Combinatorial Chemistry—Challenge and Chance for the Development of New Catalysts and Materials

Wilhelm F. Maier*

The development of new materials—that is, solids with a defined function, such as catalysts, superconductors, liquid crystals, and new polymers—together with the development of new pharmaceuticals probably represent the most important tasks for chemistry in the near future. The need for new materials and catalysts could never be satisfied with conventional methods. Large research efforts are devoted worldwide to the development of more selective new catalysts for a variety of processes (e.g. direct oxidation of benzene to phenol and of propene to propylene oxide, dehydrogenation of the C_4 fraction to isobutene and its oxidation to methacrolein or methacrylic acid) by conventional methods. The need for better superconductors, luminescent materials, photo- or thermochromic materials, new semiconductors, transparent conductors, and many other materials increases continuously. Most of the new materials have been discovered either by systematic screening or by serendipity. With respect to the discovery of new lead structures, conventional research has to be blamed for restricting itself largely to known fields and structures. Dominant here are the modification, derivatization, and preparation of analogues of well-known materials as well as the equipment-intensive and expensive detailed characterization of chemical processes on known materials and catalysts with near-atomic resolution. The strengths of conventional chemistry lie in the optimization, systematic modification, and improvement of new lead structures, not in their discovery. Discovery is the potential strength of combinatorial chemistry.

The origin of combinatorial chemistry is found in nature, where the vast diversity of life has developed through the combination of only a few building blocks, such as amino acids and nucleic acids. The immune system starts its defence against unknown organisms with the "combinatorial" production of millions of different antibodies, and then switches to exclusive production of the appropriate antibodies once they are recognized by rather complex mechanisms. Combinatorial chemistry, which started with the production of peptide and oligonucleotide libraries about 15 years ago,[1] has meanwhile established itself in the pharmaceutical industry as an important and rapidly growing technique for the discovery of new lead structures in drug development. This aspect of combinatorial chemistry utilizes the highly advanced concepts of organic synthesis for the elegant and efficient preparation of compound libraries. The parallelism involved as the concept to increase efficiency of the experimental work in the area of drug development may well be a major motivation for the strong engagement of the pharmaceutical industry as well as for the reservation of academic researchers in the area of combinatorial chemistry.

In my opinion an important argument for a more intensive engagement of academic research in this area is the huge potential of combinatorial chemistry for new discoveries and new lead structures. This can be elucidated with a few numbers. Bohacek et al. have recently attempted to estimate, based on structural considerations, how many stable organic structures are possible from the elements C, O, N, S (and H).[2] They came to the astronomical number of 10^{63} stable structures for molecules with up to 30 of the above elements. Under the assumption that this number is correct, a total mass of 10^{60} g would be obtained when only 1 mg of each compound would become available. The total mass of the earth is about 5×10^{27} g, and that of our sun is about 2×10^{33} g. This means that the mass of this organic library would be equivalent to the mass of 10^{27} suns! The total mass of the known universe is estimated to be about 10^{63} g. There are neither so many suns in the known universe, nor that much carbon! When we generously assume a total of 20 million known organic compounds, with 1 mg of each a total mass of just 20 kg represents our present "chemical universe", which is small compared with the mass of 10^{27} suns. It can be concluded that although mankind has opened a nice field of organic chemistry, it is negligibly small compared to the organic diversity that is theoretically possible. Even with combinatorial methods this diversity can never be explored comprehensively; these methods can only help to find new lead structure more often than in the past.

In the area of drug development systematic synthesis concepts of organic chemistry could be ideally combined with combinatorial principles. Through the use of well-defined synthetic building blocks and synthetic strategies libraries of almost any class of compounds have been or can be prepared. However, the major disadvantage is that only known structural elements can be combined. Combinatorial chemistry in

[*] Prof. Dr. W. F. Maier
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2987
E-mail: maier@mpi-muelheim.mpg.de

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the area of drug development only allows systematic access to structural diversity within the limits of our known chemistry. Approaches to access new areas and structures, which according to the above numbers should exist in vast numbers, are not yet known (for example systematic permutation of the elements O, C, N, S, and/or P or alteration of rings, ring sizes, and/or connectivities in any moderately complex organic structure immediately leads to plentiful new structures, most of which are not accessible by "linear" combinatorial chemistry).

The situation becomes even more problematic when we move from organic diversity to the diversity of the periodic table. Under the assumption that there are 75 useful and stable elements, about 5600 binary, 4×10^5 ternary, 3×10^7 quaternary, and over 10^{18} decanary compositions are possible, and this without even considering stoichiometric and structural diversity. Here it should also be considered that the composition is only one aspect of the vast chemical diversity (CH = one binary component = all hydrocarbons, CHO = all molecules containing just C,H, and O, independent of structure and stoichiometry; analogous for CHN, CHNO, CHS, CHNOS, etc.). The structural and stoichiometric diversity that is potentially contained in every individual combination of elements brings a second astronomical dimension to this simple-minded view of chemical diversity. Since the total number of known inorganic structures is much smaller than for the organic counterparts, it can be concluded that the little that is known in inorganic chemistry becomes negligible when compared with the possibilities contained in the periodic system. Combinatorial chemistry is presently the only rational concept offering a more effective access to this diversity, whereby it seems obvious that a systematic and comprehensive access to chemical diversity will be impossible. Any combinatorial synthesis of new materials should readily lead to new materials within a relatively short time. For the sceptic I may point out the superconductors, which were detected by conventional methods but whose existence had not been expected by traditional chemistry and physics. It can be expected that through the combination of elements of the periodic table any number of new materials with completely new, or at least extremely improved, properties can be obtained.

Combinatorial solid-state chemistry and materials synthesis differ significantly from organic chemistry. Here no advanced synthesis concepts exist, and the preparation of a materials library will almost automatically generate new solids. The following tasks of such a combinatorial solid-state chemistry are therefore of equal importance:

1. development of synthesis methods for the preparation of libraries of solid-state components
2. development of new and effective methods for the detailed characterization of library components
3. development of procedures for the simultaneous detection of desired properties of library components

There are only a few generalizable synthetic strategies in inorganic solid-state chemistry. In contrast to the organic synthesis of defined molecules, the preparation of homogeneous inorganic solids (defined phases) is dominated by the "primitive" heating of defined mixtures (mixing, milling, and heating or decomposition of fine powders). Such reactions are based upon two basic steps, the solid-state diffusion of the reactants and the nucleation of crystalline intermediates or products. The rate-determining step of such a reaction is the diffusion, owing to the high activation barrier and the large distance of diffusion as a result of the macroscopic size of common powder particles. An elegant and rarely used synthesis technique is based on the sequential deposition of thin films (thickness in the range of submonolayer to a few atomic layers) by controlled evaporation. Thus, any stoichiometry can be produced, and diffusion resistance and diffusion distances are extremely reduced. As a result new kinetically stable phases that were not yet accessible by conventional techniques have been prepared. Johnson has advanced this technique,[3] and with it many new solid phases have been identified already.

Combination of thin-film deposition with state-of-the-art masking readily provides access to materials libraries with spatial resolution. The first such library, prepared by Schultz et al. in 1995, was an array of 128 components prepared by masking and radio frequency (RF) sputtering, and led to the discovery of new superconducting materials.[4] Just two years later, searching for new luminescent materials, Weinberg and co-workers from Symyx technologies reported on investigations on 25000-component libraries prepared by the combination of masking with physical vapor deposition (PVD).[5] The advantage of such thin-film techniques is controlled access to nearly all element combinations of the periodic system. Of disadvantage is, however, that the laboratory or bulk synthesis of newly discovered compounds has to be developed subsequently.

The methods of liquid-phase synthesis—such as sol–gel and hydrothermal synthesis, polymerization, and precipitation reactions—are free of such upgrading problems and also suitable for library syntheses. Conventional synthesis robots can be used for library preparation. The use of ink-jet technology, as applied with high precision in standard color printers, has been appealing. A library of new luminescent materials has been prepared from aqueous solutions of La, Eu, Gd, and Al nitrates.[6] Here volumes as small as 0.5 nL can be dosed with high precision and spatial resolution. Such an ink-jet technique was also applied in the first combinatorial discovery of a new heterogeneous electrocatalyst for applications in the methanol fuel cell. Mallouk et al. projected three-dimensional phase diagrams of Pt, Os, Rh, Pd, and Ir onto planar libraries and investigated the activity of the components for methanol decomposition by the use of a H^+-sensitive fluorescence indicator. The best phases discovered ($Pt_{44}Ru_{41}Os_{10}Ir_5$ and $Pt_{62}Rh_{25}Os_{13}$) showed a 40% higher current yield compared to the industry standard $Pt_{50}Ru_{50}$.[7] Even hydrothermal syntheses can be carried out combinatorially for the direct preparation of materials libraries.[8]

As far as the recognition of materials properties and catalytic activities and the characterization of materials are concerned, there are no limits yet for creativity. Video cameras are useful for the spatially resolved detection of optical properties. IR cameras record with high temperature resolution spatially resolved heats of reactions and are useful

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as indicators for catalyst activities.[9] Even X-ray powder patterns with high spatial resolution from component areas larger than 50 μm[8] or X-ray fluorescence spectra from component areas larger than 100 μm can be obtained in an automated fashion with commercially available systems. Furthermore, spatially resolved mass spectra for product analysis on catalyst libraries have been reported.[10]

The strength of conventional research relative to combinatorial research has been commented on in detail by R. Schlögl.[11] However, the combinatorial approach should be discussed as complementary and not as competitive to conventional catalysis research. The combinatorial approach does not require a sound hypothesis describing the structure–activity relationship. The huge successes of the combinatorial chemistry approach in various areas of molecular chemistry should lead to similar expectations for applications in heterogeneous catalysis. That there is "no novel scientific knowledge produced [by combinatorial methods] in comparison to a typical empirical design method" has already been contradicted by the discovery of new materials.[4–7, 12] Schlögl is right when he emphasizes that there are no well-defined synthetic building blocks or synthetic strategies for the controlled synthesis of solids or catalysts and that the intuition of the chemist is still required. The design of useful libraries will be the key to success, since the above-outlined chemical diversity is much too large to be accessed comprehensively or systematically by sheer library size. Conventional catalysis and materials research remain the decisive instruments in development and evaluation, since any newly identified material or catalyst has to be synthesized on the laboratory scale and its special activity or property has to be confirmed and characterized in more detail under conventional conditions.

In summary it can be stated that there are already several effective methods for the preparation and characterization of significantly different materials libraries, and these have been highlighted just recently by Bein[12] and by Liu and Schulz.[13] In the near future a rapid development of new preparation and characterization techniques can be expected. Combinatorial chemistry presents a unique chance for the development of new materials and catalysts, and its major task, at least in the academic environment, should be the discovery of new materials and not the fine-tuning and optimization of known materials.

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