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Evolution of Catalysts Directed by Genetic Algorithms in a Plug-Based Microfluidic Device Tested with Oxidation of Methane by Oxygen

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Abstract: This paper uses microfluidics to implement genetic algorithms (GA) to discover new homogeneous catalysts using the oxidation of methane by molecular oxygen as a model system. The parameters of the GA were the catalyst, a cocatalyst capable of using molecular oxygen as the terminal oxidant, and ligands that could tune the catalytic system. The GA required running hundreds of reactions to discover and optimize catalyst systems of high fitness, and microfluidics enabled these numerous reactions to be run in parallel. The small scale and volumes of microfluidics offer significant safety benefits. The microfluidic system included methods to form diverse arrays of plugs containing catalysts, introduce gaseous reagents at high pressure, run reactions in parallel, and detect catalyst activity using an in situ indicator system. Platinum(II) was identified as an active catalyst, and iron(II) and the polyoxometalate $H_5PMo_{10}V_2O_{40}$ (POM-V2) were identified as active cocatalysts. The Pt/Fe system was further optimized and characterized using NMR experiments. After optimization, turnover numbers of approximately 50 were achieved with approximately equal production of methanol and formic acid. The Pt/Fe system demonstrated the compatibility of iron with the entire catalytic cycle. This approach of GA-guided evolution has the potential to accelerate discovery in catalysis and other areas where exploration of chemical space is essential, including optimization of materials for hydrogen storage and CO_2 capture and modifications.

Introduction

This paper demonstrates a microfluidic method that utilizes genetic algorithms (GAs) for efficient exploration of chemical space and optimization of solution-phase catalysts with gaseous reagents. Catalysts play a crucial role in a majority of chemical processes, and the search for more efficient catalysts is perpetually ongoing.[1] Many catalysts are complex mixtures of several species,[1−3] and discoveries of new catalysts are slow and difficult and require efficient methods to explore the potential solution space. When multiple variables are involved, exhaustive systematic searches quickly become impractical.

The efficiency of biological enzymes under physiological conditions shows the effectiveness of evolution at exploring solution space and optimizing catalysts.[4,5] GAs aim to replicate this process of optimization in vitro, by using the principles of evolution to identify solutions to problems where a complex mixture of parameters makes systematic exploration unrealistic.[1,5,6] GAs have been successfully applied to develop heterogeneous materials and catalysts.[2,7] Here we focus on homogeneous catalysts, as they are easier to characterize, have intrinsically higher uniformity, and typically function under less extreme conditions than heterogeneous catalysts. As GAs require many reactions for each generation, the ability to run many of these reactions simultaneously is desirable. Miniaturizing these reactions is attractive to minimize consumption of reagents, reduce waste, and improve safety.[8,9] To implement a GA on these small reaction scales, here we used a plug-based microfluidic device that compartmentalizes reactions in droplets of solutions sur-

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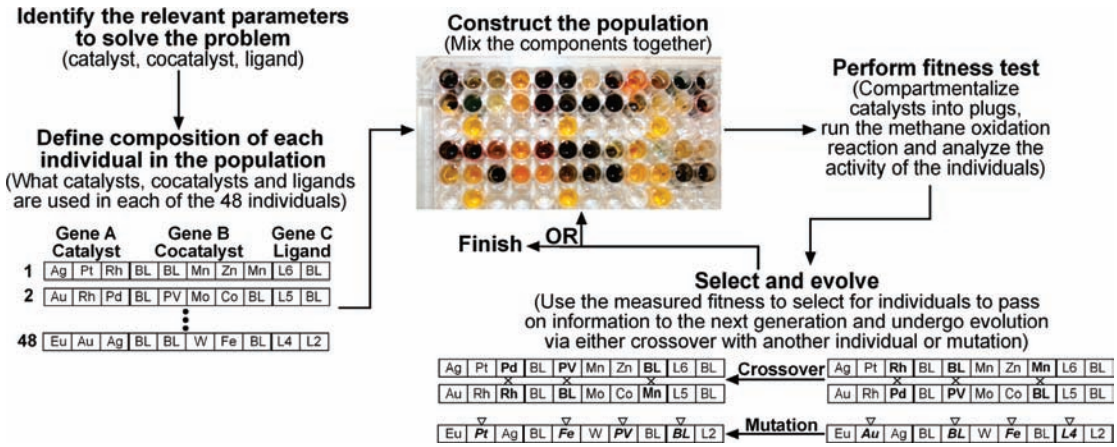

Figure 1. Schematic illustration of genetic algorithm (GA) implemented with microfluidics to search for catalysts. Each individual contained three genes to optimize the different parameters: catalyst (gene A), cocatalyst (gene B), and ligand (gene C). Each gene was composed of multiple chemical species, examples of which are shown in this schematic (BL stands for blank solution, PV for $H_5PMo_{10}V_2O_{40}$ (POM-V2), L# for a ligand defined in Table S1 (Supporting Information), and elemental symbols represent the metal present). After the first generation was produced, the catalytic activity of each individual was tested, and the results were analyzed to determine fitness. The fitness of the individuals was used to generate a new population of 48 individuals through a combination of functions that mimicked crossover or mutation. These new individuals composed the next generation, and the selection and evolution process was repeated over eight generations.

rounded by an immiscible fluorocarbon carrier fluid.[9−13] We chose to optimize the catalysis of the partial oxidation of methane because methane is an abundant and underutilized energy source.[14−17] Oxygen was chosen as the ultimate oxidant because O_2 is inexpensive and environmentally friendly.[17−19] Although methane oxidation systems using solution-phase catalysts exist,[19−23] these systems are limited by their low turnover numbers (TONs) or inability to use oxygen directly. Specifically, we used Shilov's alkane oxidation system[14,24−27] as a basis for designing the GA with the goal of finding alternatives to platinum for both the catalytic species (as Pt(II)) and the oxidant (as Pt(IV)) that can utilize oxygen. While alternative oxidants have been used,[23,28] including catalysts coupled to oxygen directly,[17,18,20] limited examples exist.

Developing a microfluidic system that implements GA-based approach for evolving catalysts required four steps: (1) defining the relevant components that make up the solution space for the catalytic system; (2) generating solutions containing multiple catalytic components within individual reactors; (3) introducing gases and pressurizing many individual reactors to allow for parallel exploration; and (4) analyzing the results of the experiments quickly and easily (Figure 1).

Results and Discussion

Development of the Genetic Algorithm. For this system, the relevant parameters were determined to be the catalyst itself, represented as gene A of the GA, a cocatalyst to assist in the reoxidation by O_2 as gene B, and ligands that could tune the activity of either the catalyst or cocatalyst as gene C. These parameters made up the three genes of the GA, and the candidates for each gene were generated largely from previous literature.[14,16−18,22−25,29] Eight different compounds were selected for gene A, 11 for gene B, and 13 for gene C (Table S1). Each of the 48 "individuals" in a generation was composed of multiple chemical species at each gene, allowing for rapid exploration of possible combinations and the potential discovery of complex catalyst compositions (Figure 1). The chemical species available for the genes also included blank samples, which allowed for the potential removal of unnecessary components over the generations (Table S1).

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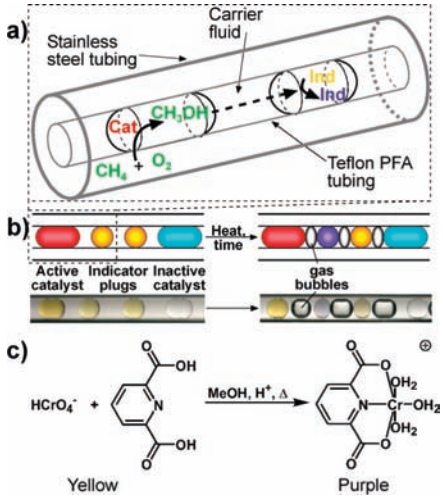

Figure 2. Arrays of microfluidic plugs containing catalyst solutions were reacted with gaseous reagents and then screened for catalytic activity. (a) Schematic of a section of Teflon tubing containing arrays of plugs inside stainless steel tubing. The pressurized methane/oxygen mixture was introduced into the stainless steel tubing and diffused through the gas-permeable Teflon tubing and into the catalyst plugs. The gas mixture reacted in the presence of active catalyst solutions to form methanol within the plugs. At elevated temperatures, the methanol subsequently diffused through the fluorocarbon carrier fluid from the catalyst plug to the neighboring indicator plug, where a color change from yellow to purple occurred. (b) Schematics (above) and microphotographs (below) show how using two indicator plugs to separate adjacent catalyst plugs allows for clear identification of active catalysts. Only the indicator plugs adjacent to an active catalyst plug changed color. Here, the catalyst plug on the left was active while the catalyst plug on the right was not. Over time, gas bubbles formed between the plugs due to pressurization and evaporation of the carrier fluid. (c) Chromic acid oxidized methanol, generating chromium(III), which coordinates to 2,6-pyridinedicarboxylate, causing a color change from yellow to purple.

Microfluidic Device To Perform Reactions. In each generation, we used 192 catalyst plugs and an additional 386 indicator plugs of microliter volumes to test the catalytic activity of each of the 48 reaction mixtures (individuals) in quadruplicate. We define plugs as aqueous droplets surrounded by a fluorinated carrier fluid. The plugs fill the microchannel but do not wet the walls, thus preventing any cross-contamination[11] due to sticking. Fluorinated amphiphiles can be used to control the interfacial interactions in these systems both to prevent[30] and to enhance[31] adsorption of molecules to the interface. The catalyst mixtures that comprised the individuals were assembled in a 96-well plate, and the carrier fluid and indicator solution were also loaded in the plate. The complex arrays of plugs were generated in Teflon PFA tubing by using a computer-controlled syringe pump coupled to a stage that moves the well plate in three dimensions[32] (movie S1 and Figure S1 in Supporting Information) to aspirate the various solutions from the well plate to generate the desired pattern of plugs (Figure 2a,b).

The high gas permeability of the Teflon tubing allowed for the introduction of gases by diffusion when the Teflon tubing was placed inside the stainless steel reactor (Figure 2a and Figure S2 in Supporting Information), eliminating the need to introduce gas bubbles during the formation of plugs.[13,33] This method of gas introduction eliminated many of the challenges associated with gas−liquid microfluidic systems, including flow and pressure fluctuations due to gas compressibility, which can lead to unstable plug formation, and stoichiometric limitations due to low reagent density in gases.[12,13,34] After pressurization, the reactor was heated to the desired temperature to initiate the reaction, and the reaction proceeded for 3−5 h. A longer reaction time was used in early generations in order to observe sufficient reactivity and had to be shortened in later generations to prevent signal saturation of the indicator plugs.

Measurement of Catalytic Activity and Analysis of Fitness. To read out the results, standard analytical options such as NMR or GC-MS were not attractive for us to rapidly analyze large numbers of small plugs microliters in volume. Therefore, an in situ colorimetric indicator system was developed to give immediate information about catalyst activity. The system relies on the diffusion of the reaction product (e.g., methanol) from the catalyst plugs to the neighboring indicator plugs at elevated temperatures, where it generates a color change (Figure 2a,b). The indicator system is based on the oxidation by chromic acid of methanol, but not methane. The ligand 2,6-pyridinedicarboxylate was used to enhance the color intensity (Figure 2c and Figure S3a).[35] During the reaction, active catalyst plugs generated methanol and potentially other products. These reaction products diffused into neighboring indicator plugs and reacted to cause the color change from bright yellow to dark purple. The transitional color change from yellow to purple allowed for semiquantitative data to be obtained by using a scoring system scaled from zero to four, where zero represents virtually no change in color and four represents complete change in color (Figure S3). Because the indicator was at a concentration of 30 mM, it required millimolar levels of reactive species (e.g., methanol) to diffuse into indicator plugs to observe a detectable color change. Thus, only catalysts with high activity produced observable results. The in situ indicator system also allows, in principle, for measurement of activity over the course of the reaction, rather than just analysis of the final quantity. This feature is useful for systems like methane oxidation in which the desired product can be consumed by other side reactions or overoxidation.

Because this system is diffusion-based, it requires that the gas entering the catalyst plugs through the Teflon tubing from the external chamber must enter faster than the rate of reaction (as described by the Damköhler number). It also requires that product (e.g., methanol) transport between plugs through the carrier fluid is faster than loss of product through the Teflon tubing into the external chamber. While published values for the specific conditions in this system do not exist, simple approximations using published values for the diffusion coefficient of oxygen through PFA[36] and fluorocarbons[37] indicate that gas transport into the catalyst plugs is fast compared to the time scale of the reaction, and that mass

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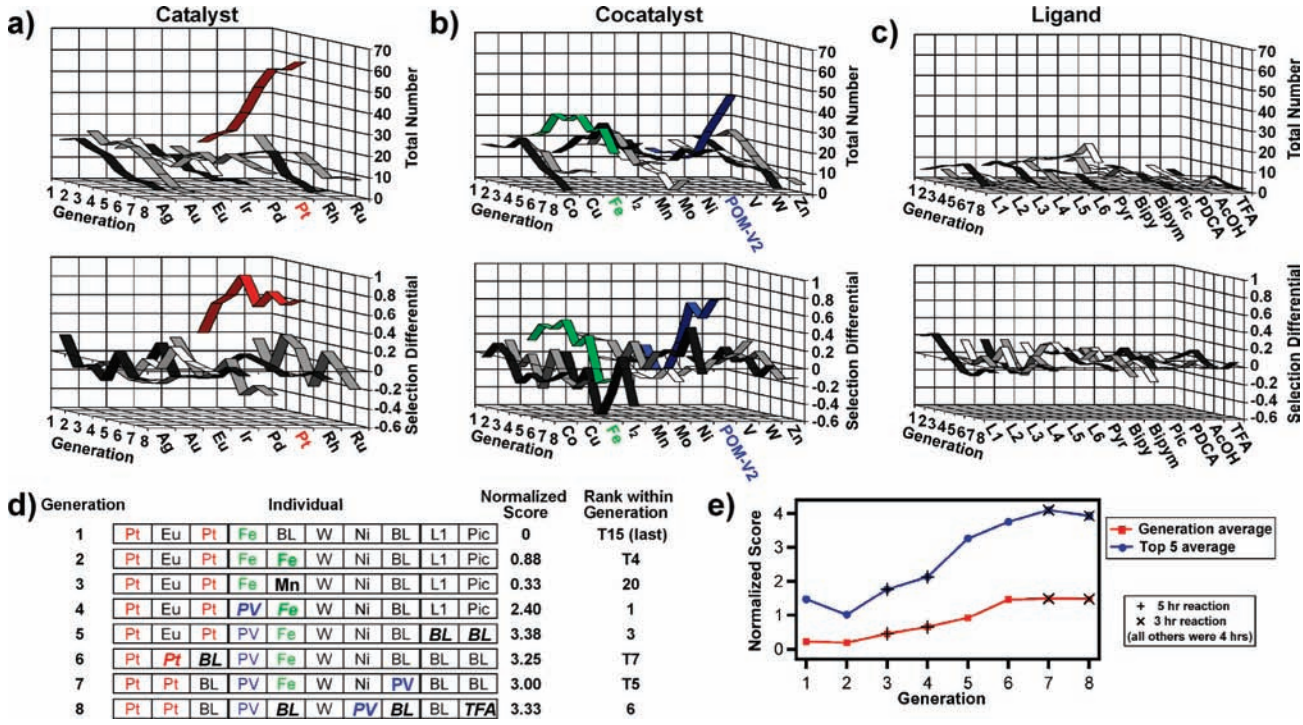

Figure 3. Total number of chemical species within a generation (top), and the selection differential (bottom), defined as the difference between the average amount of each component in the top 10 or 11 individuals in the generation and the average of the entire generation for (a) catalysts, (b) cocatalysts, and (c) ligands. Pt(II) was the only catalyst selected. Within the cocatalysts, Fe(II) was most heavily selected in early generations while POM-V2 (PV) was selected in later generations. No ligand species was selected. (d) Schematic of how one representative individual evolved through the generations. Changes from one generation to the next are designated in bold if due to crossover, and bold italics if due to mutation. The components are colored to match the graphs in a−c. T indicates a tie for that rank. (e) average fitness of the entire population (red) and the average fitness of the top five individuals (blue) over eight generations. The data were normalized to reflect expected scores based on equal reaction times.

transport between plugs dominates relative loss to the external chamber (see Supporting Information for more details). If more reactive catalysts were generated, decreasing the catalyst loading or reducing the reaction temperature would ensure that transport did not limit the system.

Due to the close proximity of plugs to one another, over the course of preparation and reaction, plug merging was a possibility. If the merging compromised reactivity or analysis, the merged plugs were not included in the analysis. Because each condition was run in quadruplicate, over 94% of reactions had at least three useful plugs per quadruplicate, and only 1.3% of conditions had only one useful plug to analyze.

The degree to which the indicator next to each individual changed color was used to determine the fitness of that individual. The fitness of the individuals was then used to generate a new population through a combination of functions that mimic mating with genetic recombination via crossover, mutation, and migration (Figure 1). This process was repeated over eight generations. While still favoring the fittest individuals, the selection parameters for generations 2−4 also allowed for continued exploration of solution space. Since it had become clear that fit individuals were being generated, the selection pressure was increased for generations 5−8. Specifically, the production of completely new individuals (i.e., migration) was eliminated, selection was modified to more heavily favor the most fit individuals, and the probability of removing unnecessary components was enhanced.

The evolution of catalysts by the GA was monitored on three levels: the changes in the chemical components (Figure 3a−c), how those changes affected the fitness of individuals (Figure 3d), and how they affected the fitness of the entire population (Figure 3e). After eight generations of GA-guided evolution, Pt(II) was selected as a catalyst, in full agreement based on expectations from previous work.[17,18,20,24,26,27] No other catalyst showed significant activity under these reaction conditions (Figure 3a, red line). In early generations, Fe(II) was selected as a cocatalyst (Figure 3b, green line), but in later generations, the polyoxometalate $H_5PMo_{10}V_2O_{40}$ (POM-V2) became more heavily selected (Figure 3b, blue line). Platinum and POM-V2 were already known to be an active catalyst system.[17,20] Other studies have demonstrated that iron is able to use oxygen to reoxidize platinum.[18,38] The result obtained here indicated that iron is compatible with all stages of the catalytic cycle[17,18,27] (Scheme 1) and can be used to turn over the cycle under homogeneous conditions. No ligand species significantly enhanced catalytic activity (Figure 3c). Overall, an approximately 7-fold increase in fitness was observed for the entire population, and an approximately 3-fold increase was observed for the top five individuals (Figure 3e), indicating that the GA-guided evolution implemented in microfluidics does produce individuals of greater fitness, and these results are meaningful in the context of the current chemical knowledge.

Characterization of Active Catalytic Components. Additional indicator-based experiments were performed without extraneous components to study the activity of the different cocatalysts. These experiments showed that Fe(III) was superior to Fe(II) and comparable to POM-V2, and that the counterion can have a significant effect on activity (Figure S4 and Table S2 in Supporting Information). To further optimize conditions for the Pt/Fe system,

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Scheme 1. Presumed Iron-Driven Reoxidation of Platinum in the Generally Accepted Catalytic Cycle[17,18,27]

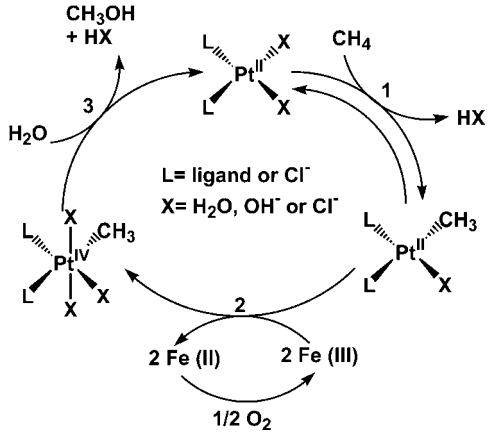

Table 1. Summary of Catalyst Activity

entry[a]	[Pt(II)]/[Fe(III)] (mM)[b]	initial O_2/CH_4 (bar)	CH_3OH TON[c]	HCOOH TON[c]	total TON[c]
1	0.05:0.75	4:46	23.0	26.1	49.1
2	0.05:0.00	4:46	<0.1	0	<0.1
3[c]	0.00:0.75	4:46	0.2	1.3	1.5
4	0.05:0.75	0:50	4.6	0	4.6
5	0.05:0.75	12.5:37.5	17.5	19.5	37
6	0.05:0.1	4:46	5.7	10.0	15.7
7	0.05:0.4	4:46	15.6	21.9	37.5

[a] Reactions were performed at 180 °C for 6 h and 50 bar initial pressure (before heating). [b] K_2PtCl_4 and $Fe_2(SO_4)_3$ were the metal sources and were dissolved in 50 mM D_2SO_4. [c] TON based on [Pt(II)] except for entry 3, where it is based on [Fe(III)].

quantitative activity information obtained in scaled-up NMR experiments was used (Figure S5). By increasing the reaction temperature and changing ratios or reagents, TONs of about 50 were achieved with approximately equal production of methanol and formic acid. It was observed that performance is sensitive to O_2 concentration (Table 1). Experiments that examined the potential for overoxidation indicated that Fe(III) may play an additional role in preventing overoxidation, when compared to reactions in the presence of platinum alone (Table S3).

Conclusion

In this work, we demonstrated the use of microfluidics as a tool to implement GAs to discover new catalytic systems. The GA evolved individuals and populations of greater fitness and identified the relevant catalytic components that enhanced fitness. The GA was made feasible by using microfluidics to miniaturize the reactors and carry out the reactions and fitness measurements of multiple individuals in parallel. This work was validated by the evolution of catalytically active components for the partial oxidation of methane by molecular oxygen. The scope of the system can be further expanded to use the hybrid method[39] and to integrate it with GC-MS or microcoil NMR[40] analytical techniques. Sequential multistep manipulations of plugs with time control are well-established.[41] Integration of this approach with the SlipChip platform[42] could enable complex multistep manipulations on many small volumes in parallel. The use of precise control of time[41] to generate and perhaps stabilize catalytically active intermediates provides a unique additional opportunity. Using the control of surface chemistry at the fluid−fluid interface around the plugs[30,31] to either induce or prevent heterogeneous nucleation of catalysts provides another opportunity, potentially providing a way of using this system for direct comparison of homogeneous and heterogeneous catalysts. This approach of GA-guided evolution in microfluidic devices can effectively explore large chemical space and could be applied to evolution in more complex catalytic systems, which possess high levels of diversity, modularity, stability, and self-assembly and include polyoxometalates,[43] metal-organic frameworks,[44] and other molecular clusters[45] and could also be applied in other areas such as optimization of materials for hydrogen storage[46] and CO_2 capture.[47] Like enzymes, these systems have complex but clearly definable structures and compositions that result in catalytic activity that is not easily predictable by examining the individual components comprising the final species.

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Supporting Information Available: Experimental section and additional figures and tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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