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Photodimerization of Maleic Anhydride in a Microreactor Without Clogging

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Abstract:

Photodimerization of maleic anhydride (MA) gives insoluble precipitated products that can be a trigger to clog a conventional microreactor. To avoid this problem, we devised a microreactor that uses liquid/gas slug flow and ultrasonication. Inert N_2 gas introduced into the reaction solution swept through the reactor tube and transported precipitated products in the liquid segments.Ultrasound vibrations inhibited the adhesion and sedimentation of precipitate in the reactor tube. The combination of gas and ultrasound prevented the tube from clogging. Fluorinated ethylene propylene (FEP) tubes of various sizes were investigated to use as a tube reactor. The tubes were wound around a high-pressure Hg lamp with a Pyrex immersion well which has been using generally as a light source of photoreaction, and the reaction solution was then passed through the tube and irradiated through the tube wall. The slug flow microreactor could be operated for more than 16 h continuously without clogging. Compared to using a batch reactor, this method achieves better product quality, improved conversion, and reduced waste.

Introduction

Chemical reactions in microchannels are important in the chemical, pharmaceutical, and analytical fields.[1] Therefore, much effort is devoted to the development of versatile microreactors that can handle various reactions.[2] When the reaction product is insoluble, clogging of the microreactor can be a serious problem, and it is highly desirable to be able to transport precipitated products out of the reactor continuously. A method for particle formation and handling in capillary flow was reported by Lilly (Indianapolis, U.S.A.).[3]

Several methods to transport precipitated products and avoid clogging have been reported. These include using the sheath flow technique to produce titania nanoparticles,[4] using droplet formation with the carrier phase to synthesize indigo,[5] using liquid/liquid segmented flow with immiscible solvent to produce inorganic nanoparticles,[6] and using a microreactor with slug flow to crystallize proteins.[7] Combinations of two solvents with different polarity are typically used to achieve liquid/liquid slug flow, but the risk with this type of flow is that some products might change to undesired byproducts (for example, by hydrolysis of anhydrides). Thus, liquid/gas slug flow achieved by introducing inert gas as a spacer is an attractive option. Ultrasonication[8] and mechanical vibration[9] are also effective in inhibiting adhesion and sedimentation of precipitates.

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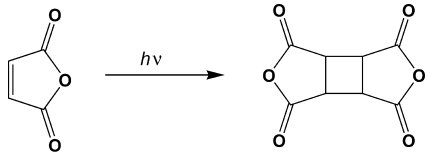
Scheme 1. **Photodimerization of maleic anhydride (MA) to form cyclobutane tetracarboxylic dianhydride (CBTA)**



When using a microreactor to produce a substance that precipitates in the microchannnel, the following points are important: (1) we must be able to control the quantity of solids and their particle size, (2) precipitates must be continuously transported, (3) and adhesion and sedimentation of precipitates must be prevented. Phototransparent materials are advantageous for observing liquid/gas slug flow in a microreactor, and this feature of the material is adequate for photochemical reactions.[10] Thus, we chose as a model reaction photodimerization of maleic anhydride (MA) to produce cyclobutane tetracarboxylic dianhydride (CBTA) (Scheme 1), which is practically insoluble in common organic solvents and precipitates during the course of the reaction, and we used a microtube reactor made of phototransparent fluorinated ethylene propylene (FEP).

Conventional photoreactions are usually performed in immersion well reactors (batch reaction). Most photoreactions occur within a short radius of the lamp, so conversion and irradiation time are much influenced by scale-up factors. Vigorous stirring is required to avoid this problem, but the cylindrical shape of the reactor prohibits effective stirring, and the reaction solution is thus exposed to a heterogeneous illumination field. In contrast, microreactions are expected to be homogeneously irradiated because of the short optical pass length involved.

Photodimerization of MA is usually performed in a conventional batch reactor. However, a batch reactor is not ideal for this reaction because precipitated product goes into suspension, adheres to the lamp cooling jacket, and scatters the irradiated light, causing the conversion to be very small even for long reaction times. To make matters worse, surplus UV irradiation may cause undesired side reactions and/or product decomposition. We envisioned that these problems could be overcome using a slug flow microreactor.

In this contribution, we present a valuable method for transporting precipitates through a microreactor without clogging, and we also describe the relative merits of the method compared to batch reaction systems, using the photodimerization reaction of maleic anhydride.

Experimental Section

General. Maleic anhydride, ethyl acetate, 4,4′-diaminodiphenylmethane, *N*-methylpyrrolidone were purchased from Wako Pure Chemical Industries, Ltd., and used without further purification. The product was confirmed by ^{1}H NMR on Varian MERCURYplus-400 (400 MHz). A 400 W high-pressure Hg lamp with a Pyrex immersion well (UVL-400HA) was purchased from Rico-Kagaku Sangyo Co. Various sizes of FEP tubes were purchased from Junkosha Inc. and were connected with union fittings and T-shaped fittings purchased from Swagelok. An ultrasonic bath (TUS-820: 100 W, 39 kHz) was purchased from Asone Co., and an external cooling unit (TRL-117NHF) was purchased from Thomas Kagaku Co., Ltd. A quartz beaker (outer diameter (OD) 64 mm, height (h) 300 mm) around which to wind the tube reactor was manufactured by Eiko CO., Ltd. A plunger pump (LC-10Ai) was purchased from Shimadzu Co. The needle valve (MF-33; 0−5 mL/min) was purchased from GL Sciences. A back-pressure regulator was purchased from Upchurch Scientific. A filter unit was purchased from Sanplatec Co., Ltd.

Single Pass Flow Microreactor. The single pass flow reactions were carried out using a setup shown in Figures 1 and 2. An FEP tube (outer diameter (OD): 1.0−3.2 mm, inner diameter (ID): 0.5−1.6 mm), was wound around the outside of a quartz beaker (Figure 2a). Inside the beaker was placed a 400 W high-pressure Hg lamp with a Pyrex immersion well. A Pyrex immersion well works as a filter for a shorter wavelength of UV (∼<280 nm), which is not suitable for this reaction. The beaker was set in an ultrasonic bath. The bath and lamp were maintained at less than 15 °C by an external cooling unit and a refrigerated water circulator, respectively, because the yield decreased when the temperature became higher than 20 °C. We used ethyl acetate (bp 76.8 °C) as solvent. A solution of MA (10 w/w % in ethyl acetate) was fed into the tube reactor by plunger pump (0.1−2.0 mL/min) through a back-pressure regulator, which reduces the effect of the pulsation of the pump. N_2 gas was fed into the tube reactor through a T-shaped connector and mixed with the reaction solution to achieve liquid/gas slug flow (Figure 2b). N_2 flow rate was controlled by a needle bulb to maintain the length of each liquid segment at about 2−5 cm and each gas segment at about 0.5−1.0 cm. Reaction solution, separated by N_2 segments, passes through the tube and was irradiated through the tube wall. The residence time was calculated on the basis of the measured velocity of the N_2 segments (Figure 2c). After the operation lasted for 1−2 h, the suspension was collected and condensed under reducing pressure (160 mmHg, 50 °C) to remove volatile materials and then cooled to room temperature (20−25 °C), filtered, and dried in a vacuum drying oven (60 °C). The conversion was estimated by the weight of CBTA.

Continuous Recycle Flow Microreactor. The continuous recycle flow reactions were carried out using the setup shown in Figure 3. Most of the apparatus was the same as in the case of the single pass flow microreactor except for a magnetic stirrer and a filter unit installed for recycling. A solution of MA (10 w/w% in ethyl acetate) was stirred by a magnetic stirrer to maintain a homogeneous concentration. Precipitated CBTA was filtered out continuously by a filter unit containing a paper filter installed above the reaction solution vessel, through which the homogeneous solution was recycled. The recycle number was calculated as the ratio of the weight of a solution (300 or 100 g)

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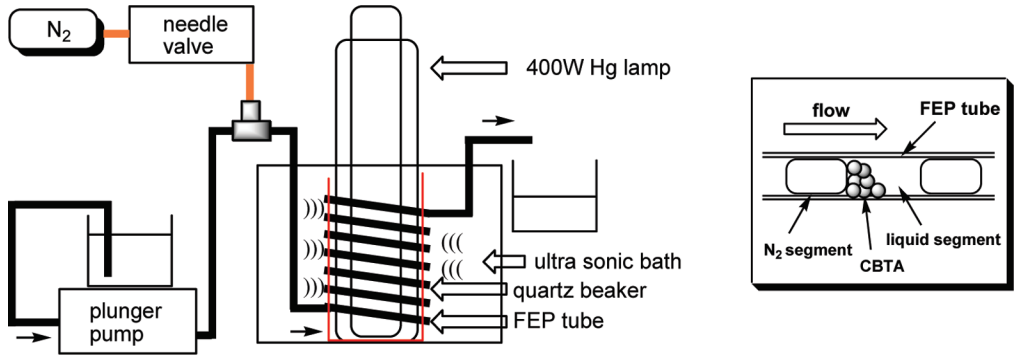

Figure 1. **Single pass flow microreactor and continuous transportation of precipitates.**

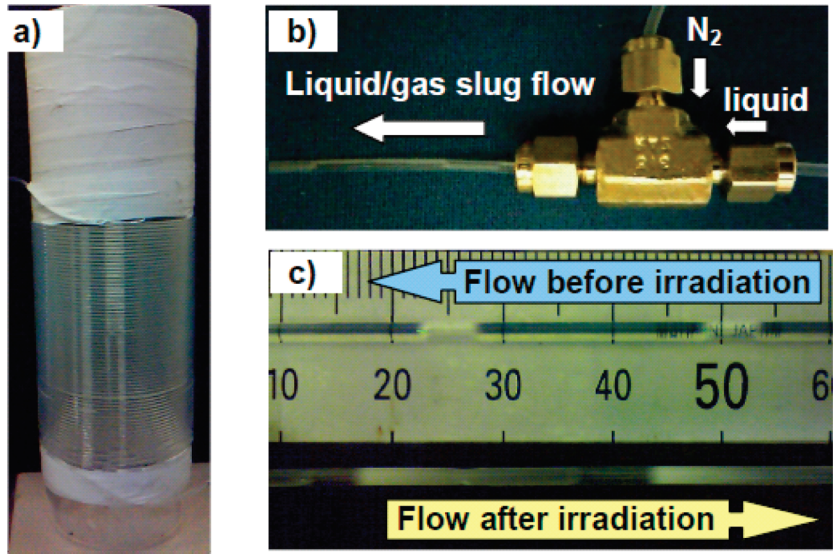

Figure 2. **Slug flow microreactor: (a) FEP tube reactor, wound around the outside of a quartz beaker; (b) N_2 gas feed, via T-shaped connector; (c) liquid/gas slug flow before and after irradiation.**

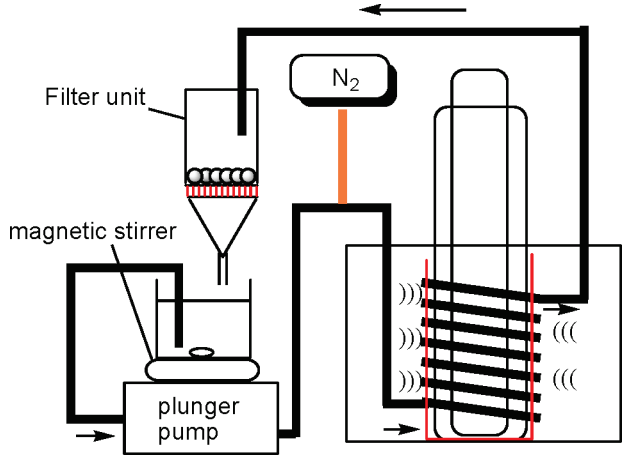

Figure 3. **Continuous recycle flow microreactor with filter unit.**

and flow rate (2.5−5.0 mL/min) compared to that for a single pass flow reaction. CBTA was filtered and worked up as described above.

Batch Reactor. A cylindrical glass vessel (ID 75 mm; h 300 mm) covered with aluminum foil was used as a reactor and set in cooled brine (0 °C). A 400 W high-pressure Hg lamp in a Pyrex immersion well was set into a solution of MA (10 wt/wt % in ethyl acetate: 600 g). After irradiation for 6 h with N_2 bubbling through a gas inlet tube, the suspended solution was worked up as described above. CBTA (15.8 g, 26%) was obtained.

The Viscosity Measurement of Polyamic Acid. Preceding polymerization, CBTA was treated with a solvent mixture of toluene (10 w/w) and acetic anhydride (10 w/w) at 120 °C for 2 h, and then was cooled to room temperature, filtered, and dried in a vacuum drying oven (60 °C).

4,4′-Diaminodiphenylmethane 0.7931 g (4.000 mmol) was placed in a 100 mL round-bottomed flask which was substituted with Ar, and 11.392 g of *N*-methylpyrrolidone was added. After 1 min of Ar bubbling, CBTA 0.7844 g (4.000 mmol) was added into the solution. The solution was stirred at 25 °C under Ar for 24 h. The resulting polyamic acid was measured by a rotational type viscometer at 25 °C.

Results and Discussion

Photodimerization of MA is a well-known reaction yielding precipitated compound, CBTA. CBTA, which is used as a raw material of polyimide and an alignment film for liquid crystal display (LCD), has been produced in commercial chemical plants in relatively large scales. Because the amount of production is increasing, much effort has been devoted to the optimization of reaction conditions. During the course of the optimization of the reaction, ethyl acetate was found to be

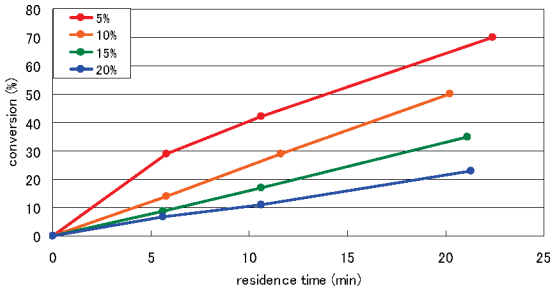

Figure 4. **Change of conversion with various MA concentrations and residence time (tube OD = 1.6 mm, ID = 1.2 mm, *L* = 11.2 m).**

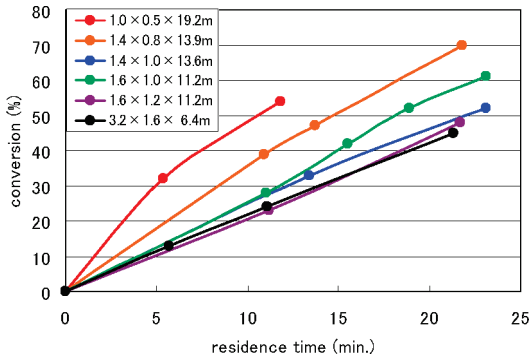

Figure 5. **Change of conversion with various tube sizes and residence time (MA concentration = 10%). Inset shows tube size (OD (mm) × ID (mm) × length (m)).**

the best solvent for the production of CBTA. Therefore, in this study we used only ethyl acetate as solvent. MA exhibits an intense UV absorption band at 250 nm and a broad absorption up to 350 nm. However, it was better to use a Pyrex filter, which cuts the UV wavelength short (~<280 nm).

Our first decision for the reactor concerned the reactor material. Different materials have been used for the reactor of a photoreaction—including glass,[11] polydimethylsiloxane (PDMS),[12] and polystyrol[13] plates and FEP tubes.[14] In terms of transparency, glass is superior. But most of the glass reactors are plate form which cannot be irradiated homogeneously by a cylindrical lamp. Glass tubing is vulnerable to breakage and cannot be wound tightly around the lamp. Our final choice was FEP tubing, which is flexible enough to wind around the lamp tightly and smooth enough to inhibit adhesion of the precipitate. FEP tubing has good UV transparency (250 μm of thickness: 80.4%, 300 μm: 75.6% at 330 nm).

Our second decision for the reactor concerned the manner of the flow because of the precipitated product. When we attempted the flow reaction with only one liquid and no segment, clogging occurred within an hour, and continuous operation was impossible. If we used a liquid/liquid slug flow formed by combining two mutually insoluble solvents, the segment transported precipitated product out of the tube. However, if one of the solvents was water, both MA and CBTA hydrolyzed and converted to carboxylic acids. Thus, we

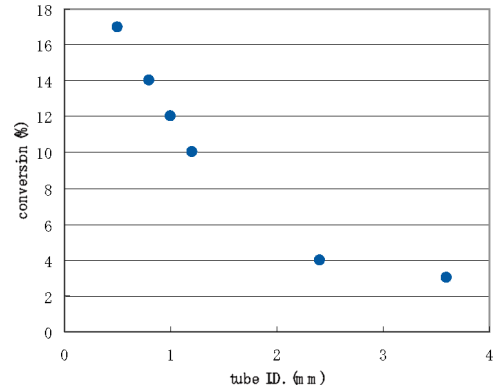

Figure 6. **Change of conversion with increase of tube ID (MA concentration = 10%, residence time = 5 min).**

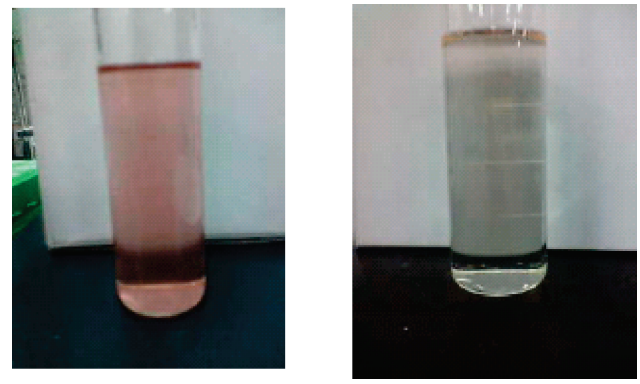

Figure 7. **Solution color after irradiation reaction followed by filtration. After batch reaction for 6 h (left); after flow reaction for 10 min (right).**

attempted to use a liquid/gas slug formed by introduction of inert N_2 gas. The role of N_2 gas is to separate the liquid into segments that transport the precipitated product, and each segment acts as a very small "micro batch reactor". Precipitated product in all segments can be transported without transferring to the following segment and the risk of clogging becomes scarce. The combination of segments of different states could transport CBTA with neither decomposition nor clogging. No connector was used after photoirradiation to avoid clogging there. Ultrasonic irradiation is better to use for reliability and long-time operation. We achieved continuous operation for more than 16 h with this system (tube ID = 1.2 mm, *L* = 11.2 m).

We examined the effect of MA concentration on conversion using a tube of ID = 1.2 mm (Figure 4). Conversion increased with an extension of the residence time. A 5% solution gave the highest conversion with 22 min of residence time, because at low MA concentration, transparency is sufficient even for a tube of large ID.

We examined the effect of tube size on conversion using a 10% MA solution (Figure 5). Conversion became higher with decreasing tube ID, because narrower tubes have shorter optical pass lengths and the solution in the reactor were irradiated homogeneously. The operation with a small tube ID (0.5 mm) required smaller flow rate (0.10 mL/min) for long residence time. It caused eventual clogging. A tube of ID = 0.8 mm was found to be the smallest and most favorable reactor to give the satisfied conversion (70%). The particles of CBTA were analyzed by SEM. Their shape was hexagonal, and the average length of long axis was about 14 μm (see the Supporting

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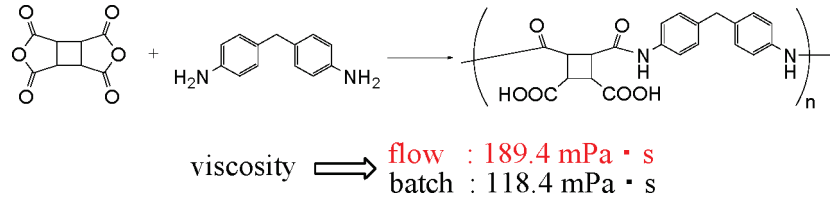
Scheme 2. **Polycondensation of CBTA and diamine compound to form polyamic acid[a]**



[a] Note the difference in viscosity achieved for flow and batch reactions.

Information). Though it was reported that CBTA produced in 1,4-dioxane was a mixture of *cis* and *trans* isomers, in the present study only the trans isomer was obtained. The *cis* isomer was not detected by ^{1}H NMR.[15]

The power efficiency (W/mmol) of each tube was estimated by lamp power (W) and CBTA (mmol) (see the Supporting Information). The reaction with a shorter residence time gave higher efficiency, but the narrower tube was not better. We think all differences need to be considered, because the tube thickness and reflectance of light were also altered as the tube size changed.

We also examined the effect of tube size on conversion at a constant residence time of 5 min with a 10% MA solution (Figure 6). As before, better conversion was obtained with decreasing tube ID. At ID > 2.4 mm, the conversion was quite small. At ID = 3.6 mm, regular liquid/gas slug flow was not achieved, because the gas segment moved individually regardless of the flow rate control. N_2 segments in a large space were not controllable, and the precipitate could not be transported through the tube at a constant rate. Thus, it is clear that formation of continuous slug flow, and hence continuous sweeping of precipitate product, is achieved only when tube IDs are from a micrometer to a millimeter in size.

It is important to note that the flow reactions gave better-quality product than batch reactions. Precise control of residence time led to fewer byproducts resulting from decomposition of product and/or undesirable side reactions. It was visually evident by changes of solution color. For the same conversion (26%), the batch reaction solution (reaction time = 6 h) turned red, but the flow-reaction solution (reaction time = 10 min) remained almost colorless (Figure 7). The flow reaction gave fewer byproducts because the irradiation time required for the reaction is shorter. The quality of the product is very important for commercial production of CBTA, but the impurities were difficult to identify by ^{1}H NMR, GC, and HPLC analyses because their amounts were too small. Thus, quality of the product was evaluated by measuring the viscosity of polyamic acid, which is important from an industrial point of view. The flow-reaction sample showed higher viscosity (Scheme 2), indicating higher purity.

When environmental friendliness is considered in a chemical process, the reduction of disposal of raw materials is important. Accordingly, we investigated the effectiveness of the slug flow microreactor, adapted for continuous circulation and recycle operation, in improving conversion and reducing MA waste. In such a system, precipitated CBTA can be filtered out and reduce some shading and scattering of light (Figure 3). The use of a convectional reactor for the dimerization of MA using self-filtering with low-density particles has already been reported.[16]

Table 1. **Conversion and the amount of MA at various recycle conditions (OD = 1.6 mm, ID = 1.2 mm, *L* = 11.2 m)**

	single pass[b]	recycle 1[c]	recycle 2[d]	recycle 3[e]
operation time (h)	6	6	6	9
residence time (min)	11.6	11.8	5.9	11.8
recycle number (times)	1	3	6	4.5
conversion (%)	29	60	52	69
waste (g)[a]	2.4	0.67	0.92	0.44

[a] The amount of wasted MA(g) per obtained CBTA(g). [b] 10% MA solution (300 g) was used. [c] MA concentration = 10% (100 g); flow rate is the same as for the single pass method. [d] MA concentration = 10% (100 g); flow rate is 2 times faster than that for recycle 1. [e] Operation time was extended with the conditions of recycle 1.

A flow reaction system is useful to test a recycling effect to improve conversion and to reduce the amount of unreacted raw materials. The results of recycling are shown in Table 1. When one-third the amount of MA solution was fed at the same flow rate as for the single pass operation, the conversion improved greatly compared to that for the single pass operation with the same operation time (6 h). However, when one-third the amount of the MA solution flowed at 2 times the flow rate for the conditions of recycle 1, the conversion decreased. Judging from the difference of irradiation time with the two conditions, a residence time of >10 min is required to improve conversion. A longer operation time resulted in higher conversion (recycle 3: 69%). The amount of MA that goes to waste to produce 1 g of CBTA was 2.4 g for single pass operation but just 0.44 g for recycle 3 conditions. This continuous circulation and recycle slug flow system can be useful when raw material is expensive or contamination of raw material into a product would be troublesome problem.

Conclusions

Use of liquid/gas slug flow in a microreactor enables operations of long times without any risk of clogging. Higher conversion than that of a batch system was achieved for photodimerization of maleic anhydride in an

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FEP tube with an ID of about a millimeter. It is also noteworthy that the flow reaction system gave better-quality CBTA than the batch system. Reduced waste of raw materials by recycling is easily realized. We hope that this methodology will be useful for reactions in which the risk of clogging is a factor.

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Supporting Information Available

This material is available free of charge via the Internet at http://pubs.acs.org.

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