

PHYSICAL ORGANIC CHEMISTRY—RETROSPECT AND PROSPECT

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THE number of compounds described in the organic chemical literature from 1965 to 1980 has been computed to be over 5 million¹. If the compounds known before 1965, with no overlap later could be taken as another 5 million, the corpus of organic chemistry would consist of properties and reactions of over 10 million unique compounds. This colossal body of knowledge poses problems of comprehension and assimilation. The need for theory and hierarchy of concepts to link and correlate the structures and properties becomes imperative.

THEORETICAL ORGANIC CHEMISTRY

The theory of organic chemistry developed only in stages and through the intuitive ideas of Kekule' (1859, 1865), Couper (1859), Le Bel (1874), Van't Hoff (1874) and of G. N. Lewis². These ideas were admittedly not based on independent evidence nor were they derived from proven physical laws.

The great discoveries of physics during late 19th and 20th centuries, made it possible to put these theories to experimental verification. The status of organic structural theory, after the impact of physical and mathematical methods is best summarized in the words of Sidgwick³.

"We have applied to their (organic structures) investigation, a whole series of physical methods based on examination of the absorption spectra in the infra-red, the visible and the ultra-violet spectral data, and of the Raman spectra; the measurement of specific heats and heats of combustion, of the dielectric properties, and of the scattering of x-rays and electron waves, as well as the study of chemical dynamics, to mention only the most important. To Kekule the links had no properties beyond that of linking, but we know now

their length, their heats of formation, their resistance to deformation and the electrostatic disturbance in which they are involve. Throughout this work the starting-point has always been the structural formula in the ordinary chemical sense. There is no better example of the effect of new discoveries in giving new meaning to a theory while they leave the truth of the theory unaffected, and of the way in which modern research, instead of being content with the evidence of one kind, as were the older organic chemists with that of chemical reaction, draws its material from every side, and from every branch of chemistry and physics"³

An early application of Bragg's method of x-ray diffraction by Lonsdale⁴ to hexamethyl benzene led to the startling conclusion that the postulates of Kekule' were essentially correct. (Scheme I)

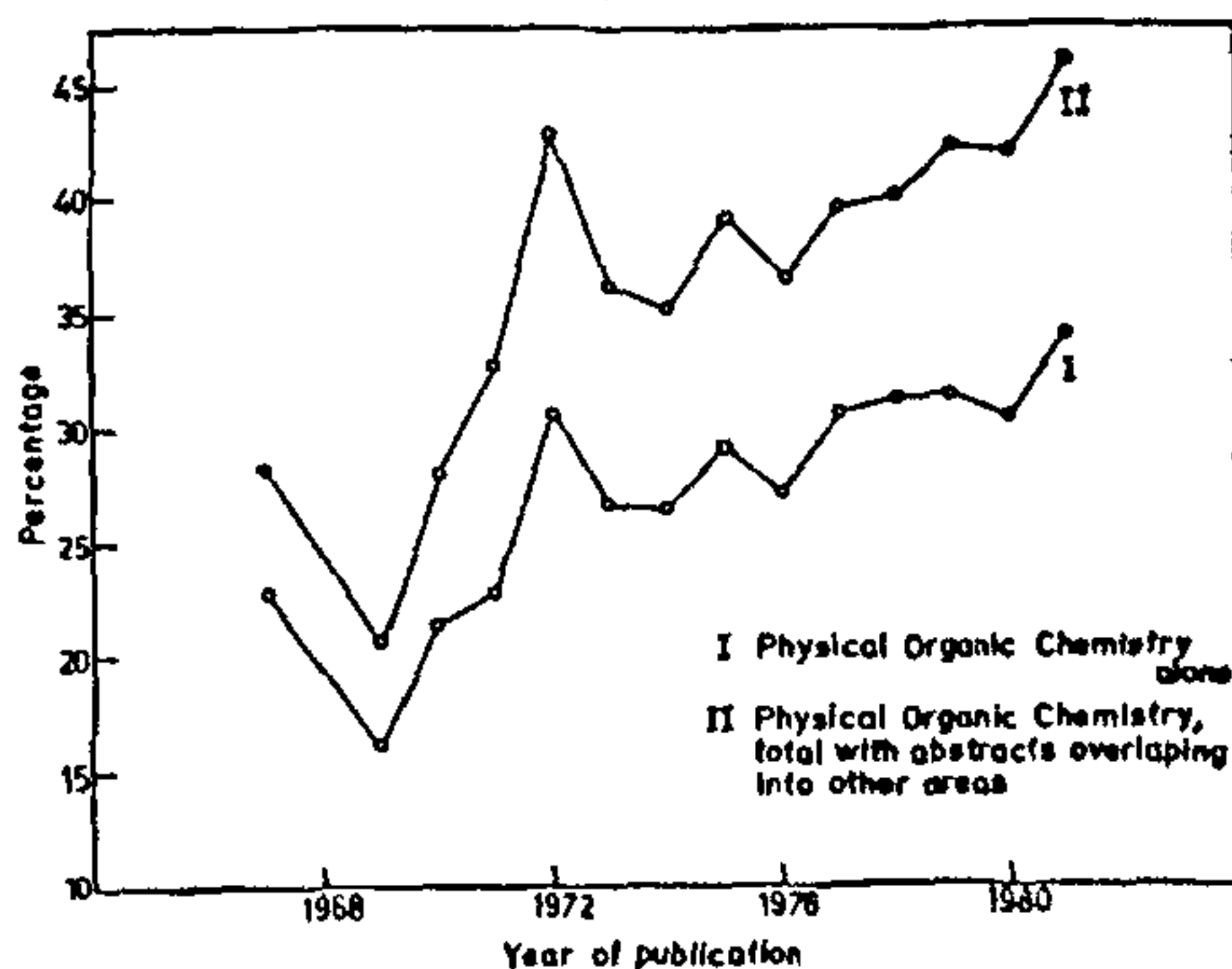


Figure 1

Similarly, the postulates of LeBel and Van't Hoff were found by Pauling⁵ to be derivable from quantum-mechanics, when applied to the problem of bonding in carbon.

Availability of physical methods of structure determination has led to some significant developments.

(a) Structure instead being a symbol, attained physical and quantitative significance, in terms of bond lengths, angles and energies. The large amount of thermochemical data patiently accumulated during the 19th century, suddenly became meaningful in view of its direct relation to the strength of bonds

(b) The nexus of reactions and structure was lifted. Structural information, could be obtained independent of reactions. This made it possible to study a number of time-dependent phenomena in organic chemistry, particularly where structure was undergoing rapid transformation on its own without the intervention of reagents.

THEORETICAL CHEMISTRY

Application of quantum mechanics to organic chemistry.

How far can one go in applying quantum mechanics to organic chemistry? In so far as chemistry is concerned with making and breaking of bonds, which are made up of electrons, should not chemistry be a branch of mechanics? In his oft-quoted paper Dirac⁶ wrote:

"The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry, are thus completely known and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble".

E. Bright Wilson Jr., Co-author of a widely used book on quantum mechanics, and a long and successful practitioner of quantum mechanical methods has summarized the status of quantum methods (1968) as follows⁷.

"Chemistry is still very largely an empirical science with a stupendous collection of observed facts, running into tens of millions at the very least. Relatively little sound theory is available to tie together and account for this overpowering mass of data. But indeed there are some very elegant theories that have proven their validity beyond a shadow of a doubt. Foremost among these I would put the atomic theory, the idea of

the tetrahedral structure of the carbon atom and related principles of organic chemistry, thermodynamics, statistical mechanics and to a lesser extent quantum mechanics.

Quantum mechanics has not attained the status of thermodynamics in chemistry. Despite fifty years of effort by thousands of investigators it is largely an article of faith that Schrodinger equation is capable of explaining all the facts of chemistry.

Despite past and prospective progress in theory, I fear that chemistry will continue to be largely empirical. A theory of chemistry that is limited to extremely small number of electrons is useful, but, of course, does not scratch the surface of what chemistry really is and cannot even begin to present models of most of the phenomena of chemistry".

The position has not substantially changed during a decade and half after Wilson's article was written, despite impressive works of Fukui and Hoffmann, and host of other eminent investigators and the availability of powerful computers.

"The problem of reaction velocities" wrote Tolman⁸ in his "Statistical Mechanics" "is nearer to the heart of most chemists than anything in the whole of their activity. Rates of reactions are the factors that determine yields and costs and possibilities and their theory must succumb to scientific treatment. Whatever may be, the way is long....". In taking stock of the position at the symposium organized by the Chemical Society (U.K.) for the purpose in 1962 G. Porter wrote⁹,

"We have travelled some distance, since 1926, but many of us today would feel that most of the road is still ahead". This view is confirmed in a more recent monograph "Chemical Reactivity and Reaction Paths" by G. Klopman¹⁰.

"Although we speak of theoretical chemistry, we must realize that from the point of view of theoretical physicist this is an applied subject and to the purist largely an empirical one. Because of the extreme complexity of molecular systems, wide and frequently crude assumptions

have to be made in most theoretical treatments, and (introduce) empirical factors into theoretical expressions except in the simplest of systems.

The variation in heat content or enthalpy which occurs during the course of a chemical reaction depends on dissociation energies, electron organization and changes in solvation energies involved in the rate determining processes. Because of the uncertainty of the entropy term, the calculation of absolute rates of reaction hardly be expected to be done. For the time being, however, calculations based on the exact solutions of the Schrodinger equation have been, in practice, impossible to realize except for the reaction of $H_2 + H$ which was successfully calculated. There is little hope that such approach may even be extended to other systems in the near future".

Where does quantum chemistry or theoretical chemistry stand today? M. Siomonetta,¹¹ a quantum chemist seems to provide the answer.

"Theoretical Chemistry is at its best when it is merged in experiment"¹².

PHYSICAL ORGANIC CHEMISTRY ORIGINS

Theory of Organic Chemistry, as we had discussed above, which had stagnated for about 50 years (1875–1925), showed spectacular development at the impact of the concepts and techniques of the physicist and the physical organic chemist.

New ideas, generalizations about structure, reactivity and interrelationship between them, resulted in the development of new methodologies for the study of organic chemistry. They involved application of quantitative methods of physical chemistry to the study of organic reactions and structure. Two groups, one led by C. K. Ingold in the U.K. and the other by L. P. Hammett in USA, pioneered this new movement. It is necessary to point out that the theory of organic chemistry itself was considerably influenced by the ideas of Lapworth and Robert Robinson. These investigators, however, are not associated with any distinctive methodology.

In his preface to the first edition, of his "Physical Organic Chemistry" 1940, a book which had

considerable influence in USA in the development of this subject, L. P. Hammett¹² wrote

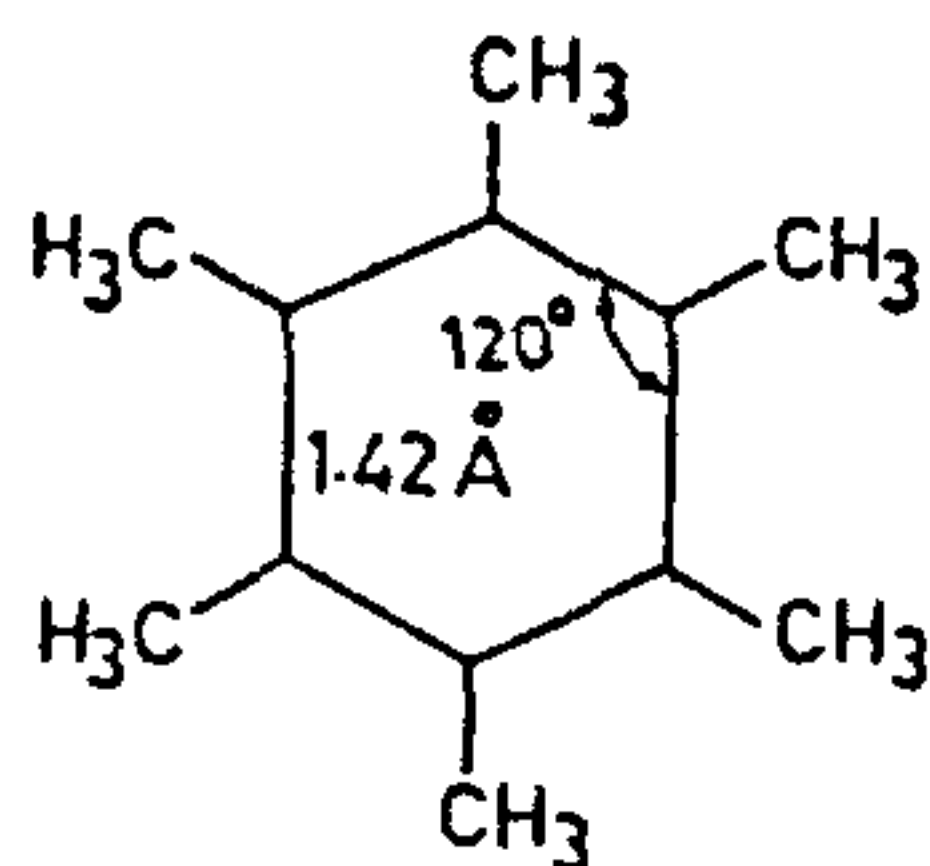
"For a time it was almost a point of honour for physical and organic chemists to profess ignorance of each others' field. Meanwhile there has grown a body of fact, generalization and theory that may properly be called physical organic chemistry. The name implies investigation of the phenomenon of organic chemistry by quantitative and mathematical tools".

What are the main directions of progress in Physical Organic Chemistry? Study of mechanisms of reactions by quantitative methods; relationships of structure and environment with reactivity.

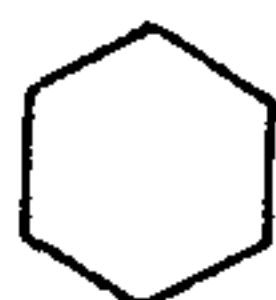
1. Conformation Analysis, and Conservation of Orbital Symmetry in chemical reactions, are two of the important generalizations with predictive capabilities, in the theory of organic chemistry. The former has influenced in a very fundamental way not only the whole of chemistry, but also biochemistry, biophysics, and biology. These two important generalizations relate ground state structure to transition state geometry. All our knowledge of transition states is derived from either rates of reactions or stereochemistry of the products. Both these developments resulted by analyzing the data obtained by the application of quantitative techniques of physical chemistry and physical organic chemistry to the structure and reactions of complex organic molecules.

2. The impact of physical organic chemistry on synthetic methodology is revealed in the complex structures of bewildering variety that have been synthesized as a result of better understanding of the reactions involved. Below are given three land marks in synthetic organic chemistry with the years of synthesis. (Schemes 1a and 1b)

3. New understanding of organic reactions has led directly to a better control of chemical processes in Industry. This is reflected in the sharp decrease in the prices of complex products like vitamins, hormones and drugs produced synthetically.



Hexamethylbenzene
Lonsdale (1929)



Benzene
Kekulé' (1865)

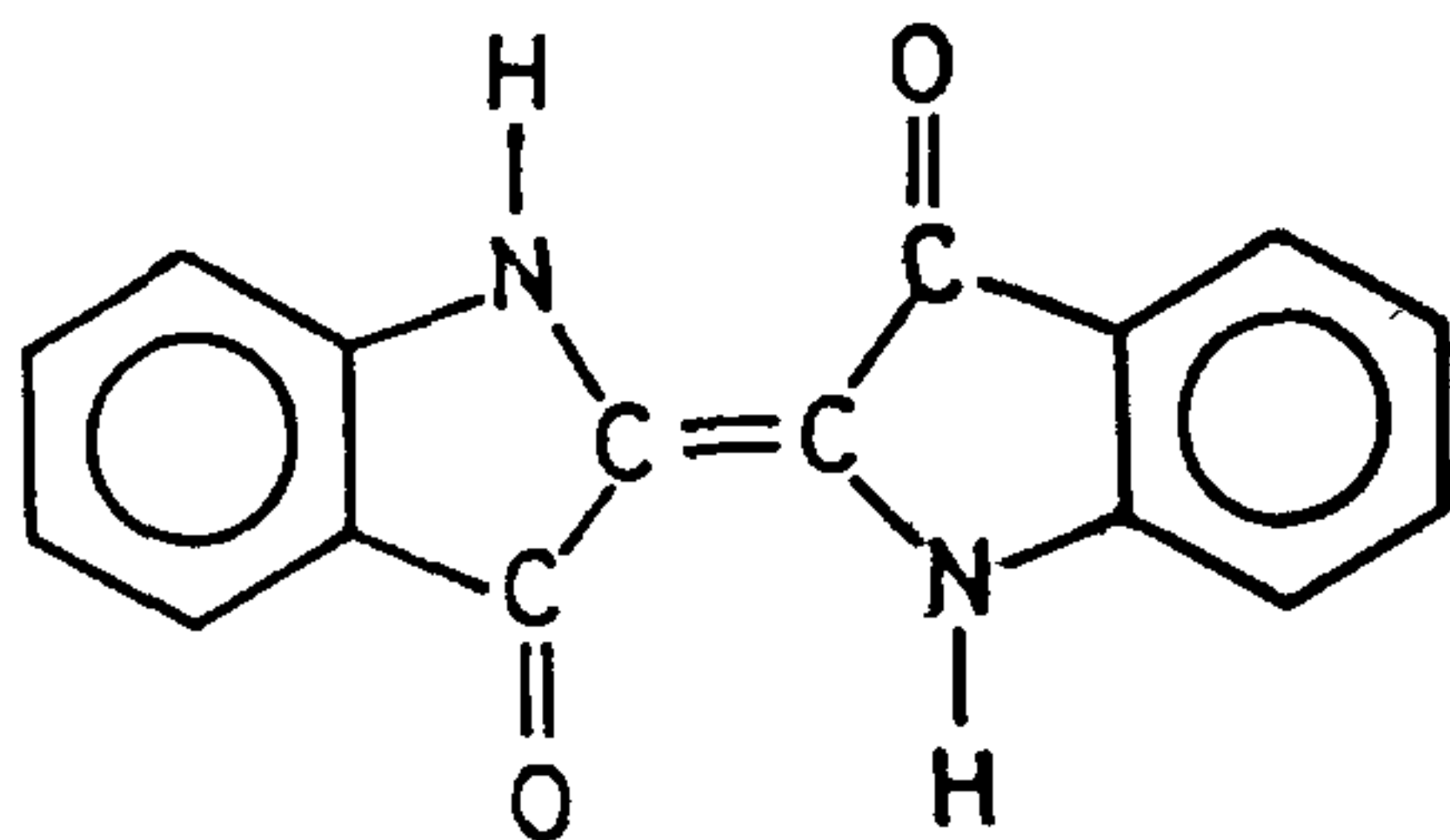


Benzene
Kekulé' (1866)

(Scheme I)



Urea (1828)

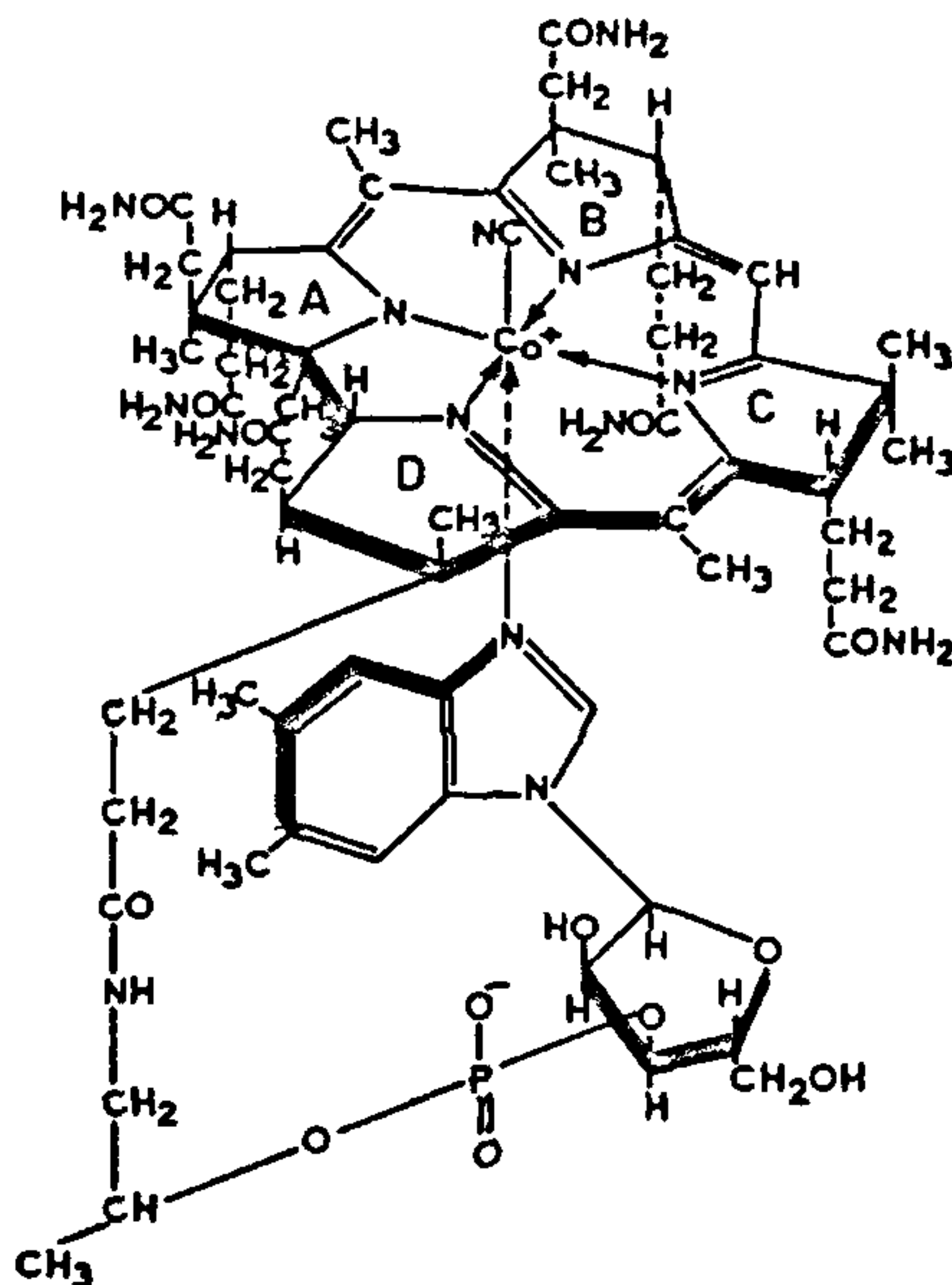


Indigo (1878)

(Scheme Ia)

4. Other important contributions of physical organic chemistry are

a) description of transient organic species



Vitamin B₁₂ (1973)

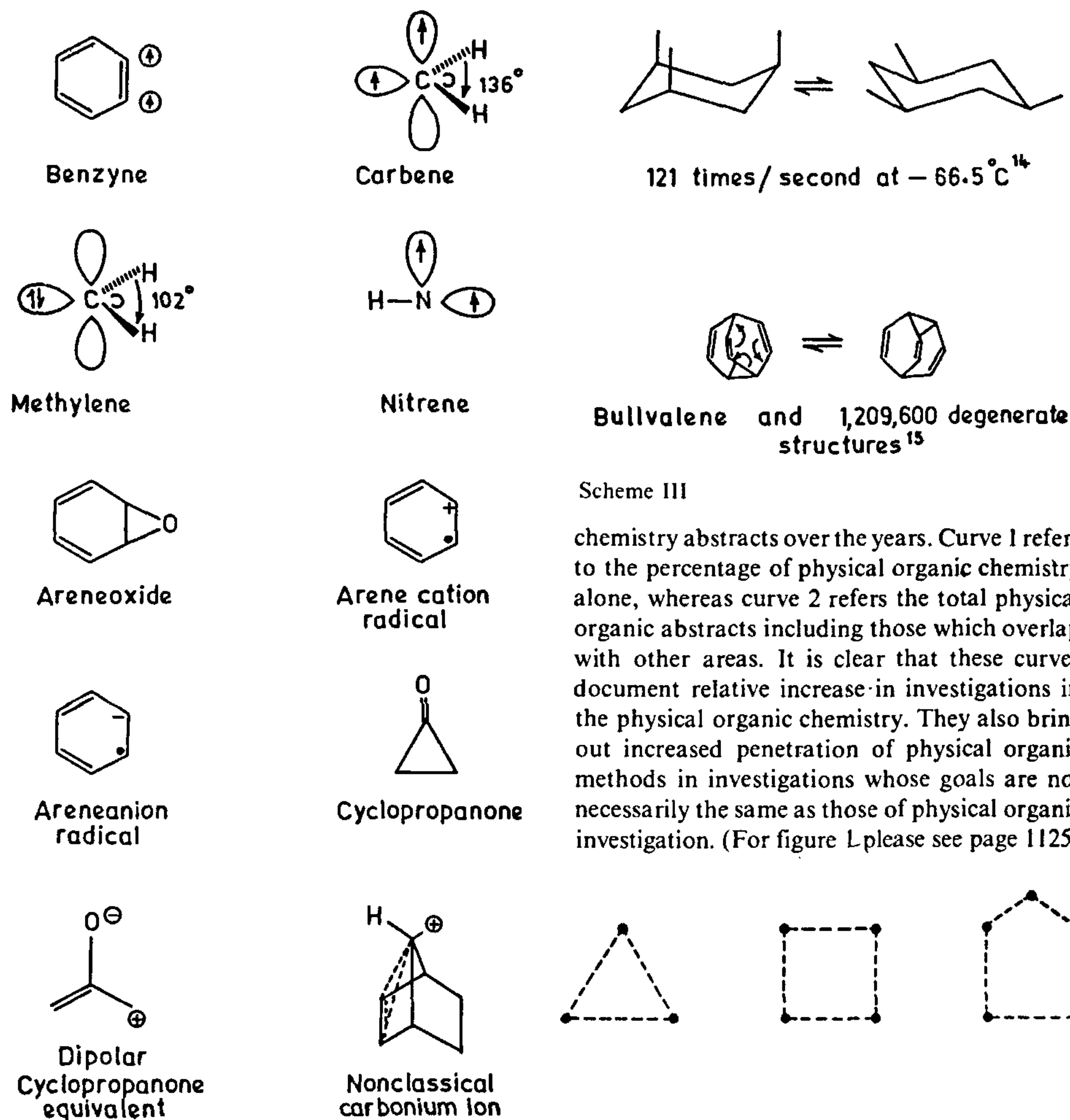


Scheme Ib

(intermediates). b) study of time variable structures and c) description of transition states which are, per se, non-isolable.

The examples given in Schemes II, III and IV are illustrative.

5. Another enduring aspect of the contribution of physical organic chemistry is in the teaching of organic chemistry itself. The latter is no longer taught as a collection of facts alone. It is now possible to teach it as phenomena embodied in rich array of structures and reactions—as how and why of things and processes. In one of the well-received books, "Comprehensive Organic Chemistry", 1979, edited by D. H. R. Barton and W. D. Ollis, it is interesting to note that the authors discuss aromaticity rather than aromatic compounds, saturated hydrocarbons are discussed with conformational analysis, strain energies and radical reactions. Factual material is always interlaced with theory.

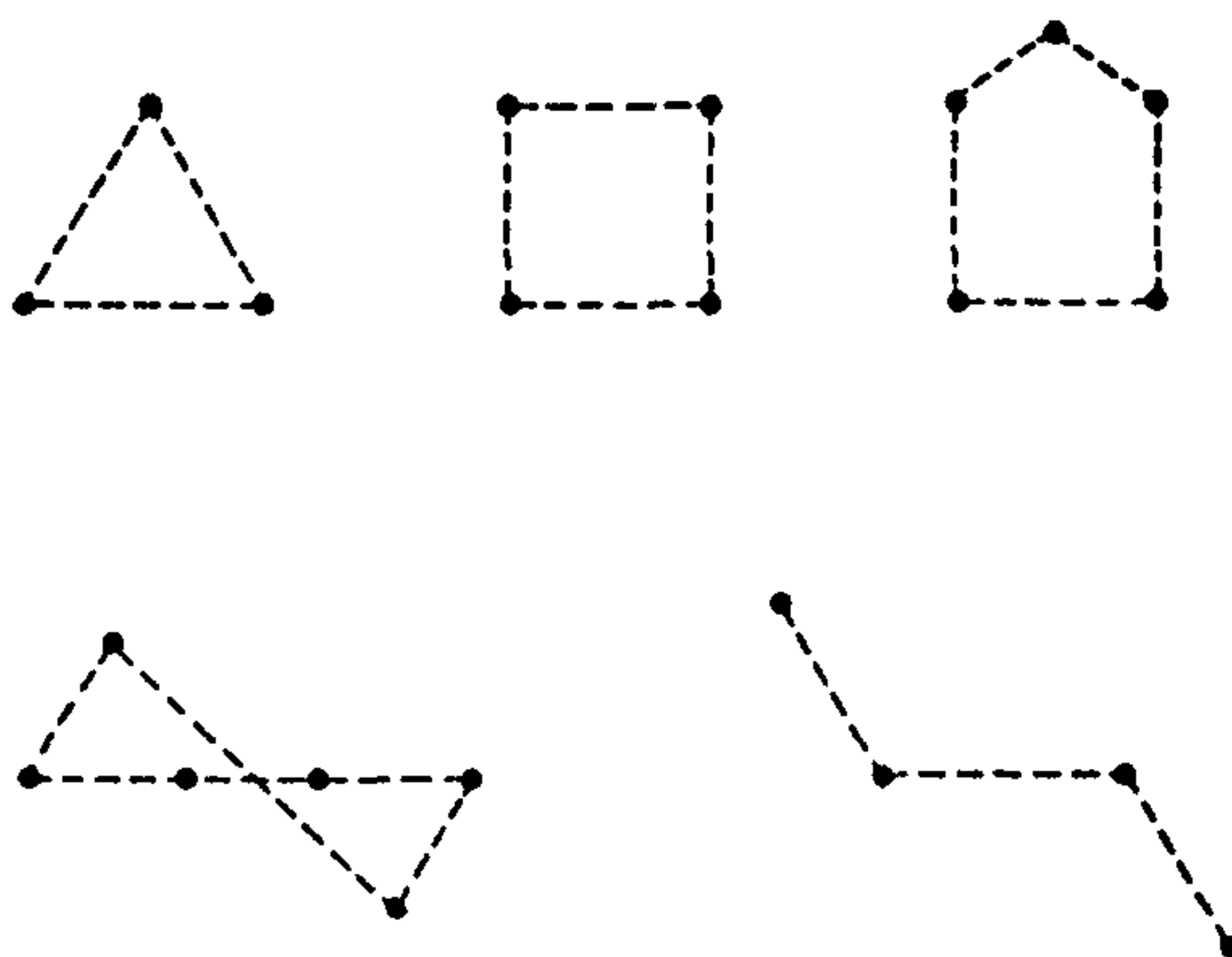


Scheme II

A separate section on Physical Organic Chemistry was started by the Chemical Abstracts in 1963 to cover its voluminous literature. The Chemical Society, (U.K.) also started, Journal of Physical Organic Chemistry in 1966. The figure 1 gives the proportion of physical organic abstracts as percentage of the total organic

Scheme III

chemistry abstracts over the years. Curve 1 refers to the percentage of physical organic chemistry alone, whereas curve 2 refers the total physical organic abstracts including those which overlap with other areas. It is clear that these curves document relative increase in investigations in the physical organic chemistry. They also bring out increased penetration of physical organic methods in investigations whose goals are not necessarily the same as those of physical organic investigation. (For figure 1 please see page 1125).



Transition states of Various Geometries

Scheme IV

FUTURE PROSPECTS

Any forecast about the directions of growth in physical organic chemistry would necessarily be subjective. Some trends, however, clearly stand out.

Perhaps the fastest growing area in organic chemistry is organometallic chemistry. This area is at the stage, where classical organic chemistry was at the time of its heyday. New reagents, reactions and synthetic methods are being discovered frequently. Most of the information that is getting accumulated is empirical, with no clear understanding of the processes involved. It is only recently that some progress has been made in understanding of the mechanisms of Grignard reactions discovered in 1901. A whole wide field awaits detailed mechanistic study.

2. Bioorganic chemistry has been defined differently by different people. There is good evidence that it developed by the interaction of physical organic chemistry with biochemistry. In the preface of the new series "Progress in Bioorganic Chemistry" E. T. Kaiser and F. Ke'zdy¹⁵ trace its origins.

To the enzymologist whose curiosity was not satisfied with the purification and the superficial characterization of an enzyme, to the physical organic chemist, who had the conviction that the elementary steps of biological reactions are identical with those observed in organic chemistry, and to the physical and organic chemists to understand and imitate the unequaled catalytic power and specificity exhibited in living organisms".

A large body of investigations in physical organic chemistry is already being pursued in this area and one can expect, important advances in design of enzyme models and recognition of newer facets of catalytic activity.

3. Most of the Industrial organic bulk chemicals are made by processes which have few parallels in common laboratory practices of making those chemicals. The chemistry of many of these industrial processes is poorly understood. They were discovered by trial and error mostly by chemical engineers or physical chemists with very little appreciation of the organic reactions

involved. This is an area where methods of physical organic chemistry could significantly contribute not only to a better understanding, but also to better processes of economic importance.

4. The development of new drugs, insecticides and agricultural chemicals like pesticides, fungicides is largely by methods of trial and error. The process of finding a new drug involves synthesizing and screening sometimes as many as 5000 similarly constituted compounds. Analogous situation holds in the field of agricultural chemicals. Enormous expense and time is involved in the development of truly effective compounds. It is no coincidence that only affluent companies hold monopolies in these fields.

Although some progress has been made in the application of the linear free energy relationship to correlate structure and activity^{16,17} we are far away from developing rationales in the design of new biologically active compounds. To correlate structure with biological activity, in a meaningful manner, with predictive capabilities is perhaps the most challenging frontier for the physical organic chemist.

ACKNOWLEDGEMENT

I wish to thank Dr. G. A. Bhat and B. M. Hosur of our research group for collecting the statistical information needed for Figure 1.

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ANNOUNCEMENT

INTERNATIONAL CONFERENCE ON LEAF PROTEIN RESEARCH

The International Conference on Leaf Protein Research organised by the Society for Green Vegetation Research, was held from 5-8 October 1982 at the Botany Department, Marathwada University, Aurangabad. There were about 200 participants. Seventyone papers and reports were presented at the conference. Members from Australia, Bangladesh, Denmark, Egypt, France, Ireland, Italy, Japan, Mauritius, Nigeria, New Zealand, Norway, Pakistan, Spain, Sri Lanka, Sweden, United Kingdom, United States of America and Venezuela also took part in the conference.

The conference was inaugurated by Dr G. R. Mhaisekar, Vice-Chancellor of Marathwada University, and the keynote addresses were delivered by Prof. N. W. Pirie (Harpenden, U.K.) and Dr Narendra Singh (Mysore). Prof. Mhaisekar identified the theme of the Conference as the integration of leaf protein research with the developmental requirements of current times. In discussing 'some controversial aspects of leaf protein research', Prof. Pirie focussed on the areas needing special research attention for promoting the use of leaf protein in human food, emphasising its great potential as the most abundant source. Dr Narendra Singh called for a comprehensive green vegetation research. He pleaded for practical farm-based programme of production, and for forage and feed use of the products.

There were five technical sessions for presentation of papers and reports. In session I, considerable data on choice of raw materials, potential crops and agronomic studies to maximise the yields of extracted

leaf protein were provided. Session II had papers on new equipment and techniques for separating protein from the juice as well as for improving the quality and getting pigment-free leaf protein. In session III, various papers presented information on widely dispersed aspects such as composition, quality and properties of extracted leaf proteins. Session IV dealt with studies on the use of extracted leaf protein in food and feeds of pressed residue as forage, and of the deproteinised "whey" in fermentation, etc. Session V had mainly reports and view-points. There were country/institution reports on leaf protein research progress in France, Italy, Japan, New Zealand, Pakistan and U.S.A. and also projection for work in South East Asian region. In addition, there were reports and viewpoints on use of leaf protein in human food. One paper on limited scope of food use of leaf protein in overcoming protein and carotene malnutrition, especially among the children, provoked a lively discussion.

It was decided to hold the next meeting as the International Conference on Leaf Protein and Green Vegetation Research in Japan or in New Zealand in 1985.

Narendra Singh,

Organising Secretary,
International Conference on Leaf Protein Research,
General Secretary,
Society for Green Vegetation Research,
Mysore.