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Split-Pool Method for Synthesis of Solid-State Material Combinatorial Libraries

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The synthesis and analysis of inorganic material combinatorial libraries by the split-pool bead method were demonstrated at the proof-of-concept level. Millimeter-size spherical beads of porous γ-alumina, a commonly used support material for heterogeneous catalysts, were modified with $Al_{13}O_4(OH)_{24}(H_2O)_{12}{}^{7+}$ cations in order to promote irreversible adsorption of the anionic fluorescent dyes Cascade Blue, Lucifer Yellow, and Sulforhodamine 101. The compositions of individual beads were easily determined through three split-pool cycles using a conventional fluorescence plate reader. Small split-pool material libraries were made by adsorbing noble metal salts (H_2PtCl_6, H_2IrCl_6, and $RhCl_3$) into the beads. Analysis of these beads by micro-X-ray fluorescence showed that quantitative adsorption of metal salts without cross-contamination of beads could be achieved at levels (0.3 wt % metal loading) relevant to heterogeneous catalysis. The method offers the potential for synthesis of rather large libraries of inorganic materials through relatively simple benchtop split-pool chemistry.

Introduction

Combinatorial synthesis and screening are now well-established tools for the discovery of solid-state inorganic materials. In a sense, this is the oldest application of the combinatorial method, dating back over 90 years to the work of Mittasch on catalysts for ammonia synthesis.[1] His experiments systematically explored combinations of catalysts, supports, and promoters using macroscale reactors. The method was later refined in the continuous phase spread approach of Hanak[2] and in the discrete combinatorial libraries developed by several groups.[3] All of these groups used planar arrays of microscale samples, enabling more rapid searches through larger numbers of compositions. These high-throughput methods have been used in the past several years to search for better superconductors,[2,3a,b] heterogeneous catalytic materials,[3c−g,4] electrocatalysts,[5] phosphors,[6] dielectrics,[7] and sensor materials.[8] Combinatorial methods are likely to continue to be used in areas of materials research in which improvements and new discoveries are most effectively made by combining heuristic chemical ideas with an Edisonian mapping of the relevant parameter space.

Until now, almost all combinatorial work on inorganic materials has employed spatially addressable libraries. These are continuous or discrete arrays in which composition and/or synthetic parameters are systematically varied. An important attribute of these libraries is that every member is uniquely identified by its position in the array. Correlating the performance of a given material with its composition or processing history is therefore quite straightforward. Spatially addressable material libraries have three important draw-backs, however. One is that the size of a planar array of materials is usually limited in the practical sense to a few hundred members. A second problem is that the cost of the synthetic equipment can be high, particularly if lithographic or high-vacuum vapor deposition techniques are needed to fabricate the array. Third, it can be difficult, particularly with dense arrays, to incorporate materials in the physical form in which they are used in the "real world". For example, heterogeneous catalysts are often made as pelletized, highly porous composites that do not lend themselves particularly well to synthesis and screening in planar arrays.

Bead libraries have been widely used in bioorganic combinatorial chemistry.[9] Their synthesis is straightforward, and very large libraries can be made quickly and inexpensively. In the split-pool method,[10] a collection of small polymer beads is split into vials and a different component (e.g., an amino acid) is added to each vial. After all the reactions are complete and excess reagents have been removed, the beads are mixed together and then split again into separate vials. The whole process is repeated several times to construct the library. A chemical or physical tagging process often accompanies the split-pool steps to aid in later identification of individual beads or of collections of beads that are processed together in each step as a "tea bag." An important property of the split-pool method is that only one compound (e.g., a single polypeptide sequence) is synthesized on a particular bead or in a particular tea bag.

In bioorganic libraries, the identity and properties of these combinatorially synthesized molecules depend on the order in which components are added to the beads. The number

of unique compositions in the library is therefore n^m, where n is the number of components (the same as the number of vials) and m is the number of split-pool operations. For material libraries, the order of addition of reagents may or may not be important because postsynthesis thermal treatments can effectively mix all the components. Planar material arrays are therefore normally prepared and screened without regard for the order of addition of reagents. In the simplest case, in which the order of addition does not matter, the number of different bead compositions N is given by

$$N(n,m) = \frac{(n + m - 2)!}{(n - 1)!(m - 1)!} \qquad (1)$$

It is apparent from eq 1 that the number of different members of a split-pool material library can become larger, in a relatively small number of simple steps, than that accessible in a very sophisticated planar array. For example, with 10 different components and 8 split-pool steps, one obtains $N(10,8) = 11\,400$ discrete compositions. A caveat in preparing such a library is that the inorganic reagents and tags (if a tagging scheme is used) must be adsorbed uniformly and irreversibly onto the beads in each synthetic step. Further, one needs a technique for rapidly identifying and screening the beads for the particular property of interest.

In this paper, we describe the split-pool synthesis of an inorganic material library. For this proof-of-concept example, we chose components (noble metals) and bead supports (porous γ-alumina) that represent realistic choices for a library of heterogeneous catalysts. In addition, we have examined the adsorption of fluorescent dye tags, which might be used for postsynthesis bead identification, on the same supports by the split-pool approach.

Experimental Section

Materials. $H_2IrCl_6 \cdot xH_2O$, $RhCl_3$, $HAuCl_4$, H_2PtCl_6, and $RuCl_3$ were purchased from Alfa Aesar and used as received. Cascade Blue, Lucifer Yellow, and Sulforhodamine 101 fluorescent dyes were purchased from Molecular Probes, Inc. and used as received. The support beads were composed of γ-alumina and had a surface area of 200 m^2/g and an average diameter of 1 mm. The average mass of the support beads was 2.3 mg. All other chemicals were analytical grade and were used as received from commercial sources.

Solutions of the aluminum Keggin ion, $Al_{13}O_4(OH)_{24}$-$(H_2O)_{12}^{7+}$ (Al_{13}^{7+}), were prepared by reaction of the sulfate salt with aqueous $BaCl_2$.[11] An amount of 50 mL of an aqueous 0.25 M NaOH solution (12.5 mmol) was added dropwise to a solution of 1.2 g of $AlCl_3 \cdot 6H_2O$ (5 mmol) in 50 mL of water. The resulting solution was heated to 85 °C in an oil bath with constant stirring. After 20 min, 80 mL of aqueous 0.12 M Na_2SO_4 (10 mmol) was added. The solution was kept at room temperature for 1 day to yield crystals of the sulfate salt $NaAl_{13}O_4(OH)_{24}(SO_4)_4 \cdot xH_2O$. The crystals were separated by suction filtration, washed with deionized water, and dried. The dry crystals (0.25 g, 0.18 mmol) were resuspended in 100 mL of deionized water. $BaCl_2 \cdot 2H_2O$ (0.28 g, 1.1 mmol) was added to the suspension, which was stirred for 4 h. The $BaSO_4$ produced in the reaction was

removed by filtration and centrifugation. The resulting aqueous solution contained Al_{13}^{7+} and Ba^{2+} at approximately 1.8 and 3.8 mM concentrations, respectively.

Modification of γ-Alumina Beads with Al_{13}^{7+}. The surface of the γ-alumina beads was made cationic by adsorption of Al_{13}^{7+} ions. The γ-alumina beads (0.150 g) were reacted overnight with 15 mL of Al_{13}^{7+} solution (ca. 1.8×10^{-3} M). The solution was then removed, and the beads were thoroughly rinsed with water and then dried at room temperature in air.

Synthesis of Dye Libraries. In a typical procedure, 15 Al_{13}^{7+} modified γ-alumina beads were equilibrated in a small vial with 2 mL of Cascade Blue (4.2×10^{-8} M), Lucifer Yellow (5.5×10^{-8} M), or Sulforhodamine 101 (8.3×10^{-9} M) solutions in water. The adsorption step took 40 min, and after that the beads were rinsed with water, they were dried at room temperature for 1 h and then dried in vacuo overnight. The beads were then combined (pooled) and distributed equally into three vials (split). The adsorption steps were repeated until the desired loading was achieved. In directed sorting experiments, the fluorescence intensity of the individual beads was measured between split-pool steps (see below).

Synthesis of Noble Metal Libraries. In split-pool syntheses, 350 mg of unmodified γ-alumina beads were reacted overnight in small vials with 1 mL of H_2PtCl_6, H_2IrCl_6, or $RhCl_3$ aqueous solution in sufficient concentration to make the final loading 0.1 wt % in metal. The extra solution was then withdrawn and was colorless, meaning that most of the metal ions had been adsorbed onto the beads. The beads were dried at 120 °C for 2 h and then at 300 °C for 3 h. The latter thermal treatment was needed with these particular metal salts in order to minimize desorption in subsequent steps. The beads were allowed to cool to room temperature and were then collected together, mixed, and divided into three parts. The adsorption and thermal treatment steps were repeated until the desired loading was achieved.

In control experiments used to calibrate analytical procedures for metal-loaded beads, individual beads were impregnated with measured amounts of aqueous metal salt solutions delivered by a robotic plotter. Five metal halide solutions (H_2IrCl_6, $RhCl_3$, $HAuCl_4$, H_2PtCl_6, and $RuCl_3$) were prepared so that 9 μL of solution (the total amount delivered to each bead) contained 0.0113 mg of metal. Each metal salt was dissolved in approximately 20 mL of water and 0.531 mL of concentrated hydrochloric acid. The solutions were heated to boiling for 15 min, cooled to room temperature, and then diluted to 25 mL. The plotter (Cartesian Technologies, PixSys 3200) was programmed to deliver the metal salt solutions into two 384-V-bottom-well plate (Nalge Nunc International) arrays. One alumina sphere was placed manually into each well. The plotter delivered 11 μL of water to each well. A total of 9 μL of metal salt solutions was added to each well to make 715 distinct compositions ($=N(5,10)$) at a resolution of 10 compositions along each binary edge in the pentanary composition map.[5b,8b] The remaining 53 wells were programmed as duplicates of a single pentanary composition, $Pt_5Ru_3Au_1Ir_1Rh_1$. The two 384-well plate arrays were dried overnight on an orbital shaker.

Fluorescence of Dye-Tagged Beads. Fluorescence measurements were made with an HTS 7000 Plus bioassay reader (Perkin-Elmer). The beads were first loaded into a 96-well V-bottom plate. Measurements were then carried out using the appropriate excitation/emission filter set for each of the three dyes. In this mode of operation, the plate reader took approximately 25 s to record the emission intensities of a single dye on 96 beads.

Elemental Analysis. Metal loadings on representative beads were determined using micro-X-ray fluorescence spectroscopy. The samples were analyzed using a ThermoNORAN Omicron system, which consisted of a microfocus X-ray source operating at 100 W with a molybdenum target X-ray tube, a selection of eight filters, and a 175 eV liquid-nitrogen-cooled Si(Li) detector, coupled to an ADC. A 100 μm collimator was used. Samples were presented to the X-ray beam using a custom tray mounted on an automated precision *XYZ* stage. A PC controlled the setup, automation, and data analysis through a Windows-based software. No special sample preparation was necessary. However, to minimize geometrical effects, care was taken to mount the beads on a level surface and to measure each bead at its center. The source was operated at 40 kV, 2.0 mA, in a vacuum with an acquisition time of 600 s. Net peak intensities were extracted using Gaussian peak-fitting together with digital background correction, which deconvolutes overlapping peaks such as those of Ir, Pt, and Au. The absolute concentrations were determined using a linear least-squares calibration.

Results and Discussion

Dye Libraries on γ-Alumina Support Beads. The split-pool principle can be demonstrated for catalyst support beads using fluorescent dyes as the adsorbate. In principle, these and other anionic dyes could be used in tagging schemes to represent the metal ions adsorbed onto the beads in the same split-pool cycle. The prerequisite for use of these fluorescence dyes is that they should have distinct excitation/emission signatures and that their adsorption must be quantitative and irreversible.

Three commercial anionic dyes (Figure 1) were used in these experiments. These dyes have previously been used in combination for three-color mapping of neuronal processes.[12] Adsorption of these dyes onto unmodified beads gave easily detectable fluorescence at loadings in the range of 1.8×10^{-11} mol per bead (or approximately 3.8×10^{-15} mol per cm^2 of support area). However, an unacceptable level of desorption was observed in subsequent split-pool steps with unmodified beads. To increase the affinity of the dyes for the beads, the beads were first modified with $Al_{13}O_4$-$(OH)_{24}(H_2O)_{12}^{7+}$ (Al_{13}^{7+}) cations. The coverage of Al_{13}^{7+} ions was 4.3×10^{-7} mol per bead (approximately 9.0×10^{-11} mol per cm^2 of support area, or roughly $^1/_3$ monolayer coverage, assuming that the diameter of the Al_{13}^{7+} ion is 7 Å). Beads with different dye loadings were then prepared by adsorption of the dyes from aqueous solutions. The optimum loading (ca. 7×10^{-12} mol per bead), which is high enough for detection while low enough that concentration quenching and energy-transfer quenching do not occur,
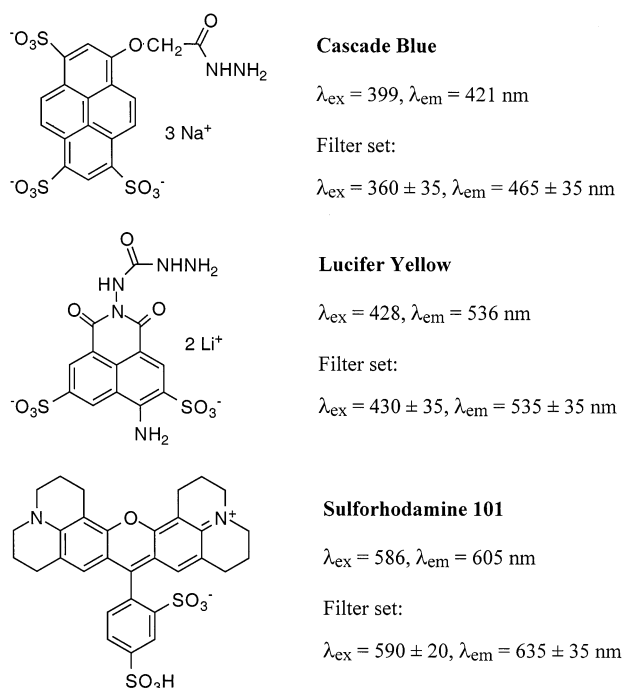

Cascade Blue

$\lambda_{ex} = 399$, $\lambda_{em} = 421$ nm

Filter set:

$\lambda_{ex} = 360 \pm 35$, $\lambda_{em} = 465 \pm 35$ nm

Lucifer Yellow

$\lambda_{ex} = 428$, $\lambda_{em} = 536$ nm

Filter set:

$\lambda_{ex} = 430 \pm 35$, $\lambda_{em} = 535 \pm 35$ nm

Sulforhodamine 101

$\lambda_{ex} = 586$, $\lambda_{em} = 605$ nm

Filter set:

$\lambda_{ex} = 590 \pm 20$, $\lambda_{em} = 635 \pm 35$ nm

Figure 1. Molecular structure, absorbance and emission maxima, and filter sets used to measure fluorescence intensities of anionic dyes adsorbed onto Al_{13}^{7+}-modified γ-alumina beads.

was then determined using a Perkin-Elmer HTS 7000 bioassay reader. This loading corresponds to saturation of approximately 0.002% of the available Al_{13}^{7+} sites with dye molecules. Using V-bottom 96-well plates, the beads were reliably located in the center of each well, which is critical for reproducible detection of fluorescence intensities.

Table 1 shows the raw fluorescence intensity signals obtained from rows of beads loaded with the three dyes and examined with the filter set appropriate for Sulforhodamine 101. The mean value is 334 counts, and the standard deviation is 23. Only one of the intensity measurements is outside the range of 2 standard deviations, which is 14% of the mean. Similar results were obtained for the second and third rows using appropriate filter sets. For beads loaded with dyes that did not match the filter set used, the detected fluorescence was not significantly different from that measured with control beads containing no dye. This implies that the resolution offered by these dyes as tags is sufficient to discriminate approximately $334/(2 \times 23) = 7$ concentration levels of each "active" component delivered in the same split-pool step. Since a tag is not needed in the last step, libraries could be made in up to eight split-pool steps with fluorescent identification of most of the beads.

The error in the fluorescence measurements can be attributed primarily to the variability in bead size, as shown in Figure 2. In this experiment, a selection of large, small, and average size beads was chosen; that is, the distribution of weights shown in the figure is not representative of the entire sample, which had a higher proportion of average-size beads. The plot shows the expected trend of increasing fluorescence intensity with bead mass. The optical micrograph of the beads confirms that there is some variability in bead diameter. This problem could be partially addressed by sorting the beads manually.

Table 1. Raw Fluorescence Intensities of Rows of Beads Loaded with a Single Dye[a]

	bead no.											
dye	1	2	3	4	5	6	7	8	9	10	11	12
SR 101	307	329	328	334	357	320	344	321	341	310	330	391
Cascade Blue	0	0	7	1	0	1	0	2	3	2	3	4
Lucifer Yellow	2	2	2	5	0	0	2	2	2	1	3	1
none	0	0	3	2	2	0	1	1	0	4	2	1

[a] The excitation/emission filter set for detection of Sulforhodamine 101 was used for all beads. Comparison with a row of Al_{13}^{7+}-modified beads containing no dye shows that the background signal from Cascade Blue and Lucifer Yellow loaded beads is minimal.
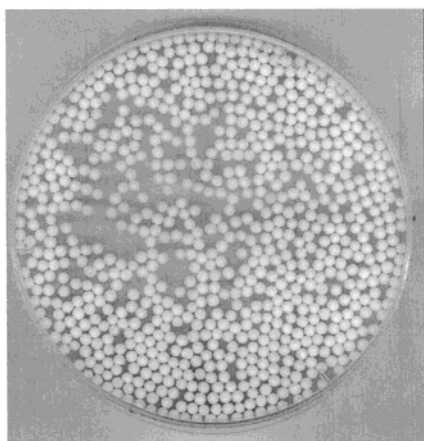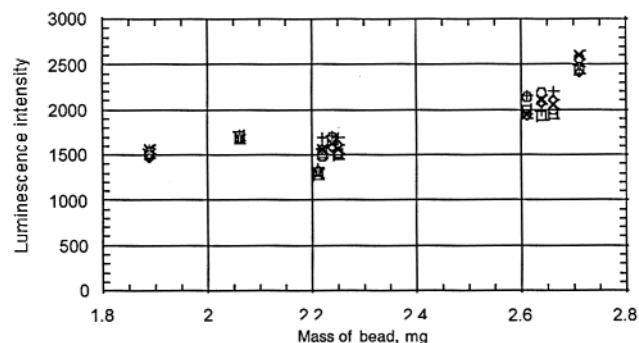

Figure 2. (Top) Fluorescence intensity of Al_{13}^{7+}-modified γ-alumina beads loaded with Lucifer Yellow as a function of bead weight (in mg). (Bottom) Optical micrograph of γ-alumina beads.

A proof-of-concept split-pool library was prepared by adsorbing the three dyes into three separate vials, rinsing, drying, and pooling the beads, and then repeating until three adsorption cycles had been completed. Figure 3 shows normalized fluorescence intensities from this small dye library using the Sulforhodamine 101 (red) filter set. The rows in this small library are color-coded according to the dye adsorbed in the last split-pool cycle; that is, each color corresponds to a set of 15 beads that were pooled in the last adsorption step. For beads onto which the last dye adsorbed was Cascade Blue or Lucifer Yellow, the number of possible Sulforhodamine 101 adsorption steps was 0, 1, or 2. Likewise, for beads onto which Sulforhodamine 101 was adsorbed in the final step, the possibilities are 1, 2, and 3. The normalized intensity data in Figure 3 are consistent with these expectations, showing "0" values only in the blue and yellow rows and "3" values only in the red row.

By repetition of this analysis with the blue and yellow filter sets, each of the beads can be identified with the number of red, blue, and yellow adsorption steps. The total should equal the total number of split-pool cycles for each bead.

Normalized intensity data for this type for a 45-bead, three-step split-pool library are shown as three-digit numbers in Table 2. Note that for each of the 45 beads, the total is 3, indicating that each one is unambiguously identified. Because this is a random library, there is a random distribution of compositions, the most common (10 beads) being the ternary (111) and the least common being the single dye compositions (300), (030), and (003), with 2, 3, and 1 beads, respectively.

One problem with the split-pool technique is that a large number of beads must be used to ensure that the whole range of compositions is represented by at least one bead. A random library generates many redundant beads, as illustrated by the binary and ternary combinations shown in Table 2. A more economical library, with fewer redundancies, can be designed by directed sorting. This method involves identification of each bead by fluorescence intensity measurements after the second and subsequent split-pool steps. The directed sorting scheme is illustrated in Figure 4 for a 36-bead library prepared in three steps, and the resulting fluorescence data are shown in Table 3. For 35 out of 36 beads, the fluorescence data match the library design. These data show that the desired number of beads of each composition can be prepared with a precisely controlled degree of redundancy.

Noble Metal Libraries. Dye libraries are convenient for illustrating the idea of sequential synthesis on inorganic support beads, and they can in principle be used as fluorescent markers for inorganic substances adsorbed in the same split-pool cycle. However, dye libraries themselves are not particularly interesting as materials. On the other hand, transition metals and metal oxides supported on alumina beads resemble the materials used in heterogeneous catalysis and other applications. Typically, these materials are prepared from metal halide salts by adsorption or impregnation. We therefore prepared several bead libraries by these techniques and used single-bead X-ray fluorescence (XRF) to analyze the results.

Table 4 shows single-bead XRF results for ternary compositions selected from a 715-member pentanary bead library prepared by simple impregnation. The nominal compositions in this (spatially addressable) array are known *a priori*, and the purpose of this experiment was to gauge the accuracy of the single-bead analysis. The agreement in the Pt, Rh, and Ir columns is generally quite good, and certainly good enough to be able to identify individual bead compositions. The scatter in the Au analysis was traced to nonuniform impregnation.

Supported Pt, Rh, and Ir are widely used in heterogeneous catalysis and therefore represent interesting candidates for
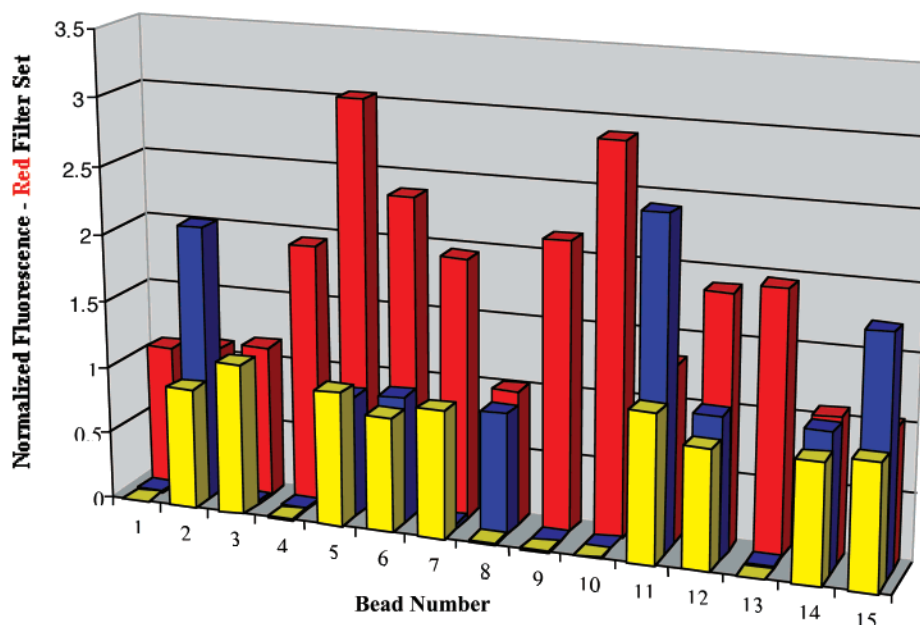
Figure 3. Normalized fluorescence intensities for a dye-loaded bead library prepared in three split-pool cycles and analyzed using the Sulforhodamine 101 (red) filter set. The color code indicates the dye adsorbed in the final split-pool cycle. The data were obtained from 45 beads arranged in three lanes of 15 beads each.

Table 2. Fluorescence Data for a 45-Bead Library after Three Split-Pool Cycles[a]

final dye adsorbed	bead composition (red, blue, yellow)														
SR 101 (red)	111	120	111	201	300	201	210	102	210	300	111	210	210	111	111
Cascade Blue	030	210	021	012	120	120	030	111	012	030	210	111	012	120	210
Lucifer Yellow	012	102	111	012	102	102	102	021	012	003	102	102	012	111	111

[a] Sulforhodamine 101, Cascade Blue, and Lucifer Yellow were adsorbed in the last cycle onto beads in the first, second, and third rows, respectively. Three-digit numbers indicate the normalized intensities using the red, blue, and yellow filter sets. For example, "210" indicates two adsorption steps with Sulforhodamine 101, one with Cascade Blue, and zero with Lucifer Yellow.
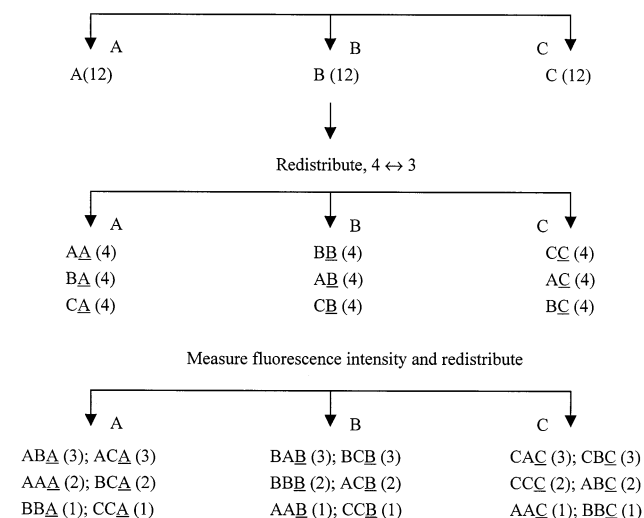

Figure 4. Directed sorting split-pool scheme. The numbers in parentheses indicate the number of beads of each type.

Table 3. Bead Compositions for a Directed Sorting Library Prepared in Three Split-Pool Cycles[a]

compositions	experimental design	experimental results
300	2	2
030	2	2
003	2	2
210	4	4
201	4	3
120	4	4
021	4	4
102	4	4
012	4	4
111	6	6

[a] The target distribution of beads matches the normalized fluorescence data with one exception.

the synthesis of split-pool bead libraries. As with the dye-loaded beads, we prepared a small random library in three split-pool steps. The concentrations of the metal solutions (H$_2$PtCl$_6$, H$_2$IrCl$_6$·xH$_2$O, and RhCl$_3$) were sufficient to add a loading of 0.1% metal to the beads in each adsorption step, meaning that the theoretical total loading was 0.3%. This library should give 10 different compositions: Pt$_3$, Rh$_3$, Ir$_3$, Pt$_2$Rh$_1$, Pt$_2$Ir$_1$, Pt$_1$Ir$_2$, Pt$_1$Rh$_2$, Ir$_1$Rh$_2$, Ir$_2$Rh$_1$, Ir$_1$Pt$_1$Rh$_1$ (sub-scripts indicate the number of adsorption steps in each metal ion solution). XRF analysis of representative beads from this library are shown in Table 5. With this simple library, and with more complex compositions (as shown in Table 4), the XRF technique is sufficiently accurate to determine the total number of adsorption steps of each metal on each bead. It is worth noting that, within the detection limits of XRF, none of these beads contain all three elements. From the absence of the third element, we can conclude that there is minimal desorption and mixing of metal ions after three split-pool steps, provided that the beads are heated to decompose the adsorbed metal chlorides between steps.

Table 4. X-ray Fluorescence Analysis of Individual
γ-Alumina Beads Prepared by Impregnation with Metal Salt
Solutions in V-Bottom Well Plates

expected composition				experimental composition			
Pt	Au	Rh	Ir	Pt	Au	Rh	Ir
0	4	2	3	0.1	2.4	1.3	2.3
3	0	2	4	3.1	0.9	1.6	3.8
5	2	2	0	4.5	3.2	1.3	0.2
0	5	1	3	0.1	5.7	0.7	2.2
6	2	1	0	5.0	2.7	0.9	0.2
7	1	0	1	7.2	1.2	0.1	1.2
3	0	3	3	3.0	1.1	2.5	2.8
0	3	3	3	0.3	2.1	2.2	2.7
7	0	1	0	5.9	1.2	0.7	0.3
4	0	2	3	3.8	1.2	1.1	3.1
1	5	3	0	1.4	5.9	2.2	0.2
6	0	0	2	5.3	1.1	0.0	2.2
5	0	2	2	4.8	1.2	1.2	2.1
5	0	3	1	4.5	1.0	1.7	1.2
4	0	3	2	5.4	1.1	2.6	2.4
2	5	2	0	1.7	6.5	1.5	0.2
3	5	1	0	3.4	3.8	0.5	0.3
4	2	3	0	3.5	1.8	2.2	0.3

Table 5. X-ray Fluorescence Analysis of Individual
γ-Alumina Beads Selected from a Pt−Ir−Rh Bead Library
after Three Split-Pool Adsorption Cycles

bead number	XRF analysis		expected composition
		%	
1	Pt	0.08	0.1% Pt_1Rh_2
	Ir		
	Rh	0.2	0.2% Pt_1Rh_2
2	Pt	0.23	0.3% Pt_3
	Ir		
	Rh		
3	Pt		
	Ir	0.09	0.1% Ir_1Rh_2
	Rh	0.14	0.2% Ir_1Rh_2
4	Pt	0.05	0.1% Pt_1Ir_2
	Ir	0.19	0.2%
	Rh		

Conclusions

We have demonstrated at the proof-of-concept level that
the split-pool method is a viable approach to the synthesis
of combinatorial libraries of inorganic materials. The key to
success in this method is to ensure uniform, irreversible
adsorption of the inorganic components onto chemically and
thermally stable support beads. Porous alumina support beads
work well for this purpose with acid salts of noble metals
and are also attractive because alumina is frequently used
as a catalyst support. We have also demonstrated the viability
of dye tagging with alumina beads. Dye tagging permits
directed sorting between split-pool steps and allows one to
control the composition of the library precisely without the
statistical redundancy of the random split-pool synthesis. This
modification can be particularly important in the design of
material libraries containing many components.

Only small libraries of supported transition metal oxides
(three components and three split-pool steps) were synthe-
sized in this work because of the length of time needed for
XRF analysis of each bead. One can imagine that it should
be possible to make much larger libraries by using a larger
variety of inorganic precursor salts. For example, a split-

pool library made in 8 steps from 10 components would
contain over 10^4 unique compositions, according to eq 1.
Both dye tagging and XRF appear adequate to differentiate
the compositions of beads prepared in eight split-pool steps.
In this case, we anticipate that analysis of the bead composi-
tions, rather than library synthesis, will be the bottleneck in
combinatorial materials discovery. The micro-XRF technique
used here gives reliable bead compositions, but the analysis
time is approximately 10 min per bead. Even at this low
level of throughput, the synthesis and analysis protocols
developed here could be useful if only selected beads (e.g.,
the most active catalysts) from a large library are analyzed.
An alternative strategy would be to combine dye tagging
and metal adsorption to minimize the need for XRF analysis.
This requires that we find conditions for irreversible metal
adsorption that do not involve heating to high temperatures
between split-pool cycles. Research along these lines is
currently in progress.

Note Added after ASAP Posting. This manuscript was
released ASAP on 8/24/2002 with errors in Table 5 for the
expected composition of bead 2 and the Ir analysis result of
bead 3. The correct version was posted on 8/28/2002.

References and Notes

(1) Mittach, A.; Bosch, C. U.S. Patent 993,144, 1911.
(2) (a) Hanak, J. J. *J. Mater. Sci.* **1970**, *5*, 964. (b) Hanak, J. J.;
    Yocum, P. N. *Gov. Rep. Announce. (U.S.)* **1973**, *73* (21),
    128.
(3) (a) Xiang, X.-D.; Sun, X.; Briceno, G.; Lou, Y.; Wang, K.-
    A.; Chang, H.; Wallace-Friedman, W. G.; Chen, S.; Schultz,
    P. G. *Science* **1995**, *268*, 1738. (b) Briceno, G.; Chang, H.;
    Sun, X.; Schultz, P. G.; Xiang, X.-D. *Science* **1995**, *270*,
    273. (c) Akporiaye, D. E.; Dahl, I. M.; Karlsson, A.;
    Wendelbo, R. *Angew. Chem., Int. Ed.* **1998**, *37* (5), 609. (d)
    Klein, J.; Lehmann, C. W.; Schmidt, H. W.; Maier, W.-F.
    Angew. Chem., Int. Ed. **1999**, *37* (24), 3369. (e) Choi, K.;
    Gardner, D.; Hilbrandt, N.; Bein, T. *Angew. Chem., Int. Ed.*
    1999, *38* (19), 2891. (f) Akporiaye, D.; Dahl, I.; Karlsson,
    A.; Plassen, M.; Wendelbo, R.; Bem, D. S.; Broach, R. W.;
    Lewis, G. J.; Miller, M. A.; Moscoso, J. *Microporous
    Mesoporous Mater.* **2001**, *48* (1−3), 367. (g) Rodemerck,
    U.; Ignaszewski, P.; Lucas, M.; Claus, P.; Baerns, M. *Top.
    Catal.* **2000**. *13* (3), 249.
(4) (a) Moates, F. C.; Somani, M.; Annamalai, J.; Richardson,
    J. T.; Luss, D.; Willson, R. C. *Ind. Eng. Chem. Res.* **1996**,
    35, 4801. (b) Senkan, S. *Angew. Chem., Int. Ed.* **2001**, *40*,
    312. (c) Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner,
    H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed.* **1999**, *38*,
    2494. (d) Nayar, A.; Liu, R.; Allen, R. J.; McCall, M. J.;
    Willis, R. R.; Smotkin, E. S. *Anal. Chem.* **2002**, *74* (9), 1933.
(5) (a) Reddington, E.; Sapienza, A.; Gurau, B.; Viswanathan,
    R.; Sarangapani, S.; Smotkin, E. S.; Mallouk, T. E. *Science*
    1998, *280*, 1735. (b) Chen, G.; Delafuente, D. A.; Saranga-
    pani, S.; Mallouk, T. E. *Catal. Today* **2001**, *2443*, 1.

(6) (a) Danielson, E.; Golden, J. H.; McFarland, E. W.; Reaves, C. M.; Weinberg, W. H.; Wu, X. D. *Nature* **1997**, *389*, 944. (b) Danielson, E.; Devenney, M.; Giaquinta, D. M.; Golden, J. H.; Haushalter, R. C.; McFarland, E. W.; Poojary, D. M.; Reaves, C. M.; Weinberg, W. H.; Wu, X. D. *Science* **1998**, *279*, 837.

(7) van Dover, R. B.; Schneemeyer, L. F.; Fleming, R. M. *Nature* **1998**, *392*, 162.

(8) (a) Dickinson, T. A.; Walt, D. R.; White, J.; Kauer, J. S. *Anal. Chem.* **1997**, *69*, 3413. (b) Sun, Y. P.; Buck, H.; Mallouk, T. E. *Anal. Chem.* **2001**, *73*, 1599.

(9) (a) Lebl, M. *J. Comb. Chem.* **1999**, *1*, 3. (b) Lam, K. S.; Lebl, M.; Krchák, V. *Chem. Rev.* **1997**, *97*, 411.

(10) (a) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82. (b) Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *354*, 84. (c) Norman, D. L. *Chem. Innovation* **2001**, *31*, 11.

(11) (a) Schönherr; et al. *Z. Anorg. Allg. Chem.* **1981**, *476*, 188. (b) Johansson, G.; Lundgren, G.; Sillen, L. G.; Soderquist, R. *Acta Chem. Scand.* **1960**, 769.

(12) *Handbook of Fluorescent Probes and Research Chemicals*, 6th ed.; Haugland, R. P., Spence, T. Z., Eds.; Molecular Probes, Inc.: Eugene, OR, 1996; pp 332−342.