CONFORMATIONAL ANALYSIS—SCOPE AND PRESENT LIMITATIONS

V. PRELOG

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Mr President, dear fellow-conformationalists:

I am grateful to the Programme Committee for giving me the opportunity to make a few introductory remarks to this Symposium on Conformational Analysis—Scope and Present Limitations, as it has been named by the Organizing Committee. There was clearly a general feeling that conformational analysis as a whole would be too great an area to cover because it has extended during the last two decades into all fields of chemistry, including biochemistry. In fact, the biochemical implications of conformational analysis are so numerous, varied, and important that it would be impossible to treat them adequately in the time at our disposal. They have therefore been placed 'off limits' of the Symposium.

I begin with a few personal reminiscences of the birth, growth and development of this so vital and important branch of chemistry. I very well remember that in the early forties, when I started teaching at the ETH, I was astonished how little electronic theories of reactivity—as developed by Robinson and Ingold—were known and used in Zürich. The efforts of Professor Plattner and myself to introduce these theories in teaching and research encountered only a benevolent detachment of my famous predecessor in the Chair of Organic Chemistry, Professor Ruzicka. He confessed frankly that in his daily work in the field of alicyclic compounds—terpenes and steroids—these theories were of very little value to him. Most of the puzzling differences of reactivities of stereoisomers could not be rationally explained at that time—neither by these theories nor by the difference of steric hindrance recognizable by examination of molecular models.

We knew too well that Ruzicka was right. It was therefore a revelation to me when I learnt at a colloquium given in the Institute of Physical Chemistry at the University of Zürich, of the work of Pitzer and others about interactions hindering the free rotation around single bonds, and later about the other interactions of non-bonded atoms that are not represented by the atomic radii of conventional molecular models. By mentioning 'others' I would like to pay a tribute to several forerunners and contemporaries of Pitzer who made important contributions towards the knowledge of these interactions. It was evident to me that these interactions contained the clue to many puzzling aspects of reactivity, especially of alicyclic compounds. I started to use them, in a rather naive way, in teaching and in our research on natural compounds, many-membered rings and asymmetric synthesis.

At about the same time several other chemists became aware of the great possibilities of such an approach. Among them, Barton showed with the

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greatest skill and zeal how these interactions, combined with electronic theories of reactivity, can be used in solving the numerous enigmas of alicyclic chemistry that Professor Ruzicka had in mind when he complained of the inadequacy of current theories. Barton used as an experimental basis for his considerations mainly examples from polyterpene and steroid chemistry, and it was important for his success that the compounds of this group are largely built from six-membered rings. It was at that time firmly established, especially by the electron diffraction studies of Hassel and associates, that the chair form of the cyclohexane ring—the symbol of our Symposium— is stable even in the gaseous state and therefore determines in great part the topography of the molecules which Barton discussed in his considerations.

Many chemists were deeply impressed by the progress achieved in this way and a new branch of chemistry based on these ideas, conformational analysis —dealing mainly with six-membered ring compounds—developed so rapidly that already by 1965 500 pages were necessary to cover the subject in a monograph. Eliel, Allinger, Angyal and Morrison define conformational analysis in this monograph as 'analysis of physical and chemical properties of a compound in terms of the conformation (or conformations) of the pertinent ground states, transition states, and excited states'. This definition and similar ones in other books and articles are based on the assumption that we know what conformation is or that we define conformation so that it becomes consistent with the definition. I shall return to this delicate point at the end of my discussion.

Let us now assume that we all know what conformation is, even if we do not agree about the wording of a definition, and return to history. In the early fifties much effort was spent in demonstrating how useful conformational analysis can be in solving various types of problems in the chemistry of natural products and in synthetic and physical chemistry. During this period a disadvantage—but also to a certain degree an advantage—was that the approach was qualitative, or semi- or pseudo-quantitative, and that the knowledge of the exact topography of molecules, even in the ground state, was rather limited. Optimistic users of conformational analysis thus often had the freedom to assume the topography that best fitted the observed facts, and they made ample use of this freedom.

A new era of conformational analysis began in the late fifties and early sixties as a consequence of the dramatic progress of instrumental analysis. All kinds of spectroscopy, above all n.m.r. spectrometry, x-ray analysis and related methods today allow us to obtain much more extensive and precise information about the topography of molecules than was ever possible before. I should not fail to mention here the important contributions in this area of our hosts in Brussels, Professor Chiurdoglu and his young colleagues. As a result of all this it is now possible to correlate physical and chemical properties of many compounds with molecular topographies determined by several independent methods and at different temperatures. The knowledge of thermodynamic parameters increased enormously, and a trend developed to make conformational analysis a quantitative method. It was unavoidable that these new developments should also lead to some healthy disappointments. The independently determined topographies revealed in several cases

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the incorrect guesses made during the first heroic era. However, even in cases where conjectured topographies were shown to be essentially correct, the relationships between the topographies and properties often failed to fit the observed facts. One of the two very important reasons for such failures is that the conformational analysis of transition states is still in a very rudimentary state. The second one is the unsolved problem of solvation. At present, unwarranted assumptions must be made about the topography of transition states, and one sometimes wonders if correct answers can be obtained at all! It is therefore urgent to improve the old and to find new methods of determining or estimating the topographies and 'thermodynamic' parameters of transition states.

I think this is the place to mention the efforts to estimate thermodynamic and quasi-thermodynamic parameters from topography and vice versa by *ab initio* or semi-empirical calculations. Whereas the *ab initio* calculations will undoubtedly yield a more fundamental basis for understanding conformational analysis, the semi-empirical approach corresponds more to our simple, intuitive concepts and also begins to yield results of practical value.

Calculation based on empirical potential functions have been especially rewarding in the field of alicyclic compounds, many membered ring compounds and steroids. The results are not only in satisfactory agreement with the available experimental data, but they have also led to predictions about the topography of the energetically favourable conformations, which have been confirmed experimentally. Special efforts have also been made to derive conformations of high polymers and to correlate the results of calculations with those of experiment. Theoretical calculations are especially important for estimating the probable topographies of transition and excited states, where experimental methods encounter formidable difficulties.

The most exciting applications of the semi-empirical approach are the calculations of secondary, and even tertiary, structures of polypeptides, proteins, polynucleotides and nucleic acids from the knowledge of their primary structures. The problem is still far from being solved, but the results are very promising and the possibilities are not at all exhausted.

The development of conformational analysis somewhat resembles the situation when a new drug is put on the market. In this case success can be measured by sales. Following a shorter or longer period of induction, sales go up steeply. After some time it becomes apparent that the positive sides are over-estimated, the drug is improperly used, failures and side-effects become known. Something has to be done to put things into a better light, improved methods and fields of application have to be found, and scepticism and optimism have to be balanced. It is one of the tasks of our Symposium to do this for conformational analysis.

Before I end these introductory remarks I would like to return to a point that I mentioned briefly at the beginning. It is astonishing that we discuss, write articles and books, and hold symposia about conformations and conformational analysis, while at the same time are unable to define conformation in a way that everybody can accept. It could be helpful in dealing with this point if I report here briefly, before a larger audience of specialists, about another conference where this and similar matters were discussed. This con-

ference took place in April 1968 in London under the auspices of IUPAC at the Ciba Foundation; 24 chemists from 10 countries were present. A detailed and prolonged discussion, in which all present participated, took place about the concepts of configuration and conformation. No agreement could be achieved, because there are several contradictory opinions about common usage of these concepts. Nevertheless, certain conclusions could be drawn: (a) All attempts to define configuration and conformation in such a way that they form two non-overlapping concepts fail. (b) It is not possible to define configurations and conformations in terms of the size of energy barriers which separate different configurations on the one hand and different conformations on the other hand. It is also not possible to distinguish between configurations and conformations by means of a characteristic operation such as bond fission, or rotation around a bond, or the continuity of these operations. (c) Sometimes the torsion angles around single bonds or formally single bonds only have been emphasized in definitions of conformations. Because of intermediate bond orders the definition of conformation should not include bond order. However, several chemists disagree with the consequence that cis–trans-isomers on double bonds should be called conformers.

An interesting unconventional suggestion made by Arigoni and Mislow was: 'Let us call configurations all geometric properties that are responsible for stereoisomerism'. At that point it was evident that chemists disagree even about the definition of stereoisomers! Some of them regard only isolatable molecular species as stereoisomers, whereas others (including myself) think that this is not practicable. It seems more reasonable to regard as stereoisomers all different molecular species with the same connectedness that corresponds to an observable energy minimum, even if they can be detected only by sophisticated methods or at very low temperatures. If we adopt this definition the number and types of stereoisomers will of course increase considerably.

As to the definition of conformation two main opinions emerged from our discussion: (a) Specification of conformation includes bond distances, bond angles and torsional (or dihedral) angles of a molecule. In this case it is practically synonymous with molecular structure as determined by x-ray analysis and related methods. It is a third synonym for the topography of a molecular species. Conformational analysis should then be called topographical analysis, which seems quite reasonable in the light of newer developments. If we adopt this proposal we have to change the title of our next symposium. (b) The characteristic features of a conformation are the torsional angles. This is a standpoint which is, at least in my opinion, much more in agreement with the historical evolution of the concept, but both standpoints are defensible. I mention the results of our discussion because disagreement about meanings of words (e.g. freedom, democracy) sometimes causes confusion and troubles that are avoidable, and moreover makes teaching difficult. But discussing the meaning of words is a time-consuming activity so let us now start with the serious work!