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Introduction: Combinatorial Chemistry

Combinatorial chemistry is in essence a brute force alternative to the reasoned, intellectual efforts of chemists to design, in a rational manner, compounds for specific purposes. As if that were not enough, many practitioners of this new "technique" discard the centuries-old goal of single compound synthesis in high yield and purity, and deliberately aim at the synthesis of enormous mixtures of compounds. It is therefore not surprising that a slightly controversial aura continues to surround combinatorial chemistry, despite its simplicity, power, and success. What then is combinatorial chemistry in practice? It is really an umbrella term that covers a wide array of topics, including the parallel synthesis of individual organic compounds, the synthesis of complex mixtures of organic compounds, the synthesis of the vast phage display and nucleic acid libraries, and all the associated technologies for handling these libraries and obtaining useful molecules from them. This issue of *Chemical Reviews* reflects the diversity of efforts that is contained within the overall framework of combinatorial chemistry. The seven articles represent a sampling of current efforts in the field. As befits a subject that has grown up at the interface of chemistry and biology, the reviewers' viewpoints vary from strictly synthetic to almost purely biochemical. Two articles describe recent work with libraries of nucleic acid sequences. The review by Osborne and Ellington focuses on the selection of binding motifs from random libraries, including efforts to increase diversity and manipulate the properties of the selected entities through the use of nucleotide analogs. The article by Breaker focuses on the exploration of the catalytic abilities of nucleic acids, and very nicely covers the use of increasingly sophisticated selections to derive catalysts for an ever wider range of chemical transformations. The third review in the "biological" set is by Petrenko and Smith on phage display of peptides and proteins; this review provides a comprehensive survey of the peptide motifs that have been isolated or defined by this powerful technique, along with some interesting comments on strategies for the exploration of sequence space. Four articles describe synthetic organic developments in combinatorial chemistry. The review of the one-bead-one-compound approach by Lam, Lebl, and Krchňák covers synthetic methods, screening technologies, approaches to decoding these pools, and many specific examples of compounds isolated in this manner. The review by Nefzi, Ostresh, and Houghten describes the remarkable range of classes of chemical compounds for which libraries have been synthesized by solid-phase methods. Pirrung's review focuses on a particular aspect of solid-phase synthesis, namely spatially addressable synthetic approaches, of which there are now a growing number. Finally, Gravert and Janda review recent progress in a hybrid approach to library synthesis, namely the use of soluble polymeric supports in efforts to combine the advantages of traditional liquid-phase synthesis with the benefits of solid-phase synthesis.

Of the different kinds of libraries described in the above reviews, the biologically based libraries (antibodies, phage display, and nucleic acid libraries) have two built-in advantages (and one big disadvantage). The first advantage is the ability to be amplified, so that multiple rounds of selection can take place—this avoids the limitation on library size that is imposed by sequential screening methods. The second advantage is the ability to generate new diversity during amplification. Multiple rounds of selection coupled with mutagenic amplification lead to Darwinian evolution, a process that automatically optimizes properties subjected to selective pressure, such as binding affinity or catalytic activity. This powerful advantage comes with a severe price, and that is a limitation on the chemical nature of the libraries involved to proteins, nucleic acids, and their close analogs. The purely chemical approaches to combinatorial chemistry allow much greater molecular diversity, but the price of this diversity is that only a single round of selection is possible—i.e., the desired compound within a library must be identified in the first pass of the screening algorithm. Fortunately, a sensitive screen and a well-designed library may yield useful lead compounds directly, with the leads subsequently optimized by more traditional medicinal chemistry approaches. Among the most interesting of recent developments are attempts to use combinatorial chemistry approaches in this optimization phase, for example through the design of secondary libraries that explore a more localized region of "shape space" surrounding the original compound. Sequential library design, aided by computational

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tools, thus brings a measure of "evolutionary" process to chemistry.

I express my thanks to the authors who contributed the careful and thorough reviews presented in this volume. These presentations should interest not only those readers who currently use combinatorial methods, but also those who are considering this approach to a particular problem, and those who are so far merely watching the amazing developments in this area. I hope that these reviews will stimulate further advances in this rapidly developing field.

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Guest Editor

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