Organic Synthesis and Computer Chemistry

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Combinatorial chemistry — a new technology developed primarily to find "lead" drugs — is expected to become a paradigm of organic synthesis in the 21st century, dissociated from traditional concepts. On the other hand, combinatorial chemistry is still far from being accepted by many modern chemists as it seems lack the rigorousness of recent synthetic chemistry based on rational design and scientific creativity.

Although I am a traditional synthetic chemist, I am impressed by combinatorial chemistry. Of course, in the 20th century organic synthesis has given rise to many valuable polymers, drugs, and so on, and has completely changed our way of life. In the next century there will be an increasing desire for new compounds with revolutional functions that are also beneficial to the environment. The creation of new compounds is indeed the main purpose of organic synthesis. How can we, therefore, actually create such significant compounds? Serendipitous discovery as well as rational design is, of course, important, but now combinatorial chemistry offers another practical way. In order to match the expectations for organic chemistry in the next century, there needs to be a renovation in the field.

Organic synthesis has another basic purpose, namely, the synthesis of certain compounds such as useful natural products via the most rational synthetic pathway, sometimes with the invention of new reactions. Every organic synthesis consists of a series of organic reactions, in which only a few reactions are usually crucial even in the multistep synthesis of complex molecules. Hence, most synthetic chemists are striving to develop innovative reactions. Numerous reactions are reported every year, and among them some reactions using organometallic compounds, for example, are certainly innovative. However, most reactions have received little attention because they are only minor versions of known methodologies and are often not useful at all. In the meantime, organic synthesis itself has remained in the stage of experientialism. Its great advances in the last 20 or 30 years are owed mainly to the progress in related research fields such as chromatography and spectroscopy, which has completely changed the methods of separation and structural elucidation of organic compounds. However, laboratory work and instrumentation of the synthesis itself, as well as its basic concepts have essentially remained unchanged for many decades. In order to emerge from the old ideas of experientialism, more application of computer chemistry and automated synthesis as well as solid-phase synthesis should be considered.

Thirty years ago, Professor Corey proposed the OCSS program for the design of synthetic pathways, which was then followed by several alternatives. Now, these should be reexamined and, if possible, improved. Current computer chemistry is even routinely accessible for the determination of electronic and conformational structures of rather small molecules and the mechanistic explanation of some reactions. Of course, many organic reactions (in the ordinary solution phase) are too complex and delicate for their exact features to be predicted by computer. Nevertheless, the technique should be used extensively in organic synthesis. Computer-aided design of crucial steps and robotic operation of conventional steps in some synthetic works have already been undertaken. These are only examples of the strategic move to the next century. Revolutionary developments by young synthetic chemists from the various standpoints of organic synthesis are earnestly desired.

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