

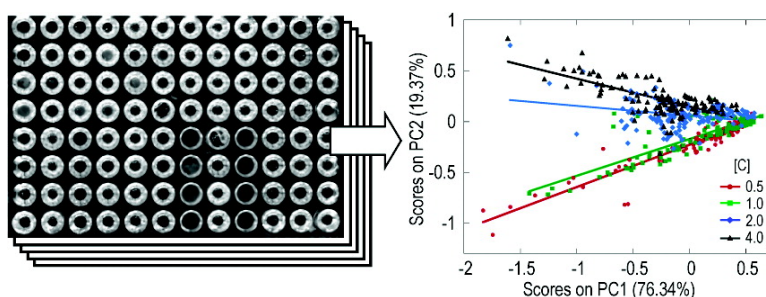
Article

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J. Comb. Chem., **2003**, 5 (1), 8-17 • DOI: 10.1021/cc020062g • Publication Date (Web): 12 December 2002

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Fluorescence Spectroscopy and Multivariate Spectral Descriptor Analysis for High-Throughput Multiparameter Optimization of Polymerization Conditions of Combinatorial 96-Microreactor Arrays

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Received July 31, 2002

Selection of optimum process conditions in combinatorial microreactors is essential if the combinatorial synthesis process is to be correlated with the synthesis process on a more conventional scale and the materials are to have the desired chemical properties. We have developed a new methodology for the high-throughput multiparameter optimization of polymerization reaction conditions in arrays of microreactors. Our strategy is based on the application of nondestructive spectroscopic techniques to measure chemical properties of polymers directly in individual microreactors followed by the multivariate spectral descriptor analysis for rapid determination of the optimal process conditions. We have demonstrated our strategy in the high-throughput multiparameter optimization of process conditions in thin-film melt polymerization reactions performed in 96-microreactor arrays for combinatorial screening of new polymerization catalysts. The combinatorial polymerization system was optimized for the best processing parameters using a set of input variables that included reactant parameters (relative amounts of starting components and catalyst loading) and processing variables (reaction time, reaction temperature, and inert gas flow rate). The measured output parameters were the chemical properties of materials and reproducibility of the material formation in replicate polymerizations in microreactors. Spatially resolved nondestructive evaluation of polymer formation was performed directly in individual microreactors and provided information about the spatial homogeneity of polymers in microreactors. It showed to be another powerful indicator of the reproducible polymerization process on the combinatorial scale. Although the methodology described here was implemented for high-throughput optimization of polymerization conditions, it is more general and can be further implemented for a variety of applications in which optimization of process parameters can be studied in situ or off-line using spectroscopic and other tools.

Introduction

At present, combinatorial and high-throughput methods are finding applications beyond the pharmaceutical industry for discovery of materials in chemistry and materials science. These materials include luminescent and magnetoresistive compounds, catalysts, polymers, high-temperature superconductors, and many others.^{1–3} High-throughput methods also have been employed for optimization of materials compositions. Recent examples include optimization of homogeneous and heterogeneous catalysts,^{4,5} multicomponent inorganic films,⁶ and nanoscale materials.^{7,8}

In addition to discovery and optimization of new chemical compositions, high-throughput approaches can provide important time savings in optimization of process parameters of materials fabrication similar to optimization of pharmaceutically relevant reactions⁹ through parallel reactions and automation.^{10,11} However, until now, high-throughput optimization of process parameters has not been explored in much detail. Limited studies of a *single*-parameter variation of process conditions include polymer blend-phase behavior

at different temperatures,¹² temperature-modulated dewetting effects,¹³ and effects of different process conditions on end-use performance of combinatorial arrays of organic coatings.¹⁴ Selection of optimum process conditions in combinatorial microreactors is essential if the combinatorial synthesis process is to be correlated with the synthesis process on a more conventional scale and the materials are to have desired chemical properties. The reaction optimization process is a tradeoff between the desire for best performance and least experimental investment.¹¹ Thus, it is highly desirable to increase the optimization throughput by performing parallel reactions at different process conditions and by rapid nondestructive measurement of chemical properties of materials.

In this report, we demonstrate our strategy in the high-throughput *multiparameter* optimization of process conditions in thin-film melt polymerization reactions performed in 96-microreactor arrays for combinatorial screening of new polymerization catalysts. In the development of melt-polymerization polymers using a combinatorial chemistry methodology,^{15,16} it is critical to find the optimal process

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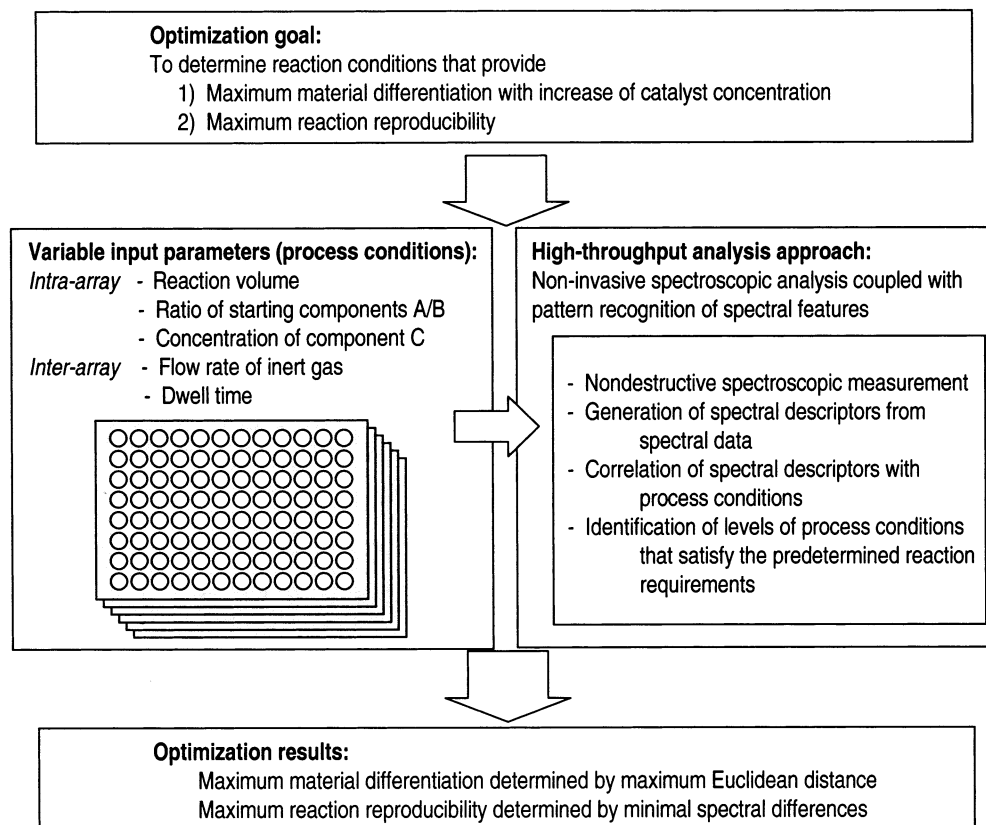


Figure 1. Methodology for the high-throughput reaction optimization using nondestructive spectroscopic measurements coupled with the pattern recognition of spectral descriptors under variable process conditions.

parameters. Unlike the traditional melt-polymerization scheme that involves stirring of the reaction components under vacuum,^{17–20} the combinatorial approach is based on the thin-film melt polymerization method at atmospheric pressure and without stirring.^{15,16} For the high-throughput optimization of process conditions of thin-film melt polymerization reactions and further screening of polymer compositions, we developed an automated analytical spectroscopic system and coupled it with a multivariate spectral descriptor analysis method. The system automatically measures fluorescence spectra of solid polymerized materials in each microreactor. The multivariate data analysis method computes the spectral descriptors related to the material properties and permits the determination of process conditions that provide the required reaction performance.

As a result, the combinatorial polymerization system was optimized for the best processing parameters using a set of input variables that included reactant parameters (reaction volume, relative amounts of starting components and catalyst loading) and processing variables (reaction time and inert gas flow rate). The measured output parameters were the chemical properties of materials and variability of the material formation within each of the microreactors as measured noninvasively using optical spectroscopy.

Approach For High-Throughput Multiparameter Reaction Optimization

Our high-throughput multiparameter reaction optimization methodology is schematically described in Figure 1. The approach included fabrication of materials arrays over a wide range of process conditions, application of nondestructive

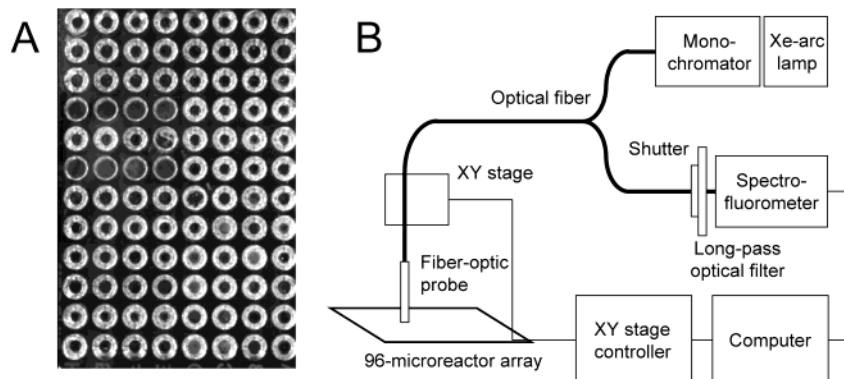
measurement techniques to collect optical spectra from the fabricated materials, multivariate data analysis to extract the desired spectral descriptors from the spectra, correlation of the variation in these spectral descriptors with the variation in process conditions, and identification of the levels of process conditions that satisfy two predetermined reaction requirements. The first requirement included an identification of process conditions that provided the largest material differentiation at a constant ratio of two reaction components A and B (ratio A/B) and increasing concentration of the third reaction component C. The second requirement included minimum reaction variability when reactions were performed in different microreactors under identical process conditions.

The process conditions included intra- and interarray variable parameters. Intra-array parameters included reaction volume, ratio of reaction component A to reaction component B (ratio A/B), and concentration of component C. These parameters were varied at different levels across multiple elements of the 96-microreactor array within each experiment. Interarray parameters included flow rate of the inert gas and dwell time. These parameters were varied at different levels in different experiments. The process conditions and their levels are listed in Table 1. These process conditions were selected on the basis of previous work on this type of polymerization reaction.¹⁶

Fluorescence spectroscopy was selected as the measurement technique because it was shown previously that fluorescence analysis provides selective chemical determinations in a variety of polymers.^{21–29} Importantly, the spectral features of bisphenol A polycarbonate used in this study were

Table 1. Variable Input Parameters (process conditions) for High-throughput Multiparameter Optimization of Polymerization Conditions of Combinatorial 96-microreactor Arrays

parameter type	parameter name	studied levels of parameters
intra-array	reaction volume (μL)	150, 200, 250
	ratio of starting components A/B (mol/mol)	1, 1.2, 1.4
	amount of catalyst C (10^{-5} mole C/mole B)	0.5, 1, 2, 4
interarray	flow rate of inert gas (L/min)	4, 6, 8
	dwelt time (min)	10, 20, 30

**Figure 2.** Optimization of multiple process parameters in 96-microreactor arrays: (A) reflected-light image of a 96-microreactor array with solid polymeric materials after a parallel melt-polymerization experiment and (B) setup for an automated acquisition of fluorescence spectra from the polymers in the microreactor arrays.

found to be well-correlated with the chemical properties of interest.^{30–33}

Fluorescence spectra were collected under excitation conditions that were optimized to correlate the emission spectral features with parameters of interest. Principal components analysis (PCA) was further used to extract the desired spectral descriptors from the spectra.^{34,35} The PCA method was used to provide a pattern recognition model that correlated the features of fluorescence spectra with chemical properties, such as polymer molecular weight and the concentration of the formed branched side product, also known as Fries product,³² which were in turn related to process conditions.³³ The correlation of the variation in these spectral descriptors with the variation in process conditions was performed by analyzing the PCA scores. The scores were analyzed for their Euclidean distances between different process conditions as a function of catalyst concentration. Further, reaction variability was similarly assessed by analyzing the variability between groups of scores under identical process conditions. As a result, the most appropriate process conditions were those that provided the largest differentiation between materials as a function of catalyst concentration and the smallest variability in materials between replicate polymerization reactions.

Experimental Section

Process Conditions of Parallel Melt Polymerization in 96-Microreactor Arrays. Details of the parallel melt polymerization in 96-microreactor arrays have been reported previously.^{15,16} Briefly, bisphenol A polycarbonate was prepared by melt polymerization according to well-known literature methods.^{16–20} The starting reaction components included diphenyl carbonate (component A) and bisphenol A (component B) monomers obtained from GE Plastics and a catalyst (NaOH, component C) obtained from Aldrich. The

reactions were performed in glass 96-well microtiter plates that served as 96-microreactor arrays¹⁶ in a sequence of steps of increasing temperature^{19,20} and a maximum temperature of 280 °C. Multiple melt polymerization reactions were performed using mixtures of A and B at different ratios with different amounts of catalyst C. Catalyst amounts were expressed as certain fractions of 10^{-5} mol of catalyst per mole of component B. In process optimization experiments, polymeric materials were fabricated in five microreactor arrays under different intra- and interarray reaction parameters as illustrated in Table 1. The combinations of these parameters were provided from design of experiments. Ranges of these parameters were selected to preserve the rank order of a variety of control catalysts from a lab-scale to combinatorial reactors.^{15,19} All parameters described in Table 1 are considered process conditions (including chemical parameters such as ratio A/B and concentration of catalyst C), because once chosen, they are not altered throughout screening of new catalysts.¹⁵

Replicates ($n = 8$) of similar conditions in each 96-microreactor array were randomized in groups of four to reduce possible effects of any position-induced variability. In addition, one set of eight microreactors in each microreactor array was always left blank, and one of the microreactors contained a thermocouple. Figure 2A illustrates one of the 96-microreactor arrays with solid polymeric materials after a parallel melt-polymerization experiment.

High-Throughput Spectroscopic Analysis Setup. An experimental setup for an automated acquisition of fluorescence spectra from the materials in 96-microreactor arrays is shown in Figure 2B. Fluorescence measurements of polymers in each microreactor were performed through the glass bottom of the microreactors using a white light source, a monochromator, a portable spectrofluorometer, and a translation stage. The white light source (450-W Xe arc lamp,

SLM Instruments, Inc., Urbana, IL, model FP-024) was coupled to the monochromator (SLM Instruments, Inc., model FP-092) for selection of the excitation wavelength and further focused into one of the arms of a "six-around-one" bifurcated fiber-optic reflection probe (Ocean Optics, Inc., model R400-7-UV/VIS). Emission light from the polymeric material in each microreactor was collected when the common end of the fiber-optic probe was positioned near the bottom of the reactor at an angle 45° to the normal to the surface. The second arm of the probe was coupled to the portable spectrofluorometer (Ocean Optics, Inc., model ST2000) through an in-line optical filter holder (Ocean Optics). The holder contained a long-pass optical filter to block excitation light from entering the spectrofluorometer. The spectrofluorometer was equipped with a 200- μm slit, 600-grooves/mm grating blazed at 400 nm and covering the spectral range from 250 to 800 nm with efficiency greater than 30%, and a linear CCD-array detector. Fluorescence spectra reported here were not corrected by the spectral response of the optical system.

For fluorescence analysis of solid polymers, each microreactor array was arranged on an X - Y translation stage, and the common end of the fiber optic probe was held stationary to measure emission spectra. The size of the excitation beam of the fiber-optic probe was in the range from 1 to 4 mm, depending on the probe-microreactor distance. Data acquisition and automatic control of the X - Y translation stage were achieved with a computer using a program written in LabVIEW (National Instruments, Austin, TX). The program provided adequate control of the data acquisition parameters and real-time communication with the translation stage.

Data Processing Algorithms. Analysis of fluorescence spectra was performed using KaleidaGraph software (Synergy Software, Reading, PA) and PLS_Toolbox software (Eigenvector Research, Inc., Manson, WA) operated with Matlab software (The Mathworks Inc., Natick, MA). Prior to PCA, fluorescence spectra from five 96-microreactor arrays were appropriately preprocessed. The preprocessing included a baseline subtraction, normalization of spectra by the fluorescence intensity at 500 nm, selection of an appropriate spectral range for the PCA, and mean-centering the spectra. The spectra from the empty and thermocouple-containing microreactors (see section 3.1) were excluded from the spectral descriptor analysis.

Upon performing the PCA, a spectral descriptor was determined for each fluorescence spectrum. The spectral descriptor was represented as a vector in PCA space. This vector was described by a unique combination of the respective scores of principal components. The spectral descriptors from materials produced under the same processing conditions were considered as a cluster S in the PCA space without the use of automated clustering algorithms.³⁴⁻³⁶ Each cluster S was represented by its mean and standard deviation with respect to k th principal component. The Euclidean distance E between two clusters of spectral descriptors was calculated as

$$E_{ij} = \left\{ \sum_1^n (W_k(S_{ki} - S_{kj}))^2 \right\}^{1/2} \quad (1)$$

where i and j are indices of clusters S_i and S_j , respectively; E_{ij} is the Euclidean distance between these clusters; W_k is the weighting factor (equal to captured percent variance) of the k th principal component; and n is the number of principal components used for multivariate analysis.

Calculations of means and standard deviations of E_{ij} according to eq 1 were performed with a Monte Carlo simulation program (Crystal Ball, Decisioneering, Inc., Denver, CO). For these simulations, means and standard deviations of S_{ki} and S_{kj} were initially calculated from multiple spectral descriptors of each cluster. Further, both the mean of each cluster and its standard deviation (assuming the normally distributed error) were entered into the program. Finally, 10 000 iterations were performed on a 700-MHz personal computer to calculate the mean and standard deviation for a given E_{ij} .

From a variety of available approaches for cluster analysis,³⁶ we selected analysis of Euclidean distances because it provides the information about both the distance between clusters and the spread of each cluster. Further, although it is possible to perform calculations of Euclidean distances on raw spectra, we performed the PCA first to reduce the noise in the data.

Results and Discussion

Characterization Conditions. Fluorescence analysis provided an adequate selectivity of chemical determinations in bisphenol A polycarbonate.³⁰⁻³³ By changing both excitation and emission wavelengths, an excitation-emission fluorescence map was constructed that revealed different species. By optimizing the excitation wavelength, fluorescence can be collected from only certain species, and the fluorescence signal from interfering species can be greatly reduced.³⁷ In initial experiments, spectral regions were identified from experimental excitation-emission maps that were correlated with chemical properties of interest,^{31,32} which were in turn related to process conditions.³³ A typical excitation-emission fluorescence map of one of the polymeric compositions is presented in Figure 3. It illustrates that while several fluorescent species contribute to the fluorescence emission, it is straightforward to identify regions for accurate analyte quantitation by selecting certain excitation and emission conditions. During these initial experiments, an appropriate excitation wavelength of 340 nm was selected for preferential excitation of species of interest in the polymer.

Determination of Key Process Parameters. For the determination of the key process parameters and their respective values, fluorescence spectra from five 96-microreactor arrays were collected and processed as described in the Data Processing Algorithms section. The normalized spectra are presented in Figure 4. The spectral features of the polymeric materials in the microreactors contained a wealth of information about the chemical properties of materials. This information was extracted using multivariate analysis, such as PCA. According to the PCA results, the first two principal components (PCs) accounted for >95% of the spectral variation among all spectra. Thus, the first two PCs were used for an adequate description of the fluorescence spectra. Results of the principal components

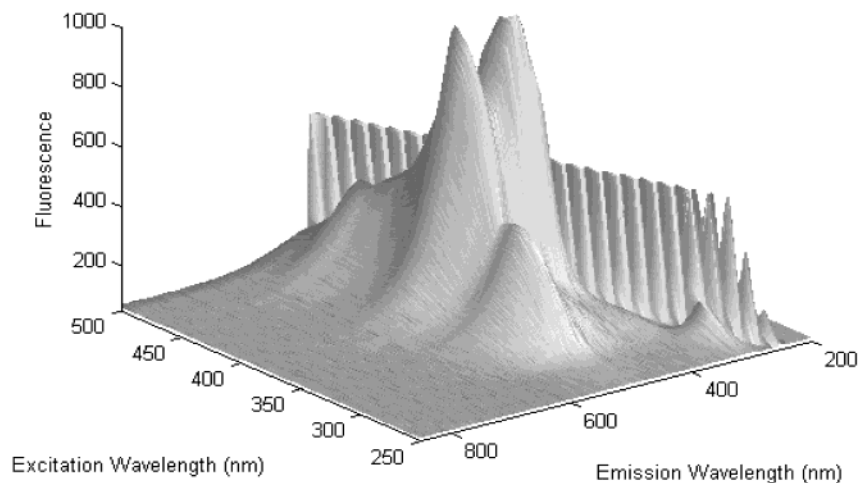


Figure 3. Typical excitation–emission fluorescence map of solid bisphenol A polycarbonate produced by melt-polymerization.

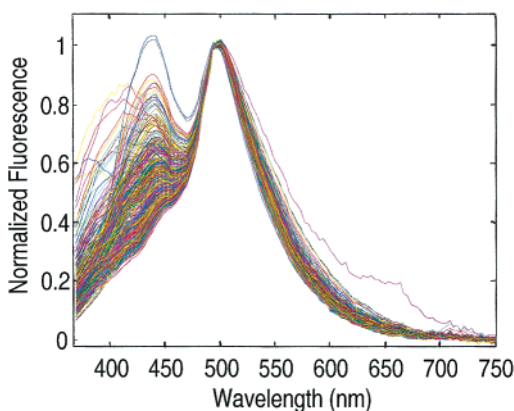


Figure 4. Normalized fluorescence spectra of the polymeric materials made in the 96-microreactor arrays under all experimental conditions.

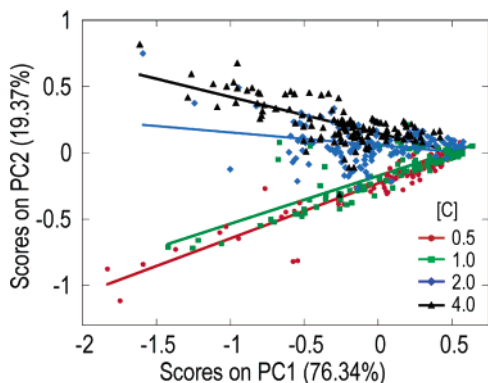


Figure 5. Results of the principal components analysis of the spectra of the polymeric materials made in the 96-microreactor arrays under all experimental conditions as a function of concentration of catalyst C.

analysis of the spectra from all 96-microreactor arrays as a function of concentration of catalyst C are presented in Figure 5. This scores plot demonstrates the existence of the major general trend in the spectral descriptors where the variation in scores of both PCs strongly depends on concentration of component C for all screened process parameters.

To determine other key process variables besides the concentration of component C that affect performance of the combinatorial thin-film polymerizations, PCA results were also analyzed as a function of individual intra- and interarray

variables. Figure 6 demonstrates PCA results as a function of variable volume, ratio A/B, flow rate, and dwell time. These data illustrate that for two intra-array parameters, such as the sample volume and ratio A/B, the significant clustering of spectral descriptors was observed only as a function of the ratio A/B. For two interarray parameters, such as flow rate and dwell time, the clustering of spectral descriptors was insignificant.

We further performed a more detailed analysis in which the spectral descriptors in *individual* 96-microreactor arrays were considered. The data were analyzed as a function of catalyst concentration, reaction volume, and ratio A/B at different flow rates of inert gas and dwell times. Such analysis evaluated the effect of these process parameters on the properties of polymerized materials and the reproducibility of replicate polymerizations in different 96-microreactor arrays. The minimum reaction variability was characterized by the smallest spread in clustering of spectral descriptors. It was found that the variation of flow rate of inert gas and dwell time affected the reproducibility of replicate polymerizations. Changes of reaction volume did not significantly affect the clustering of spectra for any of the interarray conditions. The most pronounced dependence of spectral features was provided by the variation in the ratio A/B.

This dependence of spectral features on variable levels of intra-array (ratio A/B and concentration of catalyst C) and interarray (flow rate and dwell time) process parameters is illustrated in Figure 7. In this Figure, spectral descriptors of all materials are presented similar to Figure 5. However, color codes and shapes are highlighted for materials from only two representative microreactor arrays. Spectral descriptors of polymers in a 96-microreactor array that were polymerized under an 8 L/min flow rate of inert gas and 10-min dwell time are color- and shape-coded in Figure 7A. Spectral descriptors of polymers in another 96-microreactor array that were polymerized under a 6 L/min flow rate of inert gas and 20-min dwell time are color- and shape-coded in Figure 7B. Spectral descriptors from the rest of 96-microreactor arrays are shown as gray circles. Different colors represent different concentrations of catalyst C. Different shapes of the markers represent variable ratios A/B. Under certain

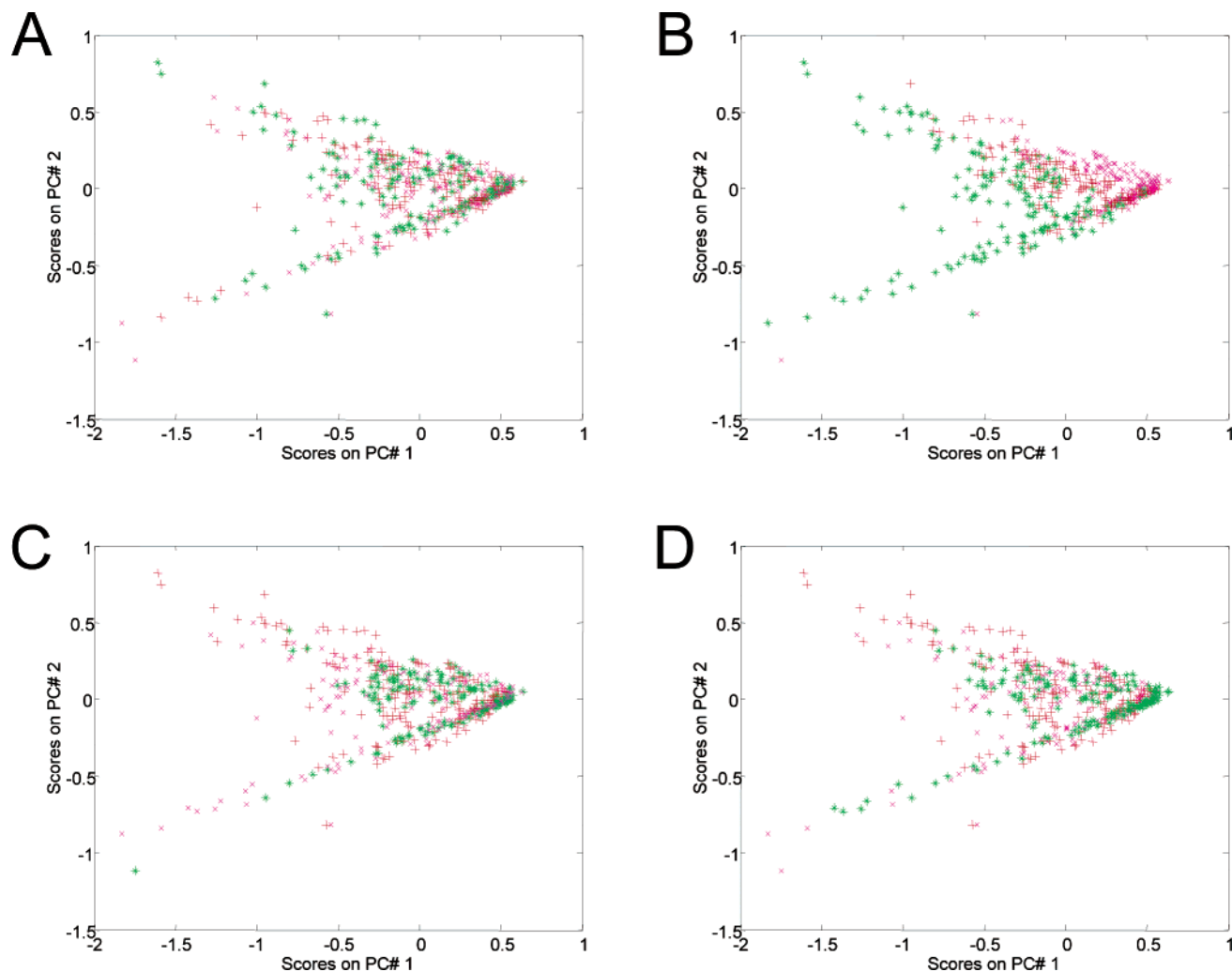


Figure 6. Results of the principal components analysis of the spectra of the polymeric materials made in the 96-microreactor arrays with variable intra-array (A and B) and interarray (C and D) parameters: (A) volume, (B) ratio A/B, (C) flow rate, and (D) dwell time. Levels: asterisks, smallest; plus, medium; X, largest. For values, see Table 1.

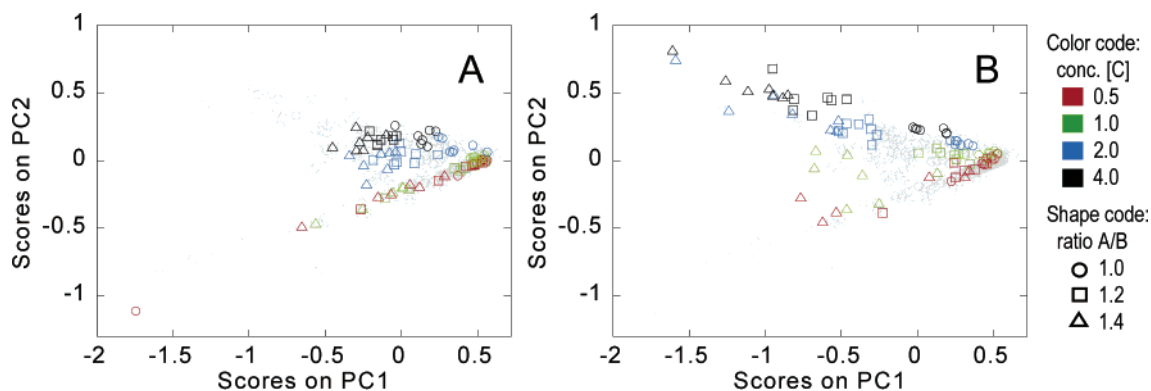


Figure 7. Dependence of spectral descriptors on ratio A/B under interarray conditions: (A) 8 L/min flow rate of inert gas and 10-min dwell time and (B) 6 L/min flow rate of inert gas and 20-min dwell time.

conditions (see Figure 7A), there is lack of sufficient discrimination among materials. This is evident from the fact that all data points are tightly clustered without significant separation. Other process conditions (see Figure 7B) are more favorable for two reasons: First, the materials are well-separated as a function of catalyst concentration. Second, within a certain concentration, materials are further separated by the different ratio A/B. For comparison, Figure 8

illustrates almost no dependence of spectral descriptors on variable levels of reaction volume under different concentrations of catalyst C, flow rates, and dwell times for the same two microreactor arrays. Thus, the process conditions of primary importance were identified to be the ratio of starting components A/B, concentration of catalyst C, flow rate of inert gas, and dwell time, whereas reaction volume did not significantly affect the polymerization performance.

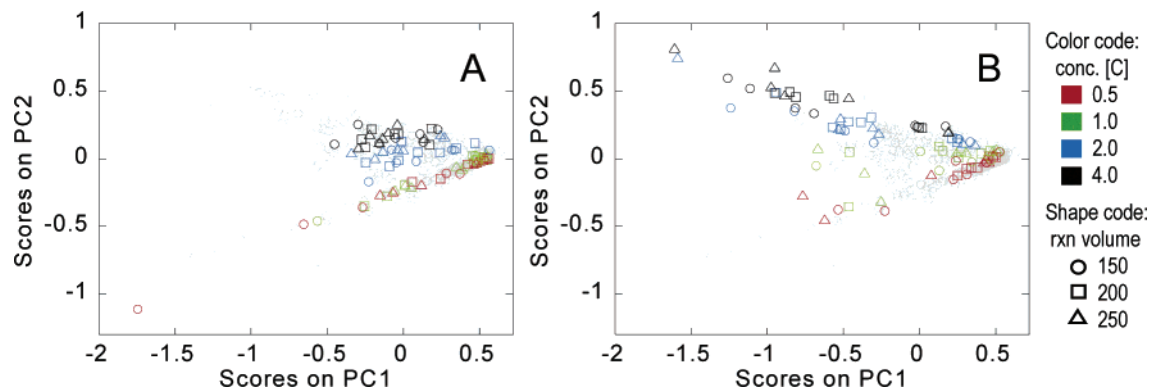


Figure 8. Dependence of spectral descriptors on reaction volume under interarray conditions: (A) 8 L/min flow rate of inert gas and 10-min dwell time and (B) 6 L/min flow rate of inert gas and 20-min dwell time.

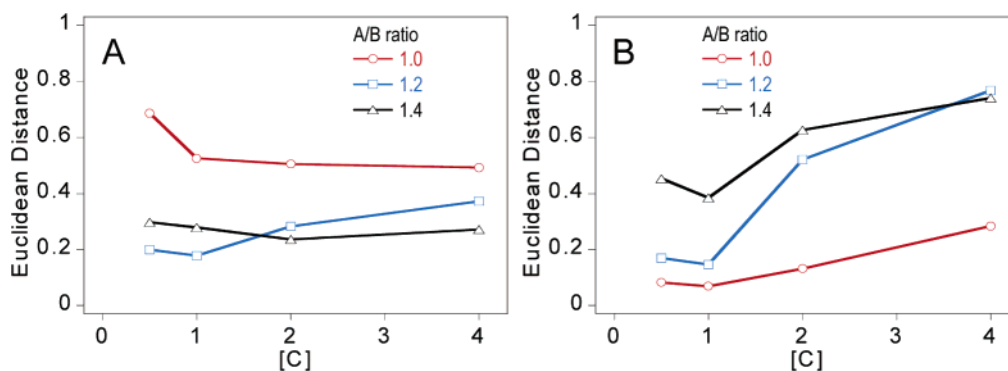


Figure 9. Results of calculation of Euclidean distances of spectral descriptors in polymer arrays produced under interarray conditions: (A) 8 L/min flow rate of inert gas and 10-min dwell time and (B) 6 L/min flow rate of inert gas and 20-min dwell time. Maximum Euclidean distance indicates best conditions for material differentiation as a function of concentration of catalyst C.

Determination of Optimal Levels of Process Conditions.

To determine the optimal levels of the identified process conditions, a more detailed evaluation was performed. Euclidean distances between different clusters of spectral descriptors and the uncertainty in these distances were computed using eq 1. Calculations were performed between spectral descriptors associated with materials produced with different amounts of catalyst and ratios A/B in all 96-microreactor arrays. Results of these calculations for all microreactor arrays used for optimization studies are summarized in Table 2.

Figure 9 illustrates two representative plots of the results of calculation of the Euclidean distance of spectral descriptors shown in Figure 7. As discussed in the Approach For High-Throughput Multiparameter Reaction Optimization section, the largest Euclidean distances indicate the best conditions for material differentiation. Thus, the best interarray conditions were found to be a 6 L/min flow rate of inert gas and 20-min dwell time. The best intra-array conditions were a combination of the catalyst concentration of 2–4 equiv and ratio A/B of 1.2–1.4 (Figure 9B). Results for the reaction variability for these microreactor arrays are presented in Figure 10. The smallest relative standard deviation (RSD) of spectral features indicates the best reaction reproducibility. This figure illustrates that the smallest RSD was achieved with the conditions of microreactor array processed under a 6 L/min flow rate of inert gas and 20-min dwell time and a ratio A/B of 1.2 over the concentration range of catalyst from 2 to 4.

Table 2. Means of the Euclidean Distances (ED) and Standard Deviations (SD) of Spectral Clusters

array	concn of C	ratio A/B					
		1.0		1.2		1.4	
		ED mean	ED SD	ED mean	ED SD	ED mean	ED SD
1	0.5	0.303	0.211	0.121	0.0872	0.699	0.511
	1	0.275	0.185	0.105	0.0761	0.518	0.379
	2	0.271	0.18	0.268	0.172	0.517	0.366
	4	0.234	0.149	0.570	0.165	0.581	0.391
2	0.5	0.687	0.499	0.199	0.146	0.297	0.218
	1	0.526	0.375	0.178	0.131	0.279	0.201
	2	0.504	0.357	0.282	0.167	0.236	0.161
	4	0.493	0.347	0.373	0.170	0.271	0.173
3	0.5	0.0830	0.0582	0.170	0.122	0.454	0.337
	1	0.0683	0.0467	0.146	0.101	0.385	0.281
	2	0.132	0.0694	0.521	0.158	0.627	0.389
	4	0.284	0.0982	0.768	0.189	0.741	0.385
4	0.5	0.149	0.107	0.117	0.0842	0.403	0.296
	1	0.164	0.113	0.129	0.0836	0.410	0.297
	2	0.116	0.076	0.190	0.117	0.388	0.265
	4	0.173	0.108	0.384	0.125	0.553	0.333
5	0.5	0.116	0.0848	0.139	0.103	0.534	0.392
	1	0.206	0.0984	0.115	0.0836	0.557	0.400
	2	0.184	0.106	0.388	0.212	0.423	0.300
	4	0.177	0.114	0.363	0.168	0.419	0.278

Spectral Features Under Nonoptimized And Optimized Process Conditions. Optimization of process parameters resulted not only in the improved reproducibility of replicate polymerization reactions and improved discrimination between materials with different levels of catalyst C, but also

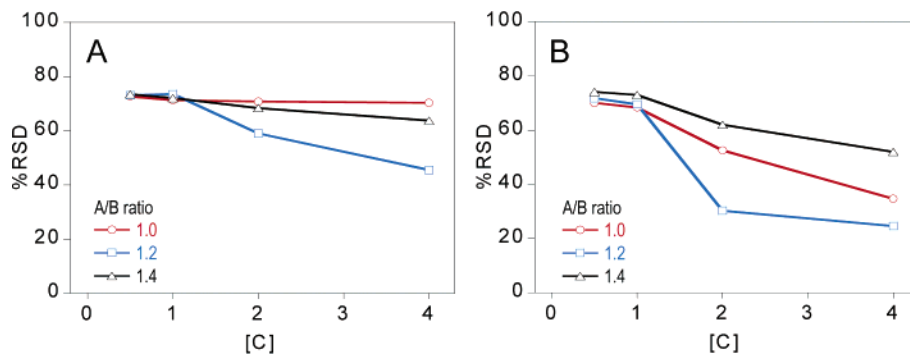


Figure 10. Results of calculation of reaction variability as %RSD of PC1 and PC2 scores of spectral descriptors in polymer arrays produced under interarray conditions: (A) 8 L/min flow rate of inert gas and 10-min dwell time and (B) 6 L/min flow rate of inert gas and 20-min dwell time. Smallest relative standard deviation (RSD) of spectral features indicates best reaction reproducibility.

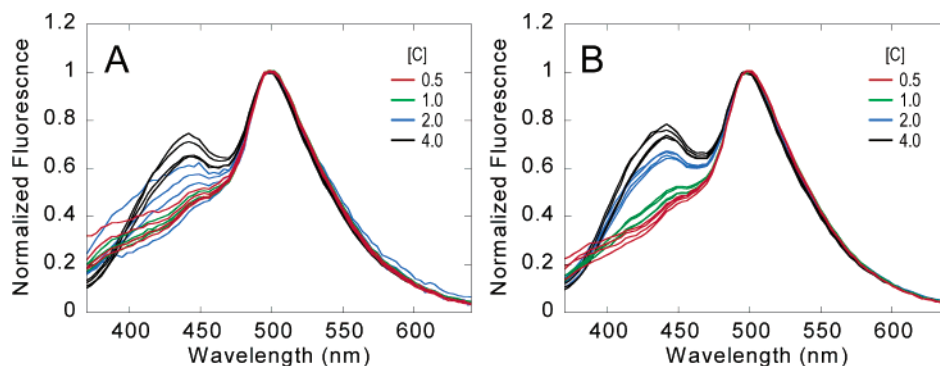


Figure 11. Typical material variability under reaction conditions: (A) 8 L/min flow rate of inert gas and 10-min dwell time and (B) 6 L/min flow rate of inert gas and 20-min dwell time. Intra-array materials parameters: ratio A/B = 1.2, reaction volume = 200 μ L.

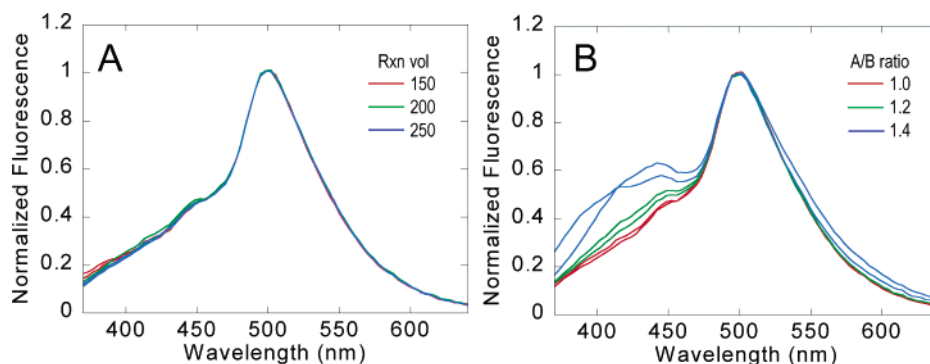


Figure 12. Effects of (A) reaction volume and (B) ratio A/B under optimized reaction conditions of 6 L/min flow rate of inert gas and 20-min dwell time. Intra-array materials parameters: (A) ratio A/B = 1.0, concentration of catalyst [C] = 1.0; (B) reaction volume = 200 μ L, concentration of catalyst [C] = 1.0.

in the improved homogeneity of polymers within individual microreactors. Typical examples of fluorescence spectra from polymer materials produced in replicate microreactors under nonoptimized and optimized conditions are presented in Figure 11. This comparison is performed for materials with increasing levels of catalyst C and constant levels of ratio A/B and volume. These plots illustrate that upon finding the optimal reaction conditions, the reproducibility of replicate polymerization reactions is improved. In addition, the discrimination between materials of increasing concentration of component C is also improved, as evidenced by the more reproducible fluorescence spectra under identical process conditions.

Under the optimized reaction conditions, the relative importance of variable reaction volume and reaction ratio A/B was confirmed. No significant difference in materials

properties was found upon changing of the reaction volume under optimized reaction conditions, as illustrated in Figure 12A. In contrast, the variation in ratio A/B had a pronounced effect (see Figure 12B), as predicted by the descriptor analysis.

The high spatial polymer homogeneity in individual microreactors is another powerful indicator of the reproducible polymerization process on the combinatorial scale. This variability is determined as differences in measured fluorescence spectra that are caused by the spatial variation in the chemical composition in the formed polymer within each microreactor. Figure 13 illustrates the fluorescence spectra of polymers within individual microreactors under non-optimized and optimized polymerization conditions. The evaluations were performed by measuring multiple regions of polymer in each microreactor. The small beam size (\sim 1-

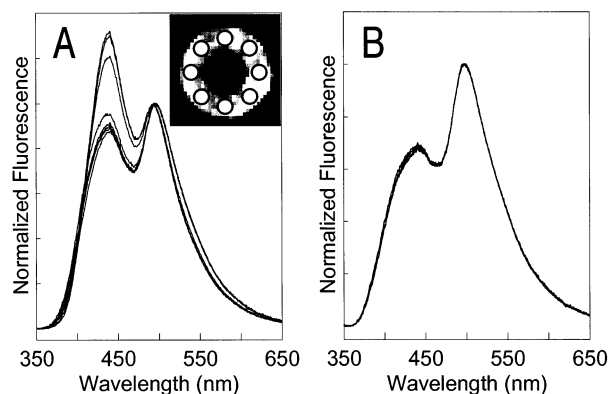


Figure 13. Spatially resolved fluorescence emission spectra of solid bisphenol A polycarbonate in a melt-polymerization microreactor before (A) and after (B) optimization of processing conditions. Inset: microreactor cross section and locations of spectral measurements.

mm diameter) permitted the detailed evaluation of the spatial distribution of polymer formation in each of the microreactors in the array. These measurements of variability can be provided only on a solid material directly in each microreactor, because this information is lost after dissolving the polymer for traditional GPC analysis.

Conclusions

The combinatorial and high-throughput experimentation infrastructure developed for screening of new materials^{31,38,39} has been implemented for the high-throughput optimization of process parameters of polymerization reactions in 96-microreactor arrays. While the system described here was implemented for high-throughput optimization of polymerization conditions, this methodology is more general and can be further applied for a variety of other applications in which optimization of process parameters can be studied in situ or off-line using optical spectroscopic and other tools. For example, this approach can also be used for optimization of synthesis reactions and derivatizations, in vapor, condensed-phase, or heterogeneous systems. Similarly, since extruders are often represented as a series of continuous unit chemical operations, the output of an extruder can be optimized against its typical process parameters (i.e., screw speed, zone temperatures, feed rates, vacuum levels, etc). The number of process parameters for optimization can be easily increased to include other parameters of interest. The major limitations most often are development of measurement techniques with good sensitivity and correlation with the properties of interest and obtaining adequate reproducibility of the measurements and the reactions. In addition, more complicated optimization procedures can be employed to correlate the process parameters with the end-use performance⁴⁰ on the basis of, for example, genetic algorithms.

Acknowledgment. The authors thank James Cifarelli and Willard Kohler for the technical assistance with data acquisition and automation and Chris Starnard and Ron Shaffer for stimulating discussions on data analysis.

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CC020062G