

# La Química en el siglo XX y lo que nos depara el siglo XXI

## Organic Chemistry

### The Last 50 Years

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#### General

The first question the reader might ask "Why only organic chemistry?" and "why only the second half of the 20th century?" One answer is to say that I am an organic chemist and that, since my independent career started in 1948, I am a professional witness only to what happened in the second half of this century. But there are more cogent answers to the two questions. Were I to try to cover all of chemistry of the entire century with its many advances, for example in chemical instrumentation, this article would become entirely unwieldy. However, I shall allude to some of these advances and I shall include, under the banner of "organic chemistry", polymer chemistry, bioorganic chemistry and some aspects of medicinal chemistry. And to the extent that I need to refer to catalysis, organometallic chemistry will be drawn in as well.

As to the time period, it is an interesting fact that—after a very productive second half of the 19th century—the first half of the 20th century was a relatively quiet one for chemistry in general and organic chemistry in particular. This is not to say that nothing happened in that period—some important work was done especially in the structure of organic compounds (carbohydrates, steroids, terpenes, porphyrins, for example)—and there were also some very notable organic chemists especially in Germany and Switzerland, such as Richard Willstätter, Heinrich Wieland, Adolf Windaus, Hans Fischer, Walter Haworth, Paul Karrer, Richard Kuhn, Adolf Butenandt, Leopold Ruzicka, Robert Robinson, to mention only Chemistry Nobel Laureates in the group (see reference under "Nobel Prizes. Chemistry"). Some very significant discoveries in organic chemistry were made in this period: the discovery of the sulfur drugs for which Gerhard Domagk received the Nobel Prize in Physiology and Medicine in 1939,

the, though now controversial, discovery of the insecticidal properties of DDT by Paul Müller who received that prize in 1948 and the discovery of Nylon by Wallace Carothers. I shall, in fact, refer to some of this earlier history. Nonetheless progress in the first half of the 20th century with respect to fundamental science was much more important in physics—where it saw the birth of relativity and quantum theory and their rapid expansion—than in chemistry.

However, a discontinuous jump forward occurred at the end of World War II and I shall examine, at least briefly, the reasons for this sudden leap. One reason was that the second World War was to a considerable extent a technological war as evidenced, for example, by the impact of rockets, nuclear weapons and radar and, in the area of organic chemistry, rubber synthesis, antimalarial research and production of penicillin on a commercial scale. As the result of the thus perceived strategic importance of technology, combined with the "Cold War" which began almost immediately after World War II ended—the United States Government decided to invest large sums of money in scientific projects. Thanks to Vannevar Bush's report "Science the Endless Frontier" (Bush, 1945) some of that money went into basic (as distinct from mission-oriented) scientific research and led to a great flourishing in that area.

Secondly in the United States—which country became a leader in many areas of science after 1945—the so-called "GI Bill" had an enormous impact on the number of chemists and other scientists. Under this law, passed in 1945, returning war veterans who chose to pursue post-secondary study received a cost of living allowance and payment of their tuition charges for several years. This arrangement allowed many Americans, who would not otherwise have been able to afford it, to obtain an advanced education and led to a large increase in the number of the college educated. Science being a wide-open field proved particularly attractive, especially to the many young men who were moving away from small family farms or from the immigrant ghettos of large

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cities. Thus, by 1950 both trained people to carry out research and funds to support such research were amply available. Also, there were many new jobs as a result of expansion of the universities to accommodate the flood of new students. Moreover the chemical industry—which had begun to flourish in the USA after the first World War—was entering into a second major expansion phase.

### Organic chemistry

The year 1950—in different ways—points to two extraordinarily important advances in organic chemistry. One is the award of the Nobel Prize to O. Diels and K. Alder for what is now known as the Diels-Alder reaction, discovered in 1928. This reaction—the addition of a diene to a dienophile (generally an alkene with an electron-withdrawing group)—is arguably the most important reaction in organic synthesis, rivaled perhaps only by hydroboration (addition of a boron hydride to an alkene) discovered by H.C. Brown and B.C. Subba Rao in 1956 and the Wittig reaction (conversion of C=O to C=C) discovered by G. Wittig and U. Schöllkopf in the same year. (Both Brown and Wittig received the Nobel prize in 1979.) Another momentous advance, which actually occurred in 1950, D.H.R. Barton's recognition of the impact of molecular shape on physical and chemical properties of molecules containing six-membered rings, now known as "Conformational Analysis" (Barton, 1950), will be discussed later.

It will be convenient to follow up these two advances—one in organic synthesis, the other in stereochemistry and reaction mechanism—separately; since major advances in both areas occurred throughout the rest of the half-century.

### Organic synthesis

The pioneer in the area of organic synthesis and the most famous organic chemist of the second half of the 20th century was, without any doubt, R.B. Woodward (Nobel Prize, 1965). One of the problems in earlier synthesis of natural products resulted from the fact that most of these compounds have a number of stereocenters; thus a synthesis carried out without stereocontrol would yield a mixture of a number of diastereomers, only one of which would correspond to the racemate of the desired natural product. (In addition, many natural products exist in nature as single enantiomers; we shall deal with this problem

later.) It was Woodward who first developed methods to synthesize single diastereomers by categorizing and using diastereoselective reactions. An early, ingenious example is his diastereoselective synthesis of reserpine (Woodward *et al.*, 1958), a compound with 6 stereocenters which, in the absence of stereocontrol, could thus lead to as many as  $2^6 - 1 = 63$  unwanted diastereomers. From there Woodward scaled ever greater synthetic heights, ultimately accomplishing the synthesis of Vitamin B-12 in collaboration with A. Eschenmoser (Woodward, 1968, 1973; Eschenmoser, 1969).

A major conceptual contribution to organic synthesis was made in the 1960's by E. J. Corey (Nobel Prize, 1990) in the development of "retrosynthetic analysis" (see Corey and Cheng, 1989). Instead of looking at synthesis in a forward direction, from starting material to desired product, and essentially using an intuitive approach, retrosynthetic analysis starts with the target and works backward through likely immediate precursors, then precursors of those precursors until one ultimately arrives at available starting materials. Such a thought process produces a multitude of potential pathways (and sometimes even starting materials) much like an inverted tree and one has to choose the one most likely to succeed on the basis of number of steps, complexity of the various reactions involved and availability of starting materials, among other factors. In recent years it has been possible, for example in the hands of S. Danishefsky and K.C. Nicolaou, to synthesize natural products of enormous complexity with large numbers of stereogenic elements. Usually these are natural products, often products of suspected or proven pharmacological activity, sometimes available in nature in too small quantities to allow clinical trials, and sometimes targets of structural modifications to enhance drug activity and to reduce toxicity.

There has also been interest in the synthesis of certain "unnatural products" for example molecules having the shapes of the Platonic solids cubane, dodecahedrane and the tetra-*t*-butyl derivative of tetrahedrane (the parent compound appears to be too strained to exist). Related to this are the synthesis of adamantane, C<sub>10</sub>H<sub>16</sub>, another beautifully symmetric molecule which occurs in Czechoslovakian petroleum but, interestingly, is the thermodynamically stable end product of the treatment of most of its isomers with aluminum chloride (Schleyer, 1957). In this category we must also mention buckminster-

fullerene, C<sub>60</sub>, the third allotropic form of carbon (next to diamond and graphite) (*cf.* Billups and Ciufolini, 1993). Although it occurs in soot, it was not discovered until 1985 (by mass spectrometry) and a practical method of obtaining it was found only in 1990. Its discovery was rewarded by the Nobel Prize to Curl, Kroto and Smalley in 1996. Present interest in its chemistry relates mainly to nanotubes made out of this material which may serve as molecular wires in future further miniaturizations of electronic circuits.

The most recent conceptual advance in this area is combinatorial synthesis (*cf.* Wilson and Czarnik, 1997). In its most fundamental aspect, this represents a multistep synthesis carried out in a number of parallel operations in which the reagents at each step are changed in blocks. The successive reactions are carried out either in parallel wells or on a solid support and it is important to devise methods both to identify the products and to test their efficacy, be it as pharmaceuticals, catalysts or biosensors.

### Reaction mechanism and stereochemistry

The area of reaction mechanism and stereochemistry was pioneered by such investigators as G.N. Lewis, Linus Pauling, Michael Polanyi, Robert Mulliken, Christopher Ingold, Paul D. Bartlett, some of them recognized by Nobel prizes. The approach was sometimes physico-chemical ("physical organic chemistry") and sometimes more intuitive ("reaction mechanism"). The confluence of these two streams culminated in the Woodward-Hoffmann rules in 1968 (*cf.* Woodward and Hoffmann, 1970) which provide guidance for the stereochemical course of electrocyclic reactions (such as the Diels-Alder reaction), both thermally and photochemically induced. In more recent years, as a result of the ever increasing power of computers, it has become possible to calculate molecular structure and energetics. The easiest—but most empirical—manner of doing such calculations is by "molecular mechanics" also called "force-field calculations" (*cf.* Rappé and Casewit, 1996). In these calculations molecules are considered as mechanical entities (like atomic balls connected with springs) and their energies are calculated by minimizing the total energy of the system. The most stable structure (conformation) is then deemed to be the arrangement of least total energy. The method is quite successful for relatively small and not highly strained molecules; it relies on experimentally deter-

mined parameters for the various components of the force field: bond stretching, bending and rotation, plus electrostatic and van der Waals interactions within the molecule. It leads to quite powerful thermodynamic (equilibrium) as well as, at least in certain cases, kinetic (reaction rate) predictions.

Of course it would be preferable if structure and energetics could be calculated "ab initio", *i.e.* on the basis of fundamental physical principles. This requires solution of the Schrödinger equation which is possible only for very simple molecules, such as H<sub>2</sub>. However, thanks to the ever increasing power of computers, and to ever more ingenious ways of simplifying the approach so as to make it computationally feasible, it is becoming possible to make approximate calculations for relatively complicated systems, (Császár, Allen and Schaefer, 1998) as long as one confines oneself to differences between relatively similar ground states (conformers or configuration isomers) or transition states. This kind of approach will no doubt become ever more powerful as computers continue to improve and will help to solve two basic problems in chemistry—one to calculate the energies of competing transition states and thereby to fathom the selectivity of competing reactions, the other to approach the problem of molecular fits, such as that of the molecules in a crystal or of an enzyme with its substrate. Despite the enormous advances in crystallography in the last 50 years, we still have no way to predict in what space group a given substance will crystallize or (and this is of considerable practical importance) whether a racemate will crystallize as a conglomerate or as a racemic compound. This is but an example of our yet incomplete understanding of the burgeoning field of "supramolecular chemistry" (chemistry of aggregates, solvates and other, mostly non-covalently bonded complexes)—a field for whose initiation D.J. Cram, J.M. Lehn and C.J. Pederson received the Nobel Prize in 1987 (*cf.* Schneider and Durr, 1991).

It must be mentioned that a new calculational method, the "density functional method" (in which one considers electron density in a molecule) can be used as an alternative or add-on to the more classical approach of using wave functions. The 1998 Nobel Prize in Chemistry has been given to John Pople, who made the wave function methods widely accessible, and to Walter Kohn, a physicist, who originated density functional theory.

Another important aspect of the mechanistic

approach is stereochemistry. The subject goes back to Louis Pasteur in the middle of the 19th century; after flourishing in the second half of that century, it made little progress in the first half of the 20th. It was revived after 1950 first as an aid in studying mechanism; an important textbook was published in 1962 (Eliel, 1962). One of the important advances of this period was the determination of the absolute configuration of a given enantiomer (Bijvoet, 1951). While Emil Fischer and others had made detailed investigation on the relative configurations of sugars, amino acids and other molecules (Klyne and Buckingham, 1978), the absolute configuration—*i.e.* whether the (+) or (–) enantiomer corresponds to what we now call the R or S configuration of the molecule—was not known for any individual chiral substance. The obvious approach to this problem—X-ray structure analysis—fails because enantiomers have virtually identical diffraction patterns. Bijvoet found that by using X-rays of wavelength close to the absorption edge of one of the atoms in a molecule (usually a heavy atom such as S or Br), a predictable difference of diffraction pattern between the R and S enantiomer could be observed and the two enantiomers thus identified as to their absolute configuration (*i.e.* the true arrangement of the atoms in space). Consequent to Bijvoet's work, it became desirable to establish a systematic symbolism for configuration based on the three-dimensional array of the atoms around the chiral element (*e.g.* the chiral CHOH center in lactic acid  $\text{CH}_3\text{CHOHCO}_2\text{H}$ ). This was done by Cahn and Ingold later joined by Prelog (Cahn, Ingold and Prelog, 1966); Prelog received the Nobel Prize for his work in stereochemistry in 1975.

A recent and exciting development in this area, pioneered by R. Lerner and P. G. Schultz, concerns the creation and use of catalytic antibodies. These are catalysts produced by immunological methodology in animals, using antigens whose structure simulates the rate-determining transition state for the reaction to be catalyzed (*cf.* Schultz, 1998).

I have already alluded to another major achievement in the general area of stereochemistry: the recognition of the relation of chemical stability and reactivity as well as of physical properties to conformation, for which D.H.R. Barton received the Nobel Prize in 1969. The importance of conformation in reactivity and in mechanistic thinking in organic and bioorganic chemistry is all pervasive and conformational analysis may well be considered the most

revolutionary advance in organic chemistry in this century.

### Medicinal chemistry

Medicinal chemistry has its origins in folk medicine: the use of natural products (usually from plants) to alleviate or cure disease. It became important to isolate the pharmacologically active ingredients of these products and later to determine their chemical structure; much of the organic chemistry of the 19th and early 20th century (see above) dealt with this problem. (Nowadays, thanks to mass spectrometry, NMR and especially X-ray crystallography it has become much easier and quicker to determine chemical structure. X-ray crystallography has been greatly facilitated by the development of the so-called "direct method" for which H.A. Hauptman and J. Karle received the Nobel Prize in 1985. This method, which avoids the artificial introduction of heavy elements, can now be extended to very large molecules.)

The next step was to synthesize these natural products (either just as an intellectual challenge or because their natural abundance is too small to allow extensive testing as a drug) and then to modify them to obtain even better synthetic drugs. Increased understanding of the targets (receptors) of the drugs also led to new pharmaceuticals capable of interacting with (or inhibiting) these receptors. This activity led to the creation of a large industry; pharmaceutical companies are the major employers of chemists today. The huge progress that has been made in the synthesis of ever more complex molecules with ever increasing numbers of stereocenters has already been discussed above.

The two most momentous discoveries in this area were made before 1950, as it happens: the sulfa drugs and penicillin. These drugs (plus the later introduced immunizations) have led to a remarkable drop in infant mortality, at least in the developed world: the life expectancy of a newborn increased from 54 years at the time of the author's birth to 74 years today, mostly as a result of the ability of sulfa drugs and penicillin (and later developed antibiotics) to cure a variety of infectious diseases, such as scarlet fever and diphtheria, that used to be attended with high mortality rates. Interestingly both discoveries were made serendipitously. Sulfanilamide (*p*-aminobenzenesulfonamide), the parent of the sulfa drugs, is an inhibitor of *p*-aminobenzoic acid, an essential

growth factor of bacilli. However, it was discovered by accident: Prontosil, a red azo dye synthesized in the I.G. Farben laboratories in Germany in 1932, was tried out as an antibacterial drug because of its affinity for protein fiber and found remarkably effective. One half of this  $R-N=N-R'$  molecule corresponds to sulfanilamide ( $R-NH_2$ ) to which it is converted in vivo by reductive cleavage of the azo linkage and sulfanilamide turned out to be actual source of the activity of prontosil; it and its analogs were then used as drugs against infections by gram-positive bacteria, such as staphylococci, streptococci and pneumococci. Penicillin was found—also by accident—by Alexander Fleming in 1929 in a mold (*penicillium notatum*) that happened to grow in a petri dish and inhibited bacterial growth in the medium around it. This finding lingered for 10 years but just before World War II was put to use if the fight against bacterial disease by Howard Flory and Ernst Chain; the three investigators involved received the Nobel prize for this discovery in 1945. Other antibiotics were discovered subsequently, they are less toxic than the sulfa drugs and some are active against gram-negative as well as gram-positive bacteria (the “gram” prefix referring to how bacteria can be stained). Unfortunately bacteria tend to develop resistance against a given antibiotic over time, a matter which is of considerable concern in medicine. This problem has led to a race to discover new antibiotics as the existing ones become ineffective.

In recent years, life expectancy not only of infants but also of elderly people has increased, and with it the incidence of diseases that are more common in older people, such as cancer, Parkinson's disease, Alzheimer's disease. The challenge now is to find drugs effective in ameliorating if not curing these scourges. Substantial advances have been made against cancer and in delaying the effects of Parkinsonism.

Some of the natural products from which drugs were originally derived have relatively complex structures. However, given that many modern drugs have to be manufactured in large quantities, active compounds of relatively small molecular size (and therefore usually comparatively easy to synthesize) are preferred. Another important aspect of drug chemistry relates to the chiral nature of most receptors and enzymes. Thus, of two enantiomeric drugs, one is likely to fit the receptor better, and hence be more active than the other (just as a right hand can

be fitted better with a right glove than with a left one). Because of side effects (which may also differ between enantiomers) the more active and less toxic enantiomer is the one indicated for drug use. This has led to great interest in obtaining enantiomerically pure drugs. This can be achieved by resolution or by synthesis of individual enantiomers, either from a relatively readily available enantiomerically pure precursor (such as a sugar or amino acid), or by use of a chiral reagent, chiral catalyst or chiral auxiliary in a so-called enantioselective (“asymmetric”) synthesis.

### Polymer chemistry

While some polymers, such as celluloid and bakelite have been known for a long time, polymer chemistry as a science is based on Herman Staudinger's insight in 1924 (Nobel Prize, 1953) that polymers were macromolecules formed by repeat units of small links (monomers) like a chain. There were at least two spectacular discoveries that followed from this insight. One is the discovery of Nylon by Wallace Carothers in 1937. The second is the production of high-density polyethylene by Karl Ziegler and of isotactic polypropylene by Julio Natta by use of special metal catalysts (so-called Ziegler-Natta catalysts. This work was recognized by the Nobel prize in 1963. Other very effective organometallic polymerization catalysts have been discovered in recent years (Coates and Waymouth, 1995; Johnson, Killian and Brookhart, 1995). These catalysts allow synthesis of polymers of well defined properties by controlling the degree of branching in polyethylene and by alternating tactic and atactic blocks in polypropylene.

The highly resistant polymer Teflon (poly-tetrafluoroethylene) was discovered by accident when Roy Plunket (like Carothers a DuPont chemist) found this material in an aged tetrafluoroethylene cylinder. Teflon for years has been polymerized in Freon (chlorofluorocarbon or CFC) solvents. Because these solvents are now environmentally unacceptable (see below), they have been replaced by supercritical carbon dioxide (Romack, DeSimone and Treat, 1995).

Thanks to the development of special detergents by DeSimone, supercritical or just pressurized liquid  $CO_2$  is also finding use in several other applications including dry cleaning. Carbon dioxide is, of course, an environmentally friendly solvent, despite concerns about the “greenhouse effect” (see below) since

in industrial applications the net atmospheric balance is zero: As much CO<sub>2</sub> is taken from the atmosphere (directly or indirectly) as is eventually returned to it.

### Bioorganic chemistry

In conclusion, we take up, if only very briefly, some of the most important advances in bioorganic chemistry. Here we must count the discovery of the alpha-helix and the pleated sheet as building blocks of protein structure by Linus Pauling (Nobel Prize, 1954) and R.B. Corey (*cf.* Pauling, 1960), the synthesis of polypeptides and proteins on solid-phase supports by Robert Merrifield (Nobel Prize, 1984) (Merrifield, 1993) and the realization of the double-helix structure of DNA by James Watson and Francis Crick in 1953 (Nobel prize, jointly with Maurice Wilkins who did the underlying X-ray work with the late Rosalind Franklin; *cf.* Watson and Crick, 1953; Watson, 1969). Numerous other protein structure determinations by X-ray diffraction analysis have been recognized by Nobel prizes. Since protein conformation in aqueous solution, (where enzymes function *in vivo*) is not necessarily the same as in the crystal, an important recent advance relates to the determination of protein structure in solution by nuclear magnetic resonance (Wüthrich, 1986). These pioneering chemical discoveries have had and are having enormous impact in the broad area of molecular biology. We shall mention here only one current problem: if proteins are synthesized in nature (or in the laboratory) in linear fashion, what is the mechanism by which they fold, usually spontaneously, into their actual secondary and tertiary structure involving helices and pleated sheets? This problem is under intense current study (see *Accounts of Chemical Research*, 1998).

### Conclusion. Environmental concerns

The advances in organic chemistry—and, for that matter, in all of chemistry—since the end of World War II in both basic understanding of the subject and in its beneficial applications have been astounding. As far as applications are concerned—and this is what most concerns the general public—there have been advances in medicinal chemistry that have contributed to enhancing health and life expectancy, advances in agricultural chemistry that have helped increase food supply, advances in the chemistry of materials, including fibers, that have led to lighter

automobiles, better utensils and more durable and more easily washable clothing, to mention just a very few of chemistry's contributions. Nonetheless, chemistry—and especially the chemical industry—do not enjoy a good reputation among the general public as we come to the end of the century. Great (and sometimes exaggerated) concern is voiced over pollution and the danger of chemical accidents. At least two major, world-wide problems have arisen in the last two decades. One of them relates to the use of chlorofluorocarbons (CFC's) as refrigerants. When these compounds were first developed, they seemed to be ideal for use in refrigerators and air conditioners and also as propellants and degreasing agents because of their stability and extremely low toxicity. Unfortunately, just because of that extreme stability, they are highly persistent in the atmosphere and eventually wind up in the stratosphere where they undergo photochemical decomposition to liberate chlorine atoms which, in turn, attack the stratospheric ozone layer. Stratospheric ozone serves to filter out UV radiation and its destruction leads to increased UV radiation at ground level which, in turn, increases the incidence of skin cancers. Once the problem was recognized, it was agreed in the so-called "Montreal Protocol" to phase out the CFC's and replace them by less persistent materials. As this process is nearing completion, it has begun to ameliorate the stratospheric ozone depletion problem. Another potentially major problem recently recognized is the deleterious effect of increasing atmospheric CO<sub>2</sub> concentrations caused by the extensive burning of fossil fuels in modern society. It seems certain now that the increase in atmospheric carbon dioxide leads to global warming and thereby potentially very serious worldwide climate changes. However, the extent of these changes (is the increase a tolerable 1 °C or a disastrous 5 °C in average temperature?) is not yet clear. In any case, there are now important global discussions about decreasing CO<sub>2</sub> emissions with potential major economic implications.

Other serious problems, which, however, are in the process of being attacked, are acid rain (due to emission of sulfur oxides from factories) and ground-level air pollution by ozone, NO<sub>x</sub> and SO<sub>x</sub>, much of it from automobile exhaust. The latter problem is being tackled by catalytic control of automobile emissions but it may, eventually, require the replacement of the gasoline-powered automobile by an electrically propelled one. Factory emissions (invol-

ving both air and water pollution) are presently combatted by so-called "end-of-pipe" treatments, *i.e.* chemical scrubbing of waste products. However, the ultimate solution to this problem requires approaches that are inherently less polluting than current ones. This so-called "green chemistry" involves development of processes that produce few by-products and preferably do not involve solvents that, even if recycled, tend to contaminate both atmospheric and aqueous effluents. The chemical industry has now adopted what is known as "Responsible Care"—a serious effort for chemical factories to reduce contamination and to become better neighbors.

To summarize this conclusion, we can say that the enormous advances of our quality of life through chemistry (and technology in general) tend to come with costs that work in the opposite direction. Part of the challenge for the future will be to maximize the benefits of chemistry while, at the same time, minimizing adverse environmental effects. ▀

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