Combinatorial Chemistry in Heterogeneous Catalysis: A New Scientific Approach or “the King’s New Clothes”?**

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When considering the future of chemistry one immediately finds that heterogeneous catalysis plays an important role. Biocatalysis and homogeneous catalysis are fields of ever increasing importance, but heterogeneous catalysis remains the workhorse for many industrial syntheses and treatment processes for environmental emissions.[1] Therefore, an enormous interest exists in the development of new, and the optimization of currently implemented, heterogeneously catalyzed processes.

The “empirical approach” is currently the only proven successful industrial approach for developing novel catalysts. However, it often proves to be very labor-intensive and uneconomical, since the potential for optimization is limited by the relatively small body of knowledge available from previous work. The “rational approach” is taken when a more detailed understanding of the fundamental reaction steps in a given catalytic process is desired. This approach is also used in industry as it provides fundamental information important to process optimization. The success of the “single-crystal approach”[2a] has provided a wealth of information about qualitative and quantitative properties of elementary steps which form a complex sequence of events in every ever so simple catalytic reaction.[2b] Further advances in the theoretical understanding of catalytic processes have been provided by microkinetic modeling studies.[3] Novel analytical tools including various in situ techniques and surface imaging by scanning probe microscopies are constantly being developed. Well thought out application of these techniques can significantly decrease the time required for process optimization.

A rational approach to catalyst development involves a series of steps, which should ideally be carried out in parallel. In the end, however, further optimization based on a fundamental understanding of the chemistry is necessary. It is also critical to assess the technical aspects of a process under study as early as possible in the development scheme. Table 1 shows the steps which are most critical when carrying out a rational approach to catalysis development. The interdisciplinary nature of this approach is also outlined with the various fields of expertise necessary for carrying out each step.

It is immediately clear that this approach is labor-intensive and requires excellent coordination. Industrial researchers typically invest most effort in the empirical component of catalyst research and very little in the rational approach. The implementation of a combinatorial chemistry[4, 5] approach interests, therefore, both those with the purely pragmatic desire to develop new catalysts[6] as well as those interested in obtaining a better understanding of fundamental catalytic processes.[7]

The combinatorial chemistry approach[8] distinguishes itself from the empirical approach in that the parallel investigation of a large number of catalysts allows statistically well-founded empirical rules to be derived for optimization strategies. In addition, the multidimensional parameter space is dramatically more precisely explored, which adds greatly to the chance of finding a global reaction optimum. Realizing such a combined approach requires the use of the most modern laboratory equipment available such as microreactors and automated microanalytical equipment[9] such as micro-gas chromatography. Accurate process control as well as data

Table 1. Important steps in the “rational approach” for the development of heterogeneous catalysts along with related disciplines.

Research step	Related discipline
catalyst screening with intuition of chemistry	chemistry
mini-reactor tests with the goal of optimizing the material and/or reaction conditions	chemistry, chemical engineering
technical relevance	chemical engineering
identification of the active phase(s)	physical chemistry
synthesis of model substances exhibiting the pure active phase(s)	solid-state chemistry
qualitative and quantitative analysis of the important elementary steps	surface science, physical chemistry, physics
development of a microkinetic model	chemical engineering, physical chemistry

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interpretation is only made possible with the help of substantial computer support. Statistical analysis of data minimizes the number of measurements needed by basing the course of future experimentation on previously obtained results. Combining statistical design strategies with good quality control results in precise and reproducible data and minimizes the likelihood of systematic errors occurring.

The huge success of the combinatorial chemistry approach in various areas of molecular chemistry has resulted in the development of a number of novel pioneering applications.[10] However, several difficulties that arise for its use in the field of heterogeneous catalysis[11] are presented below.

The combinatorial approach requires a sound hypothesis describing the structure–activity relationship for a given process. Such hypothesis are, in the case of heterogeneous catalysis, usually wide open to question. There are a number of exceptions, such as the idea of "selective lattice oxygen" in the catalysis of partial oxidations. The determination of the structure–activity relationship is one of the most sought after goals in modern catalysis research. Solution of this problem requires the combined knowledge of experimental and theoretical chemistry as well as that of the surface physics of a given reaction. Although, huge strides have been made in this area in the recent past, a complete understanding of such systems is a far removed.

A further problem is establishing clearly defined synthetic building blocks as well as determining a strategy for the reproducible preparation of the catalyst. The elementary steps involved in most solid-state synthesis are, at best, poorly understood. This is due to the enormous complexity of the heterogeneous interface reactions which form the foundation of most catalyst syntheses (precipitation, oxidation, reduction, calcination).

Identification of a well-defined "active site" as a target of optimization is a challenging problem in heterogeneous catalysis. For small molecules the structure and dynamics can be theoretically modeled with a great degree of accuracy. A large ensemble of small molecules is characterized by the individual molecular properties and/or their sphere of solvation. A material is therefore defined by the additive contribution of properties of all molecules present. The structure and reactivity of solids are, however, poorly understood in comparison, and the exact nature of the catalytically active material is often not known. This arises, in part, from the fact that solids contain a variety of defects which effect the reactivity. A correlation between the properties of the macroscopic material and its molecular building blocks is, therefore, difficult to establish for most solid materials. This naturally complicates the synthesis of the catalyst.

It is generally accepted that surface and volume defect sites function as the catalytically active sites in many reactions.[12] Typical examples of this are the phenomena of structure sensitivity, metal–support interactions, and the effect of surface deposits on catalytic activity. The development of the active phase is, in many catalyst systems, only achieved after significant structural reorientation (reconstruction)[13] of the catalyst surface and/or volume[14] under the reaction conditions. This activation period can range from minutes to many hundreds of hours,[15] and directly reflects the influence of the reaction conditions on the solid-state dynamics away from thermodynamic equilibrium. Most modern analytical tools only enable a relatively poor determination of both the type and quantity of solid-state defects. The direct synthesis of the catalytically active phase (defect structure) for relevant materials is, therefore, not possible. Close attention must be paid, when applying the combinatorial approach, to the solid-state dynamics of the test substance. An understanding of the synthesis steps involved is usually not available and a rational synthesis strategy is therefore not known beforehand. These would, however, be necessary prerequisites for performing a combinatorial chemical approach.

The micro and mesoporous materials may be considered as an exception to this rule. Here, one often has the possibility of determining the exact structure. A quantification of qualitatively well-defined active sites in the catalyst is therefore possible.[16]

Figure 1 shows an example of the complexity of the structure–activity relationship often encountered in heterogeneous catalysis. A slight variation of the long-range order of an X-ray amorphous, mixed oxide Mo_5O_{14} catalyst [17] leads to a new catalyst which exhibits greatly different catalytic activity for the oxi-dehydrogenation of methanol to form-

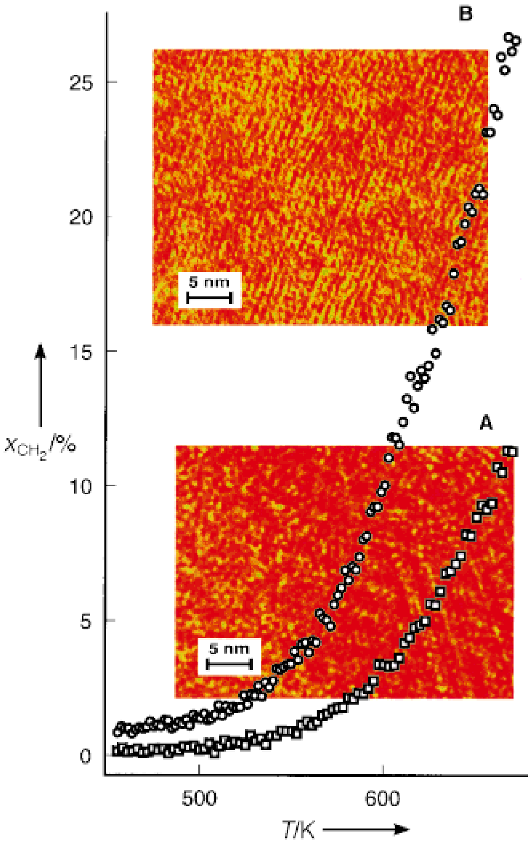

Figure 1. Yield x of formaldehyde for the catalytic oxi-dehydrogenation of methanol with a stoichiometric feed amount and 25 mg of catalyst. A) The precursor catalyst was used. B) The catalyst was heated at 573 K under argon with a slow heating rate prior to reaction. The HR-TEM micrographs (Phillips CM 200 FEG, 200kV, powder on carbon foil) emphasize differences in the long-range order. This is not observable with X-ray diffraction, but is clearly seen with differential scanning calorimetry. The catalytically active material is a metastable intermediate in the crystallization of the amorphous precursor.

aldehyde (based on product selectivity for formaldehyde). The identical precursor was used for both runs, but was first tempered in argon before the second run (Figure 1B). A slight variation in the oxygen stoichiometry, which was not measurable with standard analytical tools, was observed after close inspection of high-resolution transmission electron microscopy (HR-TEM) micrographs. A variation in the connectivity of the octahedral building blocks resulted in a dramatic change in catalytic activity. Thermal analysis was used to define the optimum conditions for activation of the precursor: gas composition, heating rate, holding temperature, and total time of activation were the parameters which had to be optimized.

A problem is encountered in automated catalyst synthesis when going from microreactor-sized tests to industrial-sized syntheses. The catalytic activity found during screening tests is usually not reproducible after scaling-up to larger processes. This last problem involves the parameter space required for the test experiments. The test conditions for life science systems or for the search for light-emitting materials[18] are set within well-defined limits. A platform for a comparison of experimental results is, therefore, guaranteed. The a priori definition of the necessary conditions for determination of the optimum performance of a heterogeneous catalyst is, in contrast, not possible. Different catalysts exhibiting nearly identical compositions often require dramatically different reaction conditions in order to obtain optimal performance. An efficient test protocol involving an automatic variation of controllable parameters such as reactant composition, temperature, pressure, space velocity, and reactor dwell time is therefore necessary. Past experience has shown that results obtained when testing catalysts under conditions where low conversions are desired for the sake of analysis are of limited practical use for the prediction of high conversion performance used in industry.

This arises, in part, from the fact that the performance of a catalyst depends on the conditions under which it is tested.[19] Not only the reaction conditions, but also the parameters of the reactor (reactor type, energy and mass transport, catalyst rheology) play a critical role. This dependence results in the well known "scale-up" problem encountered when attempting to use a laboratory-tested catalyst on an industrial scale. Implementation of microreactors and automated synthesis techniques without a reproducible catalyst ultimately leads to complications in the scale-up of the process at a very early stage. This will likely lead to serious delays in catalyst implementation.

One can therefore answer the question posed in the title very clearly. The implementation of the combinatorial chemistry approach is a novel scientific development in the field of molecular chemistry. Its application in heterogeneous catalysis is, however, very reminiscent of the strategy described 50 years ago by A. Mittasch.[20] This finding substantiates the doubts expressed in the title. Combinatorial chemistry is at best a modern variation of the Mittasch method which can never replace the efforts necessary for the rational approach. However, it provides another powerful tool for efficient catalyst screening. If one could understand all of the fundamental processes occurring at the heterogeneous interface, one could develop a device which would automatically select the best candidates as catalysts for particular chemical reactions, thus guaranteeing an efficient development process.

The results provided by such a presently still imaginary process would still not be immediately applicable to the synthesis of large amounts of catalysts. In no case is the development of a general "recipe" for catalyst preparation based solely on combinatorial chemistry experiments to be expected. Various approaches to synthesis of the target compound identified by combinatorial chemistry followed by thorough characterization will be necessary for efficient catalyst development. This essentially leads back to the rational implementation scheme outlined in Table 1. It is also not realistic to expect that one can determine a global minimum for a selected heterogeneously catalyzed reaction using combinatorial chemistry alone, since, in the overwhelming majority of cases, one cannot predict the exact material properties prior to their synthesis.

Proof that the scientific community is aware of such problems can be found in the materials science literature.[18a] Here, the development of a new material within a very well defined parameter space is carried out with the acceptance of the previously mentioned limitations.[18b] This is done using parallel synthesis routes which are contained in an inorganic "library".[18c] Despite the obviously positive results of such studies there is no novel scientific knowledge produced in comparison to a typical empirical design method. Although it is potentially useful, the combinatorial chemistry approach earns the title of this article with regard to its application in parallel synthesis and testing of new materials.

The combinatorial chemistry method provides, therefore, no new alternative to the rational method. It is rather a new tool to be used along with those currently available, such as the single-crystal approach. The combinatorial chemistry method differs greatly from the single-crystal approach in that it delivers no new fundamental understanding of the catalytic system under investigation. The latter should not be considered as a tool for developing a catalyst, but rather as an excellent means[21] for gaining fundamental insight into a catalytic reaction. Use of the combinatorial chemistry approach does, however, enable a substantially larger body of possible materials to be examined than the conventional synthesis making use of chemical intuition. This can result in a significant reduction in development time, provided the scale-up problems specifically associated with functional inorganic solids can be efficiently solved. Such an achievement may be reason enough to implement this technique in heterogeneous catalysis research. The chemist's intuition is then necessary for the optimal programming of the method as well as for the demanding analysis of the obtained data and materials.

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