking. Only one of the experts suspects, what is obvious to the layman, that Pauling was joking, making up answers based on Freudian or other psychology.[8]

Chemistry students of my generation were inspired by Pauling's *Nature of the Chemical Bond* (1939), which brought a new ordering to theories of molecular structure and chemical bonding, and answered 'No!' to a popular examination question of the time, 'Is inorganic chemistry a closed and finished subject?' The book pointed the way ahead to the physical inorganic chemistry of the postwar period, but Pauling's interests had moved on by that time to molecular biology, then to the dire consequences of radioactive fallout from nuclear explosions in the biosphere, and finally, to orthomolecular medicine.

1 Pauling's formative years

Linus Carl Pauling was the firstborn, in 1901, of a pharmacist in Portland, Oregon, who died in 1911 leaving his wife, son, and two daughters with limited means. After high school in Portland, Linus Pauling entered Oregon Agricultural College at Corvallis, precursor of Oregon State University, in 1917, and graduated in chemical engineering in 1922. He worked his way through college, serving as full-time assistant instructor in quantitative analysis 1919–1920. The experience may have dissuaded him from accepting a half-time instructor's post for five years of graduate study for a PhD at Harvard. Instead he moved, in 1922, to a three-year graduate studentship offered by Arthur Amos Noyes (1866–1936), head of the Division of Chemistry and Chemical Engineering in the California Institute of Technology (Caltech) at Pasadena.

Noyes had an eye for talent and for promising new fields of research, and it is said that Pauling was Noyes' greatest discovery. Noyes obtained his PhD with Wilhelm Ostwald (1853–1932) at Leipzig in 1890, then joined the Massachusetts Institute of Technology (MIT) where, as professor of theoretical chemistry 1899–1919, he recruited a number of able younger chemists. These included Gilbert Newton Lewis (1875–1946), who was at MIT 1908–1912 before moving to the University of California, Berkeley, as head of the chemistry department. Noyes commuted to Pasadena each winter from 1915 to build up the chemistry division of Throop College of Technology, which changed its name to Caltech shortly after Noyes moved permanently to Pasadena in 1919.

Noyes recognised the importance of X-ray crystal structure analysis from the beginning; and installed X-ray equipment at MIT and Caltech. Roscoe Gilkey Dickinson (1894–1945) was in charge of the powder and single-crystal X-ray apparatus at Caltech in 1922 when Linus Pauling was placed with him by Noyes for research supervision as a graduate student. Dickinson and Pauling published their first paper in 1923, on the structure of the mineral molybdenite, MoS_2, establishing a trigonal prismatic coordination of molybdenum by six sulfide ions. Pauling soon achieved scientific standing, as author or coauthor of about a dozen crystal-structure publications over the next three years, and G. N. Lewis offered him a postdoctoral position at Berkeley after his PhD in 1925. Noyes thereupon arranged a Guggenheim fellowship for Pauling's postdoctoral studies in Europe 1926–1927, centred on the Munich Institute of Arnold

S. F. Mason worked on antimalarials for his D.Phil. (1944–47) with D. Ll. Hammick at Oxford University, where he taught the history of science, as well as chemistry (1947–1953). He was then a Research Fellow with Adrien Albert in the Australian National University's Department of Medical Chemistry, being built up in the Wellcome Institute, London. In 1956 he moved to a lectureship in physical organic chemistry at Exeter University and became Reader in chemical spectroscopy. He was Professor of Chemistry at the University of East Anglia (1964–1970) and at King's College London (1970–1988), working on chirality in its many aspects, summarised in his Molecular Optical Activity & the Chiral Discriminations *(1982). From 1988 he has been Emeritus Professor of Chemistry in the University of London, and Honorary Research Associate in the Department of History and Philosophy of Science, University of Cambridge. Since completing his* Chemical Evolution *(1991), he has been rewriting his* History of the Sciences *(1953).*

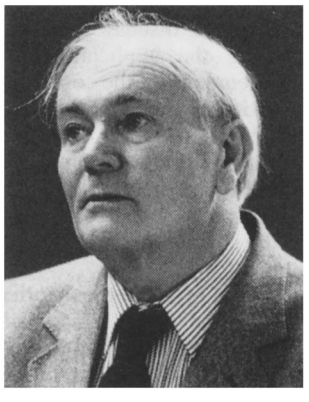


Fig. 1 Linus Pauling as a young man (courtesy of the Royal Society of Chemistry Library and Information Centre)

Sommerfeld (1868–1951), indicating that a position at Caltech would be available on Pauling's return.[9]

In Europe for nineteen months, 1926–1927, Pauling met the principal workers in the field of quantum mechanics as they came to visit Sommerfeld's Institute at Munich, or on his own visits to Copenhagen and Göttingen for a few weeks, and to Zürich for several months. As a graduate student, Pauling had attended a wide range of advanced courses on mathematics and the physical sciences, and soon assimilated the concepts and procedures of the new quantum mechanics. He said later on that he did not bother overmuch with the deeper philosophical implications of the uncertainty principle and the like. Following the pragmatic tradition of North America, Pauling adopted an operational approach to the new discipline, seeking concrete applications of quantum mechanics to chemical and physical problems.

At Bohr's Institute in Copenhagen Pauling met Samuel Goudsmit (1902–1978) who, with George Uhlenbeck (1900–1988), introduced in 1925 the physical notion of electron spin to account for the two-valued fourth quantum number needed in atomic spectroscopy. The new number had entered empirically into Pauli's principle (1925), forbidding the same set of four quantum numbers to any two electrons in any given polyelectronic system. Pauling and Goudsmit later collaborated in writing *The Structure of Line Spectra* (1930). More momentous was Pauling's visit to Schrödinger's Institute in Zürich, where he met Fritz London (1900–1954) and Walter Heitler (1904–1981), who were working on their valence bond (VB) treatment of the bonding in the hydrogen molecule, published in 1927. The two electrons (1) and (2) of the molecule are allocated to the 1s atomic orbital around each nucleus, H_a and H_b, in two ways, $[H_a(1)H_b(2)]$ and $[H_b(1)H_a(2)]$, to give two 'valence structures'. Calculations indicated that, at bonding internuclear separations, the principal source of the molecular binding came from the 'exchange energy', arising from the interchange of the two electrons, with opposed spins, between the two 'valence structures'.

About the same time Friedrich Hund (b. 1896) developed the alternative molecular orbital (MO) treatment of the bonding in the hydrogen molecule at Göttingen. On the MO model the paired electrons move in a molecular orbital resulting from the in-phase combination of the 1s atomic orbitals of the two nuclei, $[H_a + H_b]$. Subsequent comparisons of the two methods showed that the original MO treatment gave ionic structures of the type $[H_a(1,2)]$ and $[H_b(1,2)]$, additional to the neutral valence structures of the first VB treatment, and of equal weight. The two methods became identical, and gave a theoretical bond distance and bond energy closer to the corresponding spectroscopically measured values, when the weights of the contributions from the ionic structures were reduced in the MO treatment and were added to an equivalent degree in the VB treatment. The conceptual differences between the VB and the MO methods remained, however, in the simplified and approximate methods needed for the treatment of complex polyatomic molecules. These differences occasioned some contention between advocates of the VB and the MO methods until the 1950s, when the growth of chemical spectroscopy brought about the general adoption of the MO procedure, with its more fruitful treatment of excited molecular states.

In North America the principal advocate of the MO theory was Robert Sanderson Mulliken (1896–1986), at the University of Chicago from 1928. Mulliken was a close friend of Hund from the mid-1920s, and regretted that his Nobel Prize (1966) was not shared with Hund.[10] During the prewar period, chemists took little note of the MO studies of Hund and Mulliken. The early MO models regarded a molecule as a fixed array of atomic nuclei, each with its own completed inner shells of electrons, while the electrons of the incomplete outer shells of the atoms, the 'valence electrons', moved in molecular orbitals spanning the array of atoms as a whole. There were no individual 'chemical bonds' in a polyatomic molecule, according to early MO theory, contrary to classical structural theory. Traditionally, chemists constructed molecules, conceptually and in the laboratory, by adding another atom or group, through a well-defined 'chemical bond', to a simpler structure.

Mulliken opened his *Chemical Review* of 1931 with the opinion that 'the concept of valence itself is one which should not be held too sacred'. After devoting a section to the 'Superfluity of the concept of valence bonds in the "molecular" point of view', he came to the conclusion that the VB method, 'when applicable, usually gives, somewhat fortuitously in the author's opinion, the same results as the present [MO] method. The latter gives, however, a detailed insight into what is going on in the formation of the molecule'.[11] During the 1930s few chemists accepted Mulliken's views of chemical bonding. In contrast, Pauling's resonance theory, formally based on the VB method, aroused widespread interest, particularly in North America, since it preserved and rationalised much of classical structural theory and the pre-quantum mechanical theories of the role of electrons in chemical bonding, developed mainly by chemists.

In 1927 Pauling returned to Caltech as assistant professor in theoretical chemistry, and began a series of investigations on the nature of the chemical bond, alongside his resumed X-ray studies of crystal structures. In 1930 he extended his structural studies to individual molecules in the gas phase, free from complexities of the packing of molecules in crystals, with the new technique of electron-diffraction, developed by Hermann Mark in Ludwigshafen. Pauling visited Mark early in 1930 when he spent some time with William Lawrence Bragg (1890–1971) at Manchester. With Bragg he discussed various crystallographic procedures, including the applications of Pauling's rules (1928) governing the geometry of the coordination polyhedron of anions around a cation in an ionic crystal, in terms of the radius ratio of the anion and the cation, and their formal charges. These rules were elaborations of rules proposed 1923–1926 by the geochemist–crystallographer, Victor Moritz Goldschmidt (1888–1947) in Oslo, and they had particular value for the structural analysis of the silicate minerals, which Bragg and Pauling were studying.

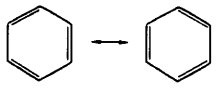
Pauling recalled in 1991 that his interest in electronic theories of chemical bonding dated from the time he served as assistant instructor 1919–1920. One of the two chemistry seminars that year at the Oregon Agricultural College was given by an agricultural chemist on the frozen fish industry, while Pauling

spoke on the shared electron-pair chemical bond. This basic idea had been proposed by G. N. Lewis in 1916 and developed in a series of papers from 1919 by Irving Langmuir (1881–1957), who coined the terms 'covalance' and 'electrovalence' for the homopolar and the heteropolar sharing. The Coulombic attraction of opposite charges provided a physical basis for the electrovalent (ionic) bond, but the homopolar shared-pair covalent bond had no immediate physical foundation, other than the significant correlation with the electron-pair of the lightest noble gas, helium, and the four duplets of the eight electrons in the outer shell of the heavier noble gases, modelling the electron configuration of the central atom in polyatomic systems, such the carbon atom in CH_4.

In Munich and Zürich 1926–1927 Pauling found what he believed to be the physical basis of the homopolar covalent bond in the quantum-mechanical 'exchange energy', arising from the interchange of spin-paired electrons between the two 'valence structures' in the VB treatment of the hydrogen molecule by Heitler and London. Pauling regarded the electron-pair exchange in a chemical bond as the quantum-mechanical analogue of the classical resonance effect observed in coupled oscillators, terming the bond energy from electron interchange the 'resonance energy'. He referred the analogy back to the 1926 treatment by Werner Heisenberg (1901–1976) of the separate *para*- and *ortho*-states of the helium atom (spin singlets and triplets, respectively), which resembled a classical case of the resonance splitting between the in-phase and out-of-phase modes of coupled oscillators. Pauling introduced his resonance theory in a 1928 *Chemical Review* and developed his ideas in a series of seven papers 1931–1933 on *The Nature of the Chemical Bond*, culminating in his George Fisher Baker Lectures at Cornell University, 1937–1938. The lectures were published, *The Nature of the Chemical Bond* in 1939, with a second edition in 1940 and a third in 1960. All were dedicated to G. N. Lewis, whom Pauling regarded as the founder of the modern theory of valence.

2 The nature of the chemical bond

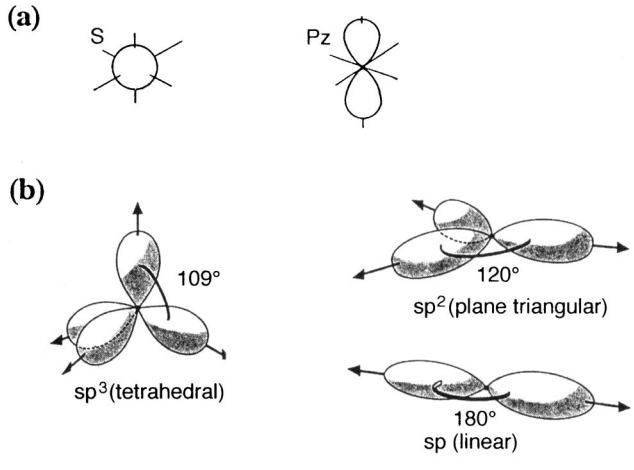
Classical chemical structural theory provided a number of examples of molecules which could not be represented by a single structure, as in the leading case of benzene, for which August Kekulé (1829–1896) had proposed in 1872 an 'oscillation' between the two alternative 'Kekulé structures', each with three single and three double carbon–carbon bonds forming a hexagon. This oscillation was required to account for the absence of two isomers of a given 1,2-disubstituted derivative. For Pauling the two Kekulé structures were classical analogues of quantum-mechanical 'valence structures'. The actual benzene molecule cannot be regarded as 'intermediate' between the hypothetical Kekulé structures. The molecule is more stable than either of these structures by a resonance energy of some 36 kcal mol^{-1} (1 cal = 4.184 J). The carbon–carbon bond lengths of benzene are shorter than the mean of standard carbon–carbon single double bond lengths.



The resonance energy of benzene, on division by Planck's constant, gives a resonance frequency on the order of 10^{15} Hz, comparable to that derived similarly from the bond energies of simple molecules. Such a frequency refers to electronic motions, being a thousand times greater than that of the nuclear motions implied by Kekulé's proposal of 1872; the nuclear motions involved in tautomerism are slower still.[12] Pauling's disciple, George Wheland, remarked that the benzene molecule is analogous to the real animal, the rhinoceros, described by a medieval traveller as a cross between two mythical beasts, the dragon and the unicorn.[13]

In 1935 Pauling judged the Heitler–London theory of bonding in the hydrogen molecule as 'the greatest single contribution to the clarification of the chemist's conception of valence since G. N. Lewis's suggestion in 1916 that the chemical bond between two atoms consists of a pair of electrons held jointly by the two atoms'.[14] Fritz London was appalled by the compliment, and was irritated by 'this Pauling', who had not only taken over and vulgarised the VB theory but had also associated the theory with the physically absurd notions of G. N. Lewis, who postulated a static cubical array of electrons around the atomic nucleus. In 1929 London began a book on *Quantum Mechanics and Chemistry*, but soon abandoned the project. By 1930 he had moved on to investigate the non-polar intermolecular forces, the 'London dispersion forces', and by 1935 worked out the 'London equations' governing superconductivity, with his brother Heinz.[15] Heitler moved on to radiation theory, also satisfied, as were Schrödinger and Dirac, that quantum mechanics had now, in principle, solved all problems in chemistry.

The first of Pauling's seven papers on the nature of the chemical bond[16] was especially important in reconciling 'spectroscopic orbitals' with 'chemical orbitals'. Quantum mechanics developed symbiotically with atomic and diatomic spectroscopy during the interwar period.[17] The atomic orbitals took their designations s-, p-, d- . . . from the sharp, principal, diffuse . . . series of lines observed in atomic spectra. The angular forms of these atomic orbitals, based on the spherical harmonic functions, bore no direct and systematic relation to the stereochemical forms of polyatomic molecules, and the character of the 'chemical orbitals' governing the angles between bonds in polyatomic systems had become problematic by 1930. On a spectroscopic basis, the four valency electrons of the carbon atom formed the atomic ground state with two electrons spin-paired in the spherically symmetric 2s orbital and the remaining two with parallel spin occupying two of the mutually orthogonal $2p_x$, $2p_y$, and $2p_z$ orbitals. In 1931, Pauling and the MIT physicist John Slater showed, independently, that the angular functions of the 2s and the three 2p orbitals of the carbon atom, taken with equal weight and mutually exclusive phase relationships give rise to four equivalent hybrid (sp^3) atomic orbitals, directed tetrahedrally. Each of these four hybrid chemical orbitals has an equal binding propensity, which is twice that of the 2s-orbital alone, as measured by the fractional overlap with, say, a 1s-orbital of a hydrogen atom at a bonding position. Pauling extended his scheme to trigonal and digonal hybrids for molecules containing the carbon–carbon double- and triple-bond and to octahedral and square-planar hybrids from the 4s-, 4p-, and 3d-orbitals of the transition metals in the first long period for the bonding established in coordination compounds.

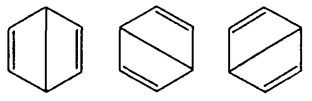


A major element of Pauling's comprehensive ordering of inorganic bonding lay in this derivation of a quantitative scale of the electronegativities of the chemical elements through the resonance theory. Chemists during the eighteenth century had endeavoured to order the known variety of chemical combinations by drawing up hierarchical 'Tables of Chemical Affinities', based on such observations as the displacement of one acid from its salts by another acid with a greater 'affinity' for the base of the salt.[18] After the chemical revolution at the end of the century, attention turned to the avidity with which oxygen combined with other elements, resulting in the 'Scale of Oxygenicity' or of universal acidity, evolved from 1809 by Amedeo Avogadro (1776–1856). Jöns Jacob Berzelius (1779–1848), one of the pioneers of electrochemistry, reformulated and extended Avogadro's concept into a 'universal scale of electronegativity' of the elements in 1818, based on the observations that oxygen, acids, and oxidised substances accumulated around the positive pole of an electrolytic cell, while metals, bases, and combustible substances passed to the negative pole.

Berzelius linked the electronegativity scale to his dualistic electropolar theory of chemical combination, based on the two-fluid theory of electricity. Each atom, Berzelius proposed, carried unequal amounts of the positive and the negative electrical fluid, and the ratio of the amounts registered the electronegativity of the element. Oxygen, the most electronegative element then known, carried the largest excess of negative fluid, and potassium at the other end of the scale carried the largest excess of positive fluid. Chemical combination entailed the partial neutralisation of the two electrical fluids, and their union resulted in the liberation of the caloric fluid (heat). The compound formed retained smaller amounts of the two electrical fluids, and so acids, with an excess of negative fluid, combined with bases, carrying an excess of positive fluid, to form salts. The dualistic theory of chemical combination lost ground during the 1840s, primarily because it was unproductive in the new field of organic chemistry. But the concept of electronegativity and chemical affinity lived on, assuming thermochemical forms with the rise of physical chemistry at the end of the nineteenth century.[19]

The qualitative electronegativity scale of Berzelius, based largely on his chemical experience and intuition, correlates element by element with the quantitative scale of atomic electronegativities which Pauling derived, from 1932. The electric dipole moment of heteronuclear molecules A–B indicated to Pauling that the bonding involved resonance between covalent and ionic valence structures, the fractional contribution of the ionic structure being gauged by the value of the dipole moment. The bond energy of the heteronuclear molecule A–B turned out to be larger than the arithmetic or geometric mean of the bond energies of the corresponding homonuclear molecules A–A and B–B by an increment Δ, which represented the additional stabilisation arising from the resonance between the covalent and ionic valence structures. The bond energy increment Δ(A–B) could be related to the difference between the traditional, but ill-defined, property of the two individual elementary atoms, their electronegativities. The direct relation between Δ(A–B) and the square of the electronegativity difference $[(x_A - x_B)^2]$ enabled Pauling to evaluate the differences quantitatively, and to draw up a comprehensive table of the atomic electronegativities, ranging from 0.7 for caesium to 4.0 for fluorine. The table of electronegativities gave expectations for the energy and the electric dipole moment of any new type of bond: *e.g.* 50% ionic character for a difference of 1.7 between the electronegativities of the two atoms. What an atomic electronegativity really respresented was not transparent. Pauling regarded electronegtivity as a measure of the affinity of a bonded atom for electrons.

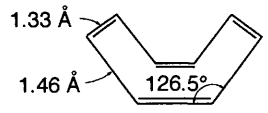
The resonance theory was extended to conjugated organic molecules in 1933, appearing in the last three of Pauling's seven papers on the nature of the chemical bond. Thereafter the theory of resonance in organic chemistry was developed mainly by his coworker, George Wheland at Caltech and then at the University of Chicago, who published two books on the subject (1944 and 1955). The application of resonance theory to conjugated organic molecules highlighted the wide latitude in the choice of hypothetical 'valence structures' contributing to the ground state of a given molecule. Pauling's approximation of the VB method gave benzene a theoretical resonance energy of 0.9 J for the two Kekulé structures alone, but of 1.1 J with the inclusion of the three Dewar structures, each with an elongated transannular bond between opposite positions. The empirical 'exchange integral' J, calibrated from thermochemical data, had a value dependent on the range of resonating structures considered. Pauling formulated rules limiting the choice of 'valence structures' to a 'canonical set', but the choice remained wide for polycyclic aromatic hydrocarbons. The stage at which to truncate the series of possible 'valence structures', judged by chemical intuition, was popularly termed the 'Pauling point' by students of chemistry in the 1940s.



A molecular orbital theory of conjugated organic molecules with much less latitude had been proposed in 1931 by Erich Hückel (1896–1980), a physicist at Stuttgart, who had been a coworker with Debye at Zürich, deriving the Debye–Hückel theory of strong electrolytes in 1923. Hückel divided the electrons of a conjugated molecule such as benzene into two distinct sets, later termed the σ and the π electrons. The molecular plane is defined by the framework of carbon–carbon σ-bonds, formed from sp^2 orbitals, while the π-electrons move over the framework in MOs nodal in the plane. Hückel showed that cyclic polyenes with $[4n + 2]$ π-electrons, where n is an integer, had a substantial additional stabilisation from the π-electron delocalisation, but not those with $[4n]$ π-electrons.

Pauling pointed out that two Kekulé-like valence structures could be written for cyclobutadiene and for cyclooctatetraene, which belong to the $[4n]$ series, and resonance between the two structures is expected to stabilise these molecules by a resonance energy comparable to that of benzene in the $[4n + 2]$ series. Richard Willstätter (1872–1942) at Munich had synthesised cyclooctatetraene in 1905 and in 1911. He found the substance to be olefinic in its properties, with none of the aromaticity predicted from a theory of partial valencies linking conjugated carbon–carbon double bonds, proposed in 1899 by his colleague Friedrich Thiele (1865–1918). Following the same prediction made by Pauling in 1935, groups of organic chemists from 1939 to 1943 at several American universities, Minnesota, Princeton, Northwestern and Purdue, attempted to synthesise cyclooctatetraene, but without success, on the supposition that Willstätter had inadvertently prepared the isomer styrene.

Willstätter, by now a refugee in Switzerland from the third Reich, heard of these efforts and commented in this autobiography that the American chemists appeared to be 'untroubled' by his reports of the reduction of his cyclooctatetraene to cyclooctane and its oxidation to suberic acid. Willstätter's synthesis of cyclooctatetraene was finally reproduced in 1947, after an Anglo–American scientific commission in 1945 discovered kilogram quantities of cyclooctatetraene in the IG Farbenindustrie laboratories at Ludwigshafen, prepared by Walter Reppe (1892–1969) by polymerising acetylene over a nickel(II) cyanide catalyst.[20] Cyclooctatetraene was shown by electron diffraction (1948) to have a tub-shaped structure: the dianion with 10 π-electrons, following the Hückel rule for aromaticity, was later found to be planar.



Cyclooctatetraene

By the late 1930s Pauling's interest had shifted to structural problems in biological chemistry, and he made relatively few positive contributions to the new problems of chemical bonding in mainstream chemistry during the postwar period. His book *The Nature of the Chemical Bond* remained conceptually unchanged between the first two editions (1939, 1940) and the third (1960). The new and intellectually inspiring book of the 1940s became a classical inorganic text of the 1960s.

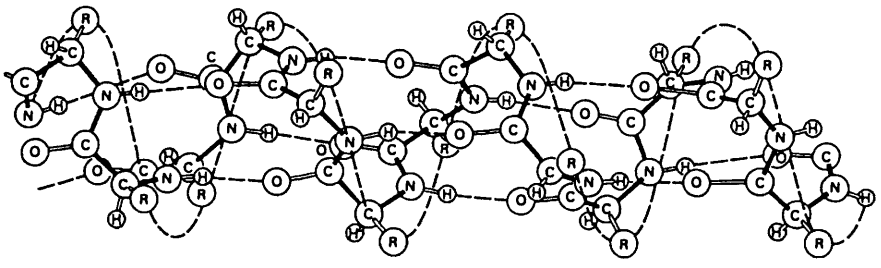
3 Biological chemistry

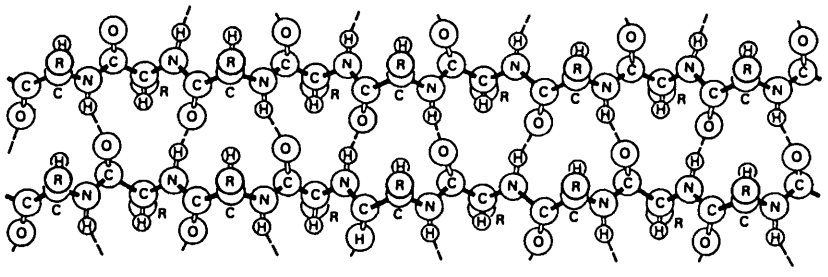
In 1931, Pauling introduced a magnetic criterion of bond type for transition metal coordination compounds, together with hybrid atomic orbitals for stereochemically defined bonding. In the 'ionic' complexes of the transition metals all five of the d-orbitals were available for occupation by unpaired d-electrons with parallel spins, whereas in the corresponding 'covalent' complexes one or two of the d-orbitals were unavailable, being employed in square-planar or octahedral hybrid formation. Accordingly, for a number of d-electron configurations, measurements of the magnetic moment arising from spin-parallel d-electrons distinguish the 'ionic' from the 'covalent' complexes of a given transition metal ion.

Magnetochemical measurements directed by Pauling at Caltech in 1935 showed that the iron(II) complex haemoglobin of red blood cells had four parallel-spin electrons per haem unit, corresponding to an ionic complex of ferrous iron (with the d^6 configuration). The addition of either carbon monoxide or oxygen produces a covalent complex, with all electrons spin-paired. This is a remarkable result for oxyhaemoglobin, since a molecule of free oxygen carries two unpaired electrons. The electronic structures of both the haem and the oxygen are profoundly reorganised on binding. Thereafter Pauling and his coworkers investigated further types of haemoglobin derivatives, and those of related biomolecules, myoglobin, haemocyanin, and the cytochromes, moving on to the problem of the chain-folding of the globulins and other proteins.

Pauling and the biochemist Alfred Mirsky (1900–1974) suggested in 1936 that the relatively weak forces of hydrogen-bonding between polypeptide chains determine the folding of protein chains. Protein solutions are denatured by heat, which breaks the weak hydrogen bonds, or by hydrogen-bonding substances, such as urea or ethanol, which compete for the protein inner-binding sites. For explorations of the secondary structure of proteins, Pauling adopted the strategy of constructing models of the likely folding in polypeptide chains, since the direct X-ray diffraction analysis of protein crystals in detail presented insuperable technical problems in the 1930s. The known bond-lengths and angles for the amide groups in polypeptides were not adequate for his purpose, and Pauling turned to X-ray structural studies of the small 'building block' units of proteins. In 1937 Robert Corey (1897–1971) transferred from the structural unit at the Rockefeller Institute to Caltech, where he took up the X-ray crystal analysis of the structures of amino acids and small peptides. During 1938, Corey reported the first detailed structure of a peptide, the cyclic dimer of glycine, diketopiperazine, and over the following years he and his coworkers determined the structures of glycine, other amino acids, and small peptides.

The acccumulated structural data enabled Corey and Pauling to formulate conditions for stable folded conformations of polypeptide chains: planar amide groups, with specific bond lengths and bond angles internally and externally. Pauling returned to model-building and, while he was George Eastman visiting professor at Oxford in 1948, he worked out the α-helix rod-like conformation of polypeptide chains, with 3.7 peptide residues per turn of the helix. Each amide group is hydrogen bonded $>C{=}O\cdots H{-}N<$ to the third residue from it in each direction along the chain. On this return to Pasadena, Pauling worked out the details with Corey, and they devised additional stable polypeptide conformations. Pauling and Corey reported the α-helix conformation in 1950, and the parallel and antiparallel β-pleated sheet conformations of polypeptide chains in the following year.


Poly-L-peptide α-helix


Poly-L-peptide β-sheet

Members of the Medical Research Council (MRC) X-ray crystallography unit in the Cavendish laboratory at Cambridge had expected on good, but limited, X-ray data that a helical protein conformation would contain four peptide residues per turn, and looked for distinguishing evidence. Max Perutz, in 1951, worked out the X-ray reflections required for the α-helix conformation, and observed them in the diffraction pattern of fibrous proteins and a synthetic L-polypeptide. The introduction of the electronic computer to X-ray diffraction analysis provided direct evidence for the prevalence of the α-helix structure in native globular proteins, first in myoglobin, solved at a near-atomic resolution by John Kendrew at Cambridge in 1960, and then in haemoglobin, four times larger than myoglobin, finally solved by Perutz two years later.

The stable β-sheet protein conformation derived by Pauling and Corey was confirmed in 1965 by David Phillips and his associates at the Royal Institution, London, by the X-ray structural analysis of the enzyme, lysozyme, from egg-white. The Royal Institution group reported the X-ray structure of lysozyme complexed with a trisaccharide fragment of its physiological substrate, a hexasaccharide unit of the polysaccharide chain in a bacterial cell wall. The report supported not only the β-sheet conformation, but also Pauling's development of the 'key and lock' hypothesis of enzyme–substrate interaction, first proposed by Emil Fischer (1852–1919) in 1894. J. B. S. Haldane (1892–1964) suggested in 1930 that a degree of misfit between the enzyme and its substrate is needed to drive the chemical reaction forward: 'Using Fischer's lock and key simile, the key does not fit the lock perfectly but exercises a certain strain on it'. In 1946 Pauling pointed out that, since enzyme reactions are reversible, there is a comparable steric misfit between the enzyme and the product, so that the complementarity of the stereochemical matching is an optimum for the transition state common to the forward and the reverse reaction, accelerating both processes.[21]

Pauling developed and applied the concept of complementary structural matching in biomolecular interactions after discussions from 1936 with the immunologist Karl Landsteiner (1868–1943). Landsteiner, a native of Vienna, had characterised the four main blood groups. A, B, AB and O, in 1909. He emigrated in 1923 to work at the Rockefeller Institute for Medical Research, discovering the blood-cell rhesus factor in 1940. The research on haemoglobin at Caltech interested Landsteiner, who encouraged Pauling to examine antibody–antigen interactions from a structural point of view. Paul Ehrlich (1854–1915), who had worked with Emil Fischer, regarded the specificity of the toxin–antitoxin and the antibody–antigen interaction as further examples of Fischer's 'key and lock' hypothesis. The work of Ehrlich established this hypothesis in immunological theory, in which a principal concern became the mechanism whereby the animal body produces the range of individually specific antibodies to combat the enormous variety of antigens to which the body is prey. In 1940, Pauling proposed that polypeptide chains fold and wind around the exterior of the antigen structure, serving as a template. The product is a close-fitting complementary antibody structure, which neutralises the toxic surface features of the antigen *in vivo*, and precipitates the antigen–antibody complex *in vitro*.[22] Pauling directed an experimental programme at Caltech on the serologial properties of simple substances throughout the 1940s. Like other template theories of the time, Pauling's hypothesis failed to account for the transmission of specific antibody formation to daughter cells from the parent cell challenged by a particular antigen.[23]

The theoretical physicist, Pascual Jordan (1902–1980) at Rostock, proposed in 1940 that the injection of an antigen into an animal body led to the natural selection of proto-antibody molecules of like kind, through the quantum-mechanical resonance force between like molecules, from a varied set of proto-antibody molecules maintained by the animal. The complex formation was autocatalytic and led to the proliferation of antibodies specific for the antigen. Pauling was critical of this view, and of Jordan's earlier (1938) analogous conjecture that the duplication of the gene and the pairing of chromosomes were dependent upon an attractive quantum resonance force which was especially strong between identical or near-identical molecules. With the biophysicist Max Delbrück (1960–1981), Pauling in 1940, argued that the autocatalysis of gene replication is expected to involve complementary rather than identical structures. During his visit to Britain in 1948, Pauling depicted the gene as two congruent templates with complementary structures, each to 'serve as the mould for the production of a replica of the other part, and the complex of the two complementary parts thus can serve as the mould for the production of duplicates of itself'.[24]

Pauling made no use of his concept of the gene as paired templates with structural complementarity in constructing his model for DNA in 1953; with other protein chemists, he was not yet convinced that DNA alone was the primary genetic substance. The twenty natural amino acids appeared to offer far more diversity by permutation and combination than the four nucleic acid bases. With hindsight, the 1944 work of Oswald Avery (1877–1955) and his associates at the Rockefeller Institute Hospital, showing that the substance transforming the non-virulent pneumococcus to the virulent form was purely DNA, is generally regarded as the first definitive evidence that the genetic material consists of DNA. Avery himself made this claim, against the opposition for several years of protein chemists such as his colleague Alfred Mirsky at the Rockefeller.[25] Pauling's model for DNA, three polynucleotide chains coiled helically around an internal core of hydrogen-bonded phosphate groups, was flawed from the outset by the assumption that the P–O–H groups (pK_a *ca.* 2) remain undissociated under physiological conditions (pH *ca.* 7) to provide the hydrogen bonding. It was left to Francis Crick and James Watson in 1953 to combine Pauling's method of model building and his conjecture that the genetic material consisted of paired complementary structures, with the view that DNA was indeed the genetic substance, to construct the successful double-helix model of DNA with antiparallel complementary strands.

One of Pauling's coworkers at Pasadena, Harvey Itano, working on the electrophoresis of haemoglobins found in 1949 that the haemoglobin from patients suffering from sickle-cell anaemia carries a charge less negative than that of normal haemoglobin. Individuals carrying the sickle-cell trait had haemoglobins of both charge types in comparable quantities. These individuals were the heterozygotes with paired genes, one for normal and the other for sickle-cell haemoglobin, affording some protection against the malaria parasite. Pauling and Itano termed sickle-cell anaemia a 'molecular disease', arising from a mutation in the protein moiety of haemoglobin which changed an acidic amino acid of a polypeptide chain to a neutral or basic type. Bulk analysis of the animo acid composition of the two types of haemoglobin protein showed only that any difference was too small to be detected by this method.

Similarly, Perutz at Cambridge detected no difference in the X-ray diffraction pattern of the two types of haemoglobin. His colleague in the MRC unit, Vernon Ingram, adopted for the haemoglobins the methods used by the Cambridge biochemist, Frederick Sanger, to determine the amino acid sequences of the two polypeptide chains of insulin, completed in 1955. Ingram in 1956 digested normal and sickle-cell haemoglobin with the enzyme trypsin, which specifically cleaves polypeptide chains on one side of a lysine or an arginine position, to obtain some thirty fragments about ten units in each case. Separation by paper chromatography and electrophoresis showed that the fragments from normal and sickle-cell haemoglobin matched one-to-one in all but one case. Subsequent sequencing of the two non-matching fragments demonstrated that an acidic glutamate residue in the fragment from normal haemoglobin had been replaced by a neutral valine residue in the sickle-cell haemoglobin fragment.

The technique of trypsin cleavage of proteins, and the characterisation of the oligopeptides formed, was taken up widely from the late-1950s. Pauling's group at Pasadena analysed the trypsin oligopeptide pattern of the haemoglobins from a number of animals in 1960, with the view of tracing genetic descent and evolution at the molecular level. In 1962 and 1965 Pauling and Zuckerkandl[26] compared the amino acid sequences of haemoglobin proteins available from a variety of species with the fossil record to construct a 'molecular evolutionary clock', calibrated to an average of one amino acid mutational change per polypeptide chain every seven million years.

Each present-day protein, it was assumed, embodies its own evolutionary history. They correlated changes in homologous polypeptide chains, due to amino acid substitutions, with the dates at which each of the species emerged in the fossil sequence, to obtain three types of evolutionary information: first, the probable amino acid sequence of the ancestral polypeptide from which the chains compared had been derived; second, the approximate epoch at which the divergence had begun; and third, the lines of descent of the changes in the amino acid sequences. Thus the α- and the β-chains of the human haemoglobin tetramer ($\alpha_2\beta_2$), show 78 amino acid differences, so that the two chains diverged from a common origin, by gene duplication, some 565 million years ago, around the beginning of the Cambrian period. The common origin, the single chain of a monomeric haemoglobin, has a modern representative in the blood of primitive jawless fishes, such as the lamprey and the hagfish. This monomer lacks the cooperative oxygen uptake and release that evolved with the haemoglobin tetramer.

After some initial scepticism, the concept of the molecular evolutionary clock and the method of comparing homologous polypeptide sequences were widely adopted for the construction of genealogical trees of organic descent. As amino acid replacements in a protein are the tertiary product of nucleotide substitutions in DNA, through transcription and translation, more detailed evolutionary information became available from comparisons of homologous nucleotide sequences, after the characterisation of the genetic code during the mid-1960s. The degeneracy of the code indicated that approximately one-third of the primary mutations in coding DNA result in no change of the amino acid residues in the polypeptide coded. Consideration of these synonymous DNA mutations, 'silent' at the tertiary protein level, established that biomolecular evolution depends upon the flow of time, the number of elapsed years, rather than the number of successive organic generations. The pioneering innovations of Pauling in the study of biomolecular phylogeny were recognised in 1969 by Kimura,[27] who proposed '*the pauling*' as the term for the standard 'molecular evolutionary unit' of 10^{-9} amino acid substitutions for each protein site per year.

By the 1990s, Pauling had come to be regarded as a principal founder of molecular biology, for the range and impact of his contributions to the subject.[28]

4 International peace and global fallout

Pauling subscribed to a long-established radical tradition, directed to the benefit of human kind at large through the advance of science and its application to social and technical problems. the 'Luther of medicine', Paracelsus (1493–1541), strove to transform the wealth-seeking metallurgical alchemy of earlier times into a new iatrochemistry with more humanitarian medical aims, securing a substantial following among the apothecaries and religious nonconformists of the seventeenth century. Iatrochemistry evolved with van Helmont (1579–1644) into pneumatic chemistry, to which the Unitarian minister, Joseph Priestley (1733–1804), made spectacular contributions. Priestley's attempts at social and religous reform met with such crude and irrational reaction, the torching of his manse, laboratory and library in Birmingham, that he felt obliged to emigrate to the newly independent United States of America in 1794.

Like Joseph Priestley, Linus Pauling was gifted with a fertile scientific imagination and worked largely by chemical intuition, regarding mathematics as the handmaiden rather than the queen of the sciences. Both adhered to the concepts of their youth long after these ideas ceased to be productive, Priestley to the phlogiston theory, Pauling to his resonance theory of chemical bonding. Both addressed social questions of concern to humanity at large, so attracting charges of disloyalty from some politicians of the time. Pauling chose as an epigraph for this *General Chemistry* (1957) and his *College Chemistry* (1964) an excerpt of a latter from Benjamin Franklin to Joseph Priestley, written in 1780, rejoicing in the progress of the natural sciences, with the lament, 'O that moral Science were in as fair a way of improvement'.

Linus Pauling and his wife, Ava Helen Miller (d. 1981), a fellow student at Oregon Agricultural College, whom he had taught in 1922 and married in the following year, supported Roosevelt's New Deal, widely opposed as socialist paternalism in Republican California. After the fall of France early in 1940 they joined the Union Now movement for a federation of the world democracies under US leadership against totalitarianism. In 1941 Pauling fell victim to Bright's disease, often considered incurable at that time, but he gradually recovered on a low-protein, salt-free diet, allowing his damaged kidneys to heal. Within a year he was back at Caltech, engaged on military research into new forms of rocket propellants, the growth of synthetic quartz for sighting optics, the development of a synthetic blood plasma, and an instrument for measuring oxygen levels in confined spaces, as in aircraft or submarines, based on the paramagnetism of oxygen. Truman in 1948 awarded Pauling the Presidential Medal of Merit, the highest US civilian award, for his war-time projects.

In 1946 Pauling joined the Emergency committee of Atomic Scientists, chaired by Albert Einstein (1879–1955), set up to inform the public of the realities and the consequences of the development of nuclear weapons. In his public lectures on atomic weaponry Pauling called for negotiations to solve all Cold War issues peacefully. President Truman introduced the loyalty oath for all federal employees in 1947, to weed out Communists and their associates, and the peace movement was soon labelled 'The Communist Peace Effort' by Senator Joe McCarthy and his followers. As President of the American Chemical Society in 1949, Pauling strongly criticised the denial of an academic career to talented young American scientists who were alleged to have present or past Communist associations, including his own former students. The FBI-funded informer, Luis Budenz, required to produce new names, denounced Pauling as a Communist in 1950 and in 1952, and his evidence was dismissed as hearsay gossip only in 1970.

Pauling preempted summonses from state and federal un-American activities committees in 1950 by a public declaration, lodged with the President of Caltech, that he was a Rooseveltian Democrat, and was not, nor ever had been a Communist, and that he had no objections to legitimate loyalty oaths, genuinely grounded on national security. Despite Pauling's affirmations of loyalty, he was denied a US passport in 1952 when he was invited to speak on his new polypeptide conformations at a Royal Society Discussion on Proteins in London. In response he organised his own protein research conference at Pasadena in 1953, but the British pioneer of protein X-ray crystallography, Dorothy Crowfoot Hodgkin (1910–1994), was denied a US visa to attend the conference. Fearing an even greater international protest than that of 1952, the US State Department restored Pauling's passport for unrestricted travel in late 1954, shortly before the ceremony in Stockholm awarding him a Nobel Prize 'for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances'.

McCarthyite hysteria during this period was such that Patrick Blackett (1897–1974), the former coworker of Rutherford and a future President of the Royal Society, was denited entry to the USA following the critical analysis of his book, *Military and Political Consequences of Atomic Energy* (1948), which exposed the fallacies of those who 'thought the unthinkable', and who advocated preemptive atomic bombing of the Soviet Union. Blackett was then arrested when an intended overflight from Mexico to Canada had to make a refuelling stop in the USA.[29] Counter hysteria in the Soviet Union extended to denunciations of all things American, including Pauling's resonance theory of the chemical bond over the years 1949–1952.[30] The 'valence structures' contributing to a given 'resonance hybrid' were denounced as 'idealistic' and 'wholly imaginary', rehearsing the criticisms made in western Europe by a brother of the MO theorist, the chemist Walter Hückel (1895–1973), and by his English translator.[31]

Pauling responded in 1957 at an international biochemistry meeting in Moscow, and again in 1961 at the Moscow celebrations of the 250th anniversary of the birth of the pioneer chemist Lomonosov (1711–1765),[32] giving a dozen or so lectures on the achievements of the 'corrupt' resonance theory of chemical bonding, on inherited molecular diseases and the underlying molecular mechanisms of Mendelian genetics, a productive science in contrast to unfruitful Lysenkoism, and on the global dangers of radioactive fallout from nuclear weapon testing, emphasising the outstanding need for negiotiated international peace. The criticisms of the 'Ingold–Paulingites' soon faded away in the Soviet Union, but they resurfaced briefly in Britain in 1976,[33] provoking Pauling's spirited defence, with a recapitulation of the history of resonance theory in quantum mechanics and in chemistry.[34]

After the award of his first Nobel Prize, Pauling promoted more actively the campaign to halt the further testing of nuclear weapons, particularly when Japanese radiochemists showed, from the isotopic composition of its exceptionally heavy fallout, that the US Bikini Atoll test of 1954 involved a new fission–fusion–fission device, a hydrogen bomb encased in a shell of uranium-238 (the U-bomb). Pauling subscribed to the manifesto drawn up by Einstein and Bertrand Russell in 1955, calling on the governments of the world to find peaceful means to settle all matters of dispute between them, and contributed to the ensuing Pugwash Conferences. These conferences took their name from the first meeting place, the Pugwash estate in Nova Scotia of the first sponsor, Cyrus Eaton, a Cleveland industrialist. Among those present were the vice-president of the Soviet Academy of Sciences, a former director-general of the World Health Organisation, and three Nobel Laureates.

In all controversy, Pauling was an assiduous collector of precise data as a basis for secure conclusions. Much of the data on the local radioactive fallout from the atomic bombs dropped on Hiroshima and Nagasaki in 1945 were in the public domain, but less was known of the radioactive products from atmospheric tests of the later H-bomb and U-bomb. In the mid-1950s it emerged that each test produced a substantial pulse of radioactive carbon-14 from the transmutation of atmospheric nitrogen, as well as dust fallout. The carbon-14, with a halflife of some 5600 years, dispersed globally as carbon dioxide, entering the food chain to produce additional mutations in all plant and animal life.

Willard Libby (1908–1980), who was a member of the US Atomic Energy Commission, and received the 1960 Nobel Prize in chemistry for his invention of the carbon-14 dating method, estimated that the carbon-14 produced in atmospheric nuclear tests was an unimportant hazard compared to the carbon-14 generated by cosmic rays. Pauling used Libby's own data to show the enormity of the new hazard. Over the period of the next scheduled series of atmospheric nuclear tests, the additional mutations, due to the carbon-14 generated, would be responsible for 500,0000 more miscarriages, 55000 more children born with gross physical and mental defects, and as much leukaemia and bone cancer as had been generated by the fission products of all the previous nuclear tests combined.

After his lecture on the global ecological consequences of nuclear weapons tests at Washington University, St Louis, in 1957, Pauling was joined by the biologist, Barry Commoner, and the quantum theorist of atomic spectroscopy, Edward Condon. They set up a petition to all nations from scientists worldwide, calling for an end to the testing of nuclear explosives. Commoner had measured the level of radioactive strontium-90 from fallout in the milk teeth of children across North America, and Condon had been a prominent target of unAmerican activities for many years, being obliged to resign as Director of the National Bureau of Standards in 1951.[35] During 1958, Pauling sent a copy of the petition opposing nuclear weapon testing, with endorsements by 11021 scientists from 49 countries, to Dag Hammarskjöld, the Secretary General of the United Nations Organisation in New York. The signatories included 2705 American scientists, 40 of them members of the US National Academy of Sciences, 216 members of the Soviet Academy of Sciences, 35 Fellows of the Royal Society of London, and 36 Nobel Laureates. Pauling enlarged on this theme in his 1958 book *No More War*! with an appeal for the peaceful settlement of political differences by negotiation.

Public opinion worldwide led the nuclear powers to schedule test-ban negotiations in Geneva for late 1958. In the meantime 63 nuclear devices, one third of the total since 1945, were tested in the ten months before the talks. A moratorium on nuclear weapon testing was agreed at the end of 1958 by the USA, the UK and the USSR, but not by France. When the French tested their first atomic bomb in the Sahara desert in 1960, Khrushchev announced the end of the voluntary test-ban agreement, and a large Soviet nuclear bomb was tested in 1961 on the island of Novaya Zemlya. The 1961 test was opposed by Andrei Sakharov (1921–1989), the 'father of the Soviet hydrogen bomb', who advised Khrushchev that a global agreement could probably be reached to confine tests to deep underground sites, even though an absolute ban internationally on all nuclear weapon tests was unrealistic, as shown by the French action. This would avoid the ecological hazards of radioactive fallout and the addition of further carbon-14 to the atmosphere worldwide.[36]

Khrushchev was persuaded, and in 1963 the partial test-ban treaty was agreed with President Kennedy and Prime Minister MacMillan banning nuclear weapon testing in the atmosphere, the oceans, and in outer space. On the day that the treaty came into force, the Norwegian Committee responsible for the Nobel Peace Prize awarded the Peace Prize deferred from 1962 to Pauling. Sakharov received the 1975 Peace Prize when his influence upon Soviet policy and his liberal humanism became generally known. By that time Sakharov's social manifesto *Reflections on Progress, Coexistence and Intellectual Freedom* (London, 1968) had been translated into English from the *samizdat* circulating in the Soviet Union, calling for tolerance, openness, and purely peaceful competition between the USA and the USSR. The publication led to Sakharov's loss of Soviet security clearance and his transfer to the Lebedev Physics Institute in Moscow, where he had devised the magnetic thermonuclear reactor, the tokomak, in 1950. Following the award of a Nobel Peace Prize and his opposition to the war in Afghanistan, Sakharov was exiled to Gorki (Nizhniy Novgorod) 1980–1986, but kept his post at the Lebedev Institute and was often visited by colleagues.

Pauling was harassed to a degree after presenting the collectively signed petition opposed to nuclear weapon testing to the United Nations in 1958, and his Nobel Peace Prize in 1963. He was ordered to appear before the Senate Internal Security Subcommittee, which termed him 'the number one scientific name in virtually every major activity of the Communist peace offensive in this country'. The Committee questioned the authenticity of some of the 11021 signatures of scientists endorsing the petition, and enquired into the source of

the funding employed in their collection, alleged to run to some $100 000. The Committee compared their own list of signatures with the originals produced by Pauling. He declared the costs of the collection to be some $250 for the postage stamps of mailings from his home address to scientific colleagues overseas, who obtained an average of 15 signatures each. An extraordinary headline in *Life* Magazine, 'A Weird Insult from Norway', greeted the award of the Nobel Peace Prize to Pauling. The editorial declared that the limited test-ban treaty had nothing whatsoever do do with Pauling's 1958 petition to the UN from scientists worldwide.[37]

At Caltech the President, Lee DuBridge, under pressure from the Trustees, asked Pauling in 1958 to resign as Chairman of the Division of Chemistry and Chemical Engineering, a post he had held for twenty-two years. Although Pauling had professorial tenure, his salary was frozen, and the area of his laboratory space was progressively eroded. Even his Nobel Peace Prize in 1963 met with a chilly response at Caltech. President DuBridge decleared 'there is much difference of opinion about the value of the work Professor Pauling has been doing' for world peace and averting nuclear war. Pauling thereupon resigned from his chair at Caltech, in his sixty-third year. Pauling also resigned from the American Chemical Society in 1963, when the Board of Directors declined to withdraw (what he considered to be) misrepresentations in *Chemical & Engineering News* of his campaign for the banning of nuclear-weapon tests.

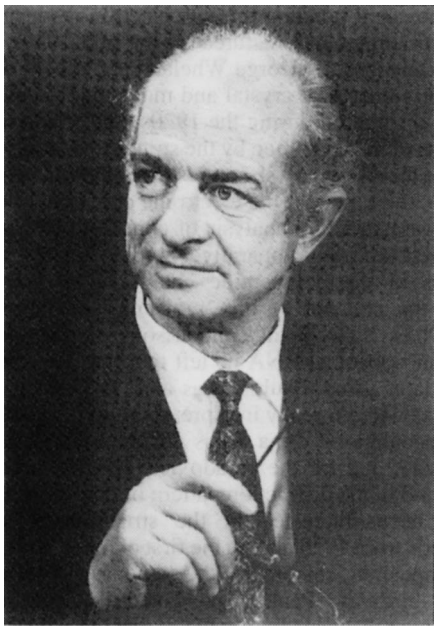


Fig. 2 Linus Pauling in later life (courtesy of the Royal Society of Chemistry Library and Information Centre)

5 Molecular medicine

After resigning from Caltech, Pauling accepted a position 1964–1967 at the Santa Barbara Center for the Study of Democratic Institutions. The Center had no laboratories, being devoted to the social sciences, and Pauling turned to theoretical studies of atomic nuclei and to evolutionary and medical issues arising from his earlier work in biological chemistry. He developed a close-pack spheron theory of nuclear properties, but physicists were unimpressed and he soon abandoned this field. Since his interests in biological and medical chemistry required access to laboratory facilities, he moved on to the University of California at San Diego 1967–1969, and then the University of Stanford 1969–1974. A network of supporters organised the funding and maintenance 1974–1994 of his own centre, the Linus Pauling Institute of Science and Medicine, at Palo Alto, California.

Pauling's concerns with medical chemistry dated back to his early studies of haemoglobins. He had close contacts with the biologists at Caltech, particularly the geneticists studying the mutations produced by X-rays in the fruitfly, then in a simpler organism, the pink bread mould *Neurospora crassa*. George Beadle (1903–1989) and Edward Tatum (1909–1975) traced out the biosynthetic pathways in *Neurospora* by generating mutants which could no longer produce an intermediate substance in a given metabolic sequence, and so required the addition of that substance for normal growth. Their studies from 1941 created the new field of biochemical genetics, with the slogan 'one gene–one enzyme'.

The work, recognised by the award of the 1958 Nobel Prize for medicine or physiology to Beadle, Tatum and Joshua Lederberg, drew attention to the long-neglected medical studies of Archibald Garrod (1857–1936) at St. Bartholomew's Hospital, London. Garrod investigated rare inherited diseases running in families, such as the production of black urine (alcaptonuria) and analogous disorders. Garrod in his book, *Inborn Errors of Metabolism* (1909, 1923) ascribed such diseases to a genetic error of recessive Mendelian character, leading to the loss or malfunction of an enzyme essential for a particular step in normal metabolism.

Pauling drew on the new field of biochemical genetics for his characterisation of inherited haemoglobin abnormalities as molecular diseases. He developed the view that the human nutritional needs for the vitamins, due to the genetic loss of stages in common metabolic pathways, were not always met by normal foodstuffs, and often required augmentation. The loss of a capacity to manufacture essential biomolecules, available from foodstuffs, had lightened the overall biosynthetic load, giving the affected organisms an advantage in natural selection. Thus, organisms had developed the biosynthesis of ascorbic acid, vitamin C, as an anti-oxidant when photosynthetic oxygen began to appear in the atmosphere. Some 25 million years ago the common ancestor of the hominids and other primate species lost the liver enzyme converting L-gulonolactone to ascorbic acid, following a genetic mutation. Other mammalian species, except for the guinea pig and a fruit-eating bat, retained vitamin C biosynthesis, as did most of the vertebrate species.

The loss of vitamin C biosynthesis had little adverse affect on the early development of humankind, judging from the skeletons of palaeolithic hunter–gatherers, who appear to have been as large and well-built as modern Americans. Following the development of agriculture, and the early urban civilisations, the human diet was based largely on grains, which produced small and stunted people, judging again by their skeletal remains. From the 16th century on, the long voyages of geographical exploration, and then of overseas trade and colonisation, promoted the deficiency disease of scurvy, alleviated by the addition of citrus fruit juice to the diet. Early 20th century studies of such deficiency diseases resulted in the discovery of the vitamins and their biochemical role in normal human metabolism.

Pauling noted that many people in modern urban societies live close to the edge of vitamin deficiency. The National Research Council under the US National Academy of Sciences has a Committee on the Feeding of Laboratory Animals, and a Food and Nutrition Board concerned with human diet. The Committee recommends an optimum daily intake of vitamin C (ascorbic acid) for laboratory primates, between 1.75 grams per day for rhesus monkeys and 3.50 grams per day for squirrel monkeys, scaled to 70 kg body mass. The Nutrition Board, however, recommends a human allowance of only 60 milligrams per day, corresponding to the minimum human intake of vitamin C required to avoid scurvy. Animals which manufacture their own ascorbic acid produce an average of *ca.* 10 g per day, scaled to 70 kg body mass. Pauling deduced that the

diet of an adult human should contain at least 2.3 to 10 g of vitamin C per day.

The human immune system depends for efficient action on the vitamin level available in its several components, and some of these levels are depleted during a viral attack. The common cold virus reduces by one half the vitamin C level in leucocytes, impairing their action as phagocyctes. A regular daily intake of 0.25 to 4 g of the vitamin decreases the chances of catching a cold or influenza and of developing a secondary bacterial infection. Some 16 trails, with placebo-taking controls, showed a decrease in illness of 34% on average, even though the daily dose of vitamin C administered, 0.07 to *ca.* 1 g, was smaller than the dose Pauling recommended. Pauling found that the habitual colds from which he suffered were reduced in number and severity by taking several grams of vitamin C each day from the mid-1960s, as described in his book, *Vitamin C and the Common Cold* (1970), which enjoyed wide popular appeal. By the 1990s substantial support had emerged for a reduction of the severity, if not the frequency, of common colds by vitamin C administration.

The medical profession in general dismissed Pauling's work, but individual physicians had made similar or related trials and reported their experience to him. In 1971, Pauling heard from Ewan Cameron, surgeon of the Vale of Levan Hospital near Glasgow, who had treated terminal cancer patients with 10 g of vitamin C a day over several years, finding that the treatment extended the survival time and the quality of life of his patients. Cameron held that vitamin C reinforced connective tissues that were weakened in cancer as in scurvy. Collaboration followed, with trials of vitamin C for the treatment of animal cancer at Pauling's Institute, and the visit of Cameron for a year in 1978, resulting in a joint publication of the book, *Cancer and Vitamin C* (1979). The US National Cancer Institute (NCI) sponsored trials in the 1970s which reported no benefit to cancer patients from large doses of vitamin C. Pauling pointed out that Cameron's protocol had not been adopted in these trials. By 1990, the NCI was more sympathetic, and sponsored an international symposium on 'Vitamin C and Cancer' with Pauling as a main speaker. The symposium, and a New York Academy of Sciences meeting in 1992, brought to light the general role of vitamin C and vitamin E as antioxidants, quenching the free radicals implicated in the genesis of cancer and other maladies.[38]

In his last book, *How to Live Longer and Feel Better* (1986), Pauling summarised the evidence and outlined the potential of his 'orthomolecular medicine'. His therapy involved the boosting of normal essential metabolites to an optimum level, usually higher during illness than in normal health. These substances are generally limited in supply from foodstuffs or commensal gut flora, and have a wide range of beneficial functions and of tolerance in the body. In contrast conventional medicine involved the administration of physiologically alien natural or synthetic pharmaceutical products, with specific therapeutic effects, undesirable side-effects, and often-limited tolerance. His approach led Pauling to support and popularise medical reports of the value of vitamin treatments of viral and cardiovascular diseases, cancer, some forms of mental retardation or mental disorder, allergies, arthritis and rheumatism, and the moderation of the infirmities of old age.

Pauling attracted the support of physicians in the Orthomolecular Medical Association, which numbered some 500 members by 1986. Albert Szent-Györgyi (1893–1986), who had first isolated ascorbic acid in 1928, receiving the 1937 Nobel Prize in medicine and physiology for his discovery of the biochemical dicarboxylic-acid oxidation cycle, joined the crusade for vitamin C supplementation, as did other biochemists. Szent-Györgyi wrote in 1970 that the medical profession misled the public by specifying only the ascorbic acid intake required to avoid scurvy, which he called 'a premortal syndrome'. The optimum vitamin C intake was uncertain, but Szent–Györgyi considered it to be much higher than the medical recommendation, and he himself took about a gram a day. Pauling allowed for biochemical individuality, recommending his readers to discover their own optimum daily intake of vitamin C, which he thought probably lay between 6 and 18 g. He specified a daily supplementation of other vitamins and minerals, together with regular exercise and dietary moderation, particularly sucrose and alcohol, to promote a general regimen for longer life and better health.

6 Conclusions

Pauling's remarkable achievements came from his fecundity of imagination, the zealous collection of data to frame his theories, and a crusading spirit to popularise his conclusions. He confessed that many of his new ideas turned out to be non-productive. Examples from his troubled 1960s were his spheron theory of the atomic nucleus (1964–1967), or his theory of general anaesthesia (1961–1965). The latter theory illustrates Pauling's general approach of coordinating diverse studies of a common subject. From the discovery of the anaesthetic action of xenon, and the X-ray analysis of the clathrate hydrate crystals formed by the noble gases, Pauling surmised that anaesthetic action involved the formation of clathrate crystals in nervous tissue around the anaesthetic agent, thereby reducing the electrical activity of the nerves and the brain.

Clearly, he was extraordinarily versatile. He engaged in each of his highly productive enterprises for a decade or so, then left further development to others and took up new projects. His theories of atomic orbital hybridisation, atomic electronegativity, and covalent bonding through electron-resonance between valence structures, had matured by the mid-1930s, and he left further extensions to George Wheland and others. Pauling was one of the pioneers of crystal and molecular structure analysis by X-ray diffraction during the 1920s, and countered the early limitations of the technique by the strategy of model-building to determine the secondary structures of biopolymers from the late 1930s. By the time that the electronic computer allowed direct X-ray crystal structure analysis of complex molecules Pauling had moved on to comparative studies of the amino acid sequences in the polypeptide chains of the haemoglobins, deriving the concept of the 'molecular evolutionary clock' (1960–1965). Subsequent comparisons of the nucleotide sequences in ribosomal RNA he left to other workers.

In his later years, Pauling was alert to striking or puzzling discoveries with no ready interpretation. In the 1980s he joined in the speculations on a basis for high-temperature superconductivity, and for the paradoxical fivefold rotational symmetry found in the diffraction pattern of quasicrystalline alloys. He had been interested in the structure of intermetallic compounds from 1923 and, in the first of his contributions to the 1991 symposium, celebrating the centenary of Caltech and his ninetieth birthday, Pauling presented the evidence he had gathered over the years for the thesis that these quasicrystals are essentially icosahedral twinnings of cubic crystals with large unit cells.

At Caltech the disapproval of trustees and administrative officials of Pauling's political activities declined after his departure in 1963. Later trustees and officials appreciated that both of Pauling's Nobel Prizes enhanced the standing of Caltech. After a symposium in 1986 celebrating his eighty-fifth birthday, Caltech honoured him by instituting the Linus Pauling Professorship of Chemistry, together with a lecturehip and lecture hall bearing his name. His efforts to eliminate the global dangers of increased radioactivity in the biosphere from nuclear weapon tests, and his campaign for negotiated world peace, were increasingly appreciated over time, and he came to be regarded as the American scientist comparable to the Russian physicist, Andrei Sakharov, for humanitarian leadership of the scientific community worldwide during the chillier years of the cold war.

Historically, Pauling takes a place among the major figures in the development of modern chemistry, recapitulating some of

their contributions and social concerns at a new level. The supporters of his orthomolecular medicine reflect the Paracelsian iatrochemists, who merged with orthodox medicine, as their more successful innovations, such as the treatment of anaemia with iron salts, were generally adopted. Pauling's opposition to the contamination of the atmosphere with the radioactive products of nuclear weapon tests recalls Joseph Priestley's dismay, during the early phase of the industrial revolution, with the degradation of our atmosphere, the providential sustainer of the breath of life. Priestley's concern led him to introduce his nitric oxide test for 'the goodness of the air', then to discover the atmospheric component supporting vitality, oxygen (1774), and the property of green plants in sunlight to restore the oxygen lost from air 'spoiled' by respiration or combustion.

The influence of Pauling's resonance theory of chemical bonding from the 1930s to the 1950s was comparable to that of Berzelius's dualistic theory from the 1820s to the 1840s. Both theories, with the common concept of a universal scale of atomic electronegativities, appealed primarily to inorganic chemists. Theoretical physicists regarded both theories as primitive, relative to the current principles of physics, classical electrostatics in the 1820s and quantum electromagnetism in the 1930s. Each theory first lost ground in the organic field. During the 1830s, such discoveries as the replacement of electropositive hydrogen by electronegative chlorine in acetic acid to give products of a common vinegar-type cast doubts on the theory of dualistic electropolar chemical bonding. Likewise, the confirmation in the late-1940s that cyclooctatetraene is indeed an olefinic substance, with none of the aromatic properties of benzene, indicated that resonance theory of unsaturated organic molecules was flawed.

Pauling worked in so many different fields that he had no single contemporary peer in chemistry. Biochemistry, molecular biology, and geochemistry, he held, were all chemical sciences, alongside the mainstream subdivisions, and so too were the nutritional and pharmaceutical aspects of medicine. The range of his major contributions over these sciences mark him out as the greatest chemist of the century.[39]

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