

From a synthetic organic chemist

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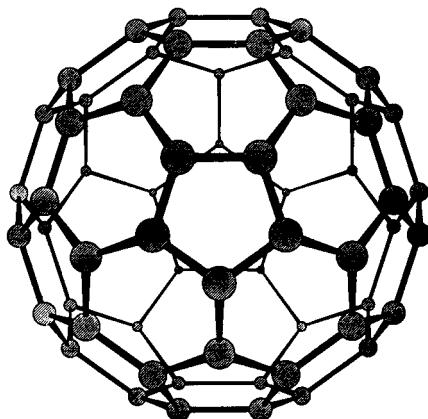
Biography: Teruaki Mukaiyama was born January 5, 1927, in Nagano, Japan, and received his B. Sc. from the Tokyo Institute of Technology and the Ph. D. from the University of Tokyo. He is a Distinguished Professor; Science University of Tokyo, and President, Research Institute of Science and Technology, and has research interests in Synthetic Organic Chemistry.

The great advance in physical organic chemistry during the past sixty years has made an invaluable contribution to wide areas of organic chemistry, such as in natural products and in synthetic chemistry. Physical methods were adapted to the structural chemistry of organic compounds as powerful tools for elucidating the structures of even complex molecules in a period when many important and interesting synthetic targets appeared one after the other. The elucidation of reaction mechanisms enabled us to understand pathways necessarily employed in a synthetic approach and led us to find the most suitable methods and proper reaction conditions. Assisted by this understanding, we now have a strong background in the development of synthetic organic chemistry, using the above as the weft in an utterly routine way.

From the synthetic organic point of view, however, there still are chances for many unpredictable events to happen, and in such cases, experimentation is important when one wants to take a new leap. "Practice first" has been the motto and our basic concept for many years since it is not easy to find something "new" from logical thinking alone. In order to overcome such restriction, better theoretical approaches which are effective in the precise understanding of physical properties and reactions are strongly desired.

Some examples for the contribution of physical organic chemistry to the new chemistry are described here.

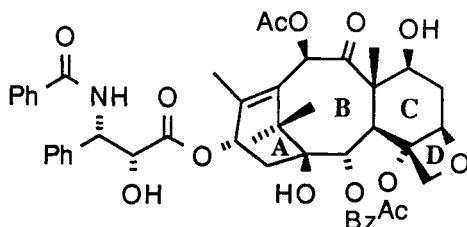
Fullerene and its related compounds, the most-recently-discovered pure carbons, have been of current interest from many aspects including the possibility of new functionalized materials. Since this unique soccer ball-like structure has attracted many scientists, great advance has been made in the areas of synthesis, reactivity, structure, bonding, dynamics, thermodynamics, cage formation, and geometry of fullerene. In this, physical organic chemistry has played an important role, and has revealed these unique properties more precisely and scientifically. High resolution and dynamic NMR techniques in both solution and solid phases are among the powerful weapons in this area. One feature of these studies is that the experiments are combined closely with chemical bonding, molecular orbital, and crystal structure theories assisted by computer systems, which contributes to the development of this chemistry. This fusion of experiments and theories will be a goal of physical organic chemistry, not only in fullerene chemistry, but also in chemistry of various compounds of interest related to other scientific fields such as physics, biology, *etc.*



A conventional "trial and error" approach without deep analysis and suitable designing of the precise key intermediates cannot help us to develop new methods for controlled reactions such as stereocontrolled reaction and asymmetric synthesis, which are of growing importance today. Careful construction of chiral molecules through "exact understanding" of transition states is needed to attain our goal.

Also, the so-called "solvent effect" has great influence on research work in organic synthesis. With repeated screening, we select what seems to be the best solvent of all that we have in the laboratory. Therefore, it would be a big gift if essential elucidation of solvent behavior in reaction systems can be made clear theoretically. That is, to combine the physical approach and the synthetic organic sense is quite worth the effort. Physical organic chemists can thus be expected to turn their attention to the development of synthetic chemistry because it is more and more related to such control of synthetic methods: that is, if one catches an interesting hint, then the development can be effectively realized by making a working hypothesis which is backed up and tested by more analytical approaches.

In dealing with the total synthesis of compounds of interest today by planning an experimental strategy to follow to reach to the goal most effectively, we often face problems in realizing a selective reaction limited to one site in a multi-functionalized complex molecule during the synthetic procedure. However, it is not so successful to try to solve these problems using knowledge based on experimental experience alone. Many "detouring" synthetic steps have to be taken into consideration before we come to a goal. Further, in accomplishing a total synthesis of a complicated molecule, conformational control is often quite effective; for example, in the total synthesis of taxol, which has been standing as a major challenge for organic chemists for over 20 years. The calculation-based approach made a useful contribution by treating these conformationally flexible molecules. Holton, *et al.* (1) successfully accomplished the total synthesis of taxol by controlling the reactions skillfully based on the concept of conformational control. They used molecular mechanics in preparing key intermediates having the 8-membered B ring, which led to the functionalized ABC ring system. For the future it is desired, therefore, to develop methods even more "directly" useful for this approach by providing useful techniques to even more suitable methods in the synthesis. It could be very helpful if the necessary factors to control and to minimize the number of reactions involved in the synthetic strategy were defined by precise estimation.



It is our task to dig out further effective synthetic methods hidden in the mines of wisdom. They may be unseen but are inexhaustible. Exploration of excellent methods (reactions) will eventually help to accomplish the total synthesis of complex molecules. Therefore, cooperation between what is "predictable" and "unpredictable" will be the key to our future.

REFERENCE

1. R. A. Holton, C. Somoza, H.-B. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile and J. H. Liu. *J. Am. Chem. Soc.* **116**, 1597 (1994); R. A. Holton, H.-B. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, and J. H. Liu, *ibid.*, **116**, 1599 (1994).