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Reaction Kinetics of a Condensation Polymer between 1,10-Dibromodecane and Hexamethylenediamine: Scale-Up Considerations

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Abstract:

The end point, rates of reaction, and heat of reaction have been determined for the reaction of 1,10-dibromodecane and 1,6-hexamethylenediamine, which forms a moderately cross-linked polymer useful as a bile acid sequestrant in the treatment of elevated cholesterol. The parameters have been used to predict scale-up of the polymerization from the laboratory to pilot plant and full-scale production. A novel application of a bromide-specific electrode analytical method was developed to determine the extent of polymerization.

Introduction

Successful scale-up of a reaction from the laboratory through pilot plant to production scale requires an understanding of the reaction end point, the kinetics, and the heat effects of the reaction process being scaled. This article presents the kinetic and thermal data as well as a method to determine reaction completion from the successful process development of a new polymeric bile acid sequesterant, DMP 504, currently in Phase II clinical trials. DMP 504[1-3] is a cross-linked polymer formed from the polymerization of 1,10-dibromodecane (DBD) and 1,6-hexamethylenediamine (HMDA) in a dimethylacetamide/methanol solvent system in the presence of hydroxypropylcellulose and sodium carbonate. The resulting polymer is moderately cross-linked and, therefore, is not soluble in any solvent. The polymerization and structure in the bromide form are illustrated in Scheme 1. After the polymerization is complete, the polymer is purified by a series of alternating NaOH/HCl washes to remove residual monomers, low-molecular-weight oligomers, and solvents and to replace the bromide with chloride ions.

The heat balance is particularly important for scale-up since thorough mixing must be provided, even after the polymer has reached the gel point. Vigorous mixing at these very high viscosities results in a high heat input.

In addition, the scale-up of this polymerization is complicated by its therapeutic indication—a bile acid sequestrant to be taken on a daily basis to reduce cholesterol in humans. Therefore, the bromide must be reduced to less than 0.06%. The bromide level is based on the known toxicity of bromide, a safety margin, and the expected dosage. It follows that the reaction of the dibromodecane must be complete since the total bromide content of the final product is determined by combustion, which does not distinguish between organic and inorganic bromide.

This article is divided into three sections in order to simplify the separate areas of concern for the process scale-up. Section 1 describes the development of a method to determine when the reaction has reached completion. Section 2 describes the development of the kinetic data in order to model the polymerization reaction up to its gel point and determination of the heat of reaction. Section 3 describes the development of the heat of reaction data and mixing energy in order to successfully scale-up the heat removal requirements of the commercial reactor.

1. Completion of Polymerization

Samples taken periodically during the polymerization were analyzed for inorganic bromide using a bromide specific electrode (see the Experimental Section for details). The extent of reaction was calculated from the inorganic bromide and the amount of DBD charged to determine when the reaction was essentially complete.

The analysis was done in three stages. The first stage was to test the analysis method in a ContraLab reactor up to about 75% completion at 40 and 60 °C. At this point, the slurry thickens and cannot be agitated with typical laboratory equipment. The results are shown in Figure 1.

The reproducibility suggested that the analytical method was sufficiently reproducible to obtain the necessary data, at least up to the point at which the slurry could not be agitated in the ContraLab equipment. It was necessary to follow the analytical procedure carefully, including daily standardizations, to obtain reproducible results.

The second stage was to prepare the polymer in a Ross 1-qt double-planetary mixer, as described in the Experimental Section. This is the type of mixer planned for commercial scale reactions, and it provided good mixing, even after the gel point of the polymerization. A typical run is shown in Figure 2. It should be noted that the polymerization in the double-planetary mixer is not isothermal. The temperature is held at 40 °C during the DBD feed and for 30 min after the feed and then ramped up to 80 °C over a controlled period of time.

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(1) Royce, S. D.; Figuly, G. D.; Khasat, N. P.; Matos, J. R. U.S. Patent 5,556,619, September 17, 1996.

(2) Gillies, P.; Grimminger, L.; Figuly, G.; Jensen, J.; Royce, S.; Shimshick, E. *DMP 504: A Hydrogel Bile Acid Sequestrant; Part 1—Equilibrium Binding and Kinetics*; Poster, DALM Conference (Drugs Affecting Lipid Metabolism), November 1995.

(3) Billheimer, J.; Fischer, R.; Germain, S.; Figuly, G.; Jensen, J.; Royce, S.; Gorko, M.; Hainer, J.; Gillies, P. *DMP 504: A Hydrogel Bile Acid Sequestrant; Part 2—Mechanism of Action Studies in the Hamster*; Poster, DALM Conference (Drugs Affecting Lipid Metabolism), Houston, TX, November 1995.

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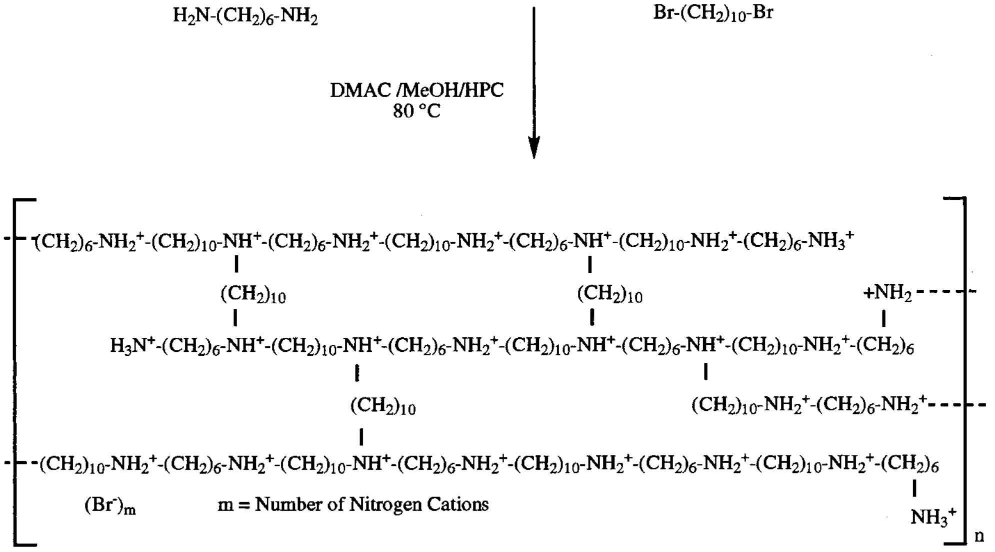
Scheme 1



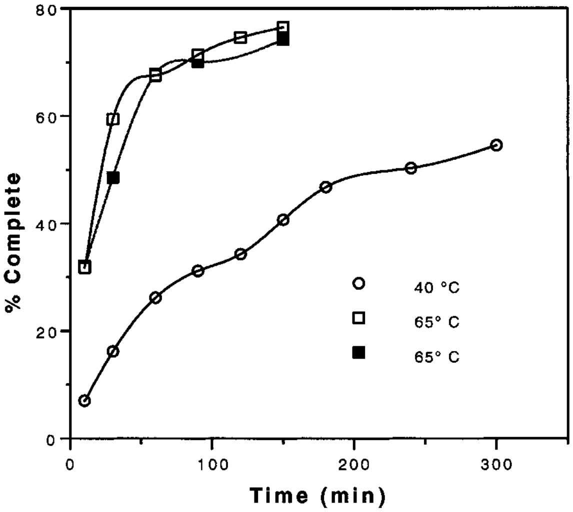


Figure 1. **Reproducibility of the determination of the percentage completion of the polymerization by bromide analysis with a bromide ion-specific electrode.**

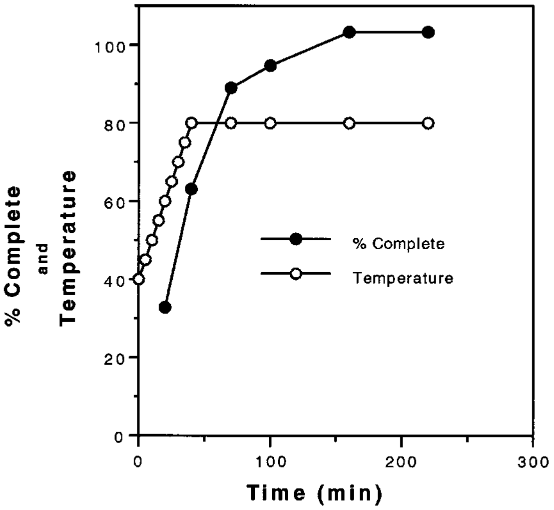


Figure 2. **Percentage completion of the polymerization by bromide analysis in the Ross 1-qt double-planatary reactor.**

Table 1. **Time for polymerization completion in 1-qt and 160-L double-planetary reactors**

ramp time[a] (min)	% complete	time to completion[b] (min)
	1-qt Reactor	
40	104	160
40	102	160
40	103	160
70	101	190
114	101	244
120	105	240
	160-L Reactor	
70	105	250
70	103	310
70	105	310
85	104	205

[a] Time to ramp from feed and hold temperature. [b] Time to completion from the start of the DBD feed.

The exact temperature of the slurry in the laboratory mixer was not known when the data were obtained. The temperature shown is the jacket temperature. Later, the reactor was modified to place a thermocouple in the slurry, and the internal reaction temperature was closer to 75 °C, not 80 °C, as indicated by the jacket temperature. The reactor agitation speed was also adjusted from the maximum, 60 Hz or 90 rpm, to 20 Hz or 30 rpm before the gel point was reached to prevent the formation of particles that were too small to filter.[4]

In all cases, the reaction appears to be more than 100% complete (101−105%, Table 1). We have concluded that this is not an artifact of the analytical method but is due to the loss of solvent during the reaction. During the polymerization, about 5% of the total weight is lost. Noncondensable carbon dioxide formed by reaction of Na_2CO_3 with HBr carries some methanol through the condenser. Correction for this weight loss at each point was not possible, since it was not known at what point in the polymerization the carbon dioxide was produced. In any case, it was more important to be able to determine when the reaction was

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(4) Bedle, R. W. *Chem. Eng. Educ.* **1995**, *29* (3), 168.

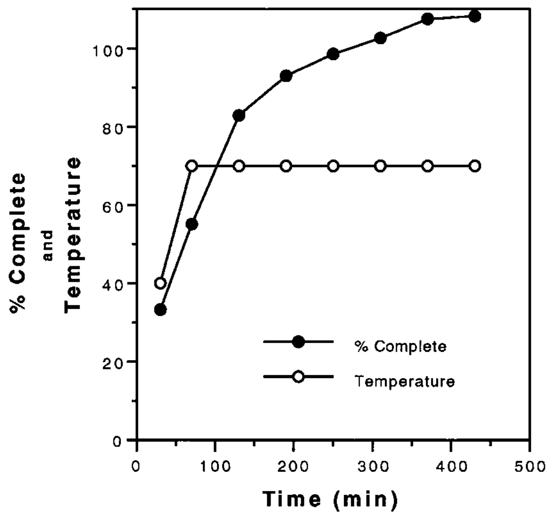

Figure 3. **Percentage completion of the polymerization by bromide analysis in the 160-L double-planatary reactor.**

essentially complete, not to make a complete material balance.

The time to completion depends on the temperature profile. As can be seen in Table 1, the time to completion was about 160 min when the jacket temperature was ramped to 80 °C in 40 min and 240 min when the jacket temperature was ramped to 80 °C in 120 min.

The third stage was to demonstrate that the reaction could be scaled up from the laboratory reactor to a pilot plant scale double-planetary mixer. Samples were taken during the production of DMP 504 for clinical studies in a 160-L double-planetary mixer. A typical reaction profile is shown in Figure 3.

The internal reaction temperature was reduced to 30 °C during the feed and hold period in the 160-L reactor to ensure complete mixing before the slurry thickened significantly. The final hold temperature was reduced to 70 °C because the reflux caused by the carbon dioxide evolution flooded the available condenser. The results are not as consistent in the larger pilot plant equipment. The lower temperatures extended the time of complete reaction to 250−310 min, or about 6 h after the feed is started (Table 1).

For production in a moderate-scale production reactor (500 L), the reaction time was extended to 10 h to ensure that the low bromide specification would be met for initial clinical production. All of the polymers produced at this scale have had a bromide content of less than the level of detection of 0.04%. The additional 4 h beyond what we believe is the completion adds about 20% to the reactor cycle time. Future plans include optimizing the cycle time when commercial facilities are installed.

2. Kinetic Analysis and Heat of Reaction

The kinetic data were obtained using a 1-L glass ContraLab reaction vessel, as detailed in the Experimental Section.

Table 2. **Kinetic rate data for reaction between DBD and HMDA at 20, 30, 40, and 50 °C**

20 °C		30 °C		40 °C		50 °C	
(min)	% complete	(min)	% complete	(min)	% complete	(min)	% complete
40	6.4	30	8.2	30	12.9	30	20.2
95	13.5	60	20.2	60	28.2	60	45.3
185	21.5	120	31.4	90	37.5	90	54.5
215	22.5	180	39.2	120	44.3	120	61.2
275	27.3	240	46.4	150	49.9	150	71.7
315	30.6	300	51.0	180	51.2		
370	31.6						

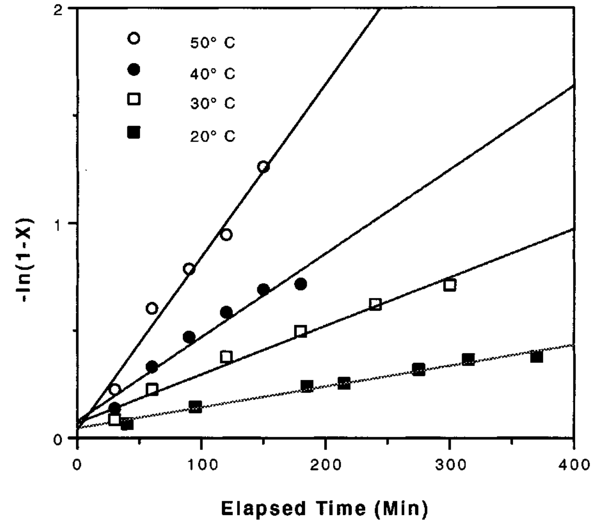

Figure 4. **Reaction rates at 20, 30, 40, and 50 °C in the ContraLab reactor, 30−70% complete.**

Reaction rates were obtained at 20, 30, 40, and 50 °C, up to about 65% reaction, using the bromide-specific electrode, as shown in Table 2 and in Figure 4. The reaction followed first-order kinetics for the first 60+% of the reaction. First-order kinetics can be determined for a reaction of the form

$$A \rightarrow \text{products}$$

where

$$-r_A = -dC_A/dt = kC_A$$

and

$$k = k_0^{(-E_A/RT)} \qquad \text{(typical Arrhenius relationship)}$$

The fractional conversion of the reaction, X, can be expressed as[5]

$$-\ln(1 - X_A) = kt$$

where t is the elapsed reaction time and k is the rate constant, as defined above. A plot of $-\ln(1 - X_A)$ **vs** t will have k as its slope. The data (Table 2 and Figure 4) for each temperature were plotted in this manner, with the resulting rate constants determined, (see Table 3). The data are not as good as we had hoped, but they are adequate for the analysis. The reaction rates all show downward curvature because, for the first part of the reaction, the DBD reacts with primary amines. However, as the reaction proceeds,

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(5) Levenspiel, O. *Chemical Reaction Engineering*, 2nd ed.; John Wiley and Sons: New York, 1972; p 46.

Table 3. **Reaction rate, *k*, and heat of reaction**

temp	k (min^{-1})	ΔH (kJ g-mol^{-1}) mol^{-1} Br
20 °C isothermal	0.001 14	
30 °C isothermal	0.002 59	−143.4
40 °C isothermal	0.004 51	−140.3
50 °C isothermal	0.008 42	−125.1
adiabatic 1		−128.9
adiabatic 2		123.5
average		−132.1 ± 9.2

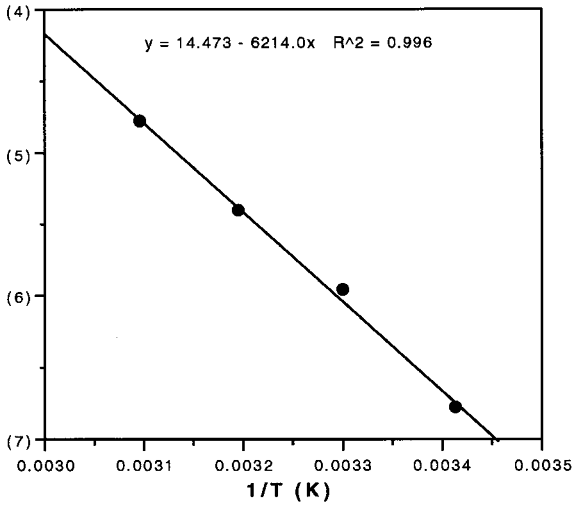

Figure 5. **Graphical determination of kinetic rate constants.**

the DBD reacts with an increasing concentration of secondary amines. Model reactions between 1-bromodecane and hexylamine and dihexylamine showed that the primary amine reacts about twice as fast as the secondary amine in the same solvent systems and in the presence of Na_2CO_3. The rate constants at each temperature were used to calculate k_0 and E, either mathematically or graphically (Figure 5). The resulting values were $k_0 = 1.93 \times 10^5$ min^{-1} and $E = 6214$ K g-cal/g-mol.

To demonstrate that the reaction is being modeled accurately, the normal nonisothermal reaction was sampled during the standard reaction cycle and the percent conversion determined. The reaction conversion for the nonisothermal reaction was calculated from the temperature as a function of time, rate equation, and rate constants. The resulting plots of the experimental and the modeled reaction progress are presented in Figure 6. These results showed that the model is a good predictor of reaction conversion, up to conversion levels of 60−70%.

To complete the model, it was necessary to measure the heat of reaction. The heat evolution measured with the ContraLab reactor during the kinetic runs and two adiabatic runs gave an average heat of reaction of 132.1 kJ [−63.1 kcal]/g-mol of bromide produced (see Table 3).

3. Application of the Kinetic Model

A major purpose for developing the kinetic model was to be able to estimate the amount of heat which has to be removed from the polymerizer in commercial scale production. The heat input to the reactor comes from two sources—heat of reaction from the polymerization reaction and heat of mixing from the viscous shear forces which occur as the polymer begins to thicken and gel. The viscosity rises steadily as the reaction progresses, from about 400 cP until the viscosity is extremely high as gelling of the reaction mass occurs (>100 000 cP).

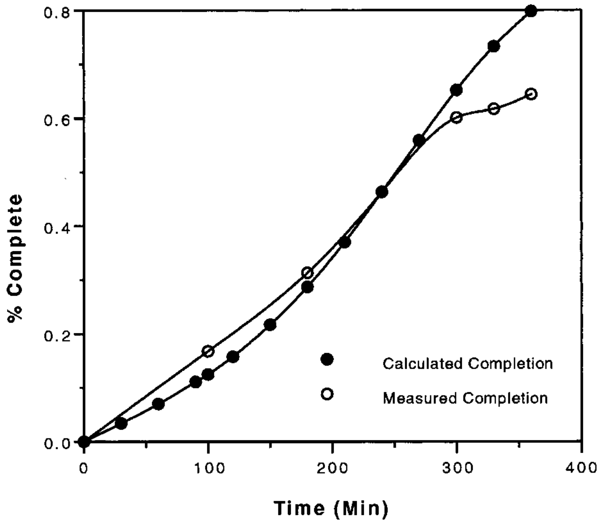

Figure 6. **Comparison of calculated and measured percentage completion in the 160-L double-planatary reactor.**

Production scale polymerizations were performed in a 500-L reaction vessel, which contained both a U-shaped scraped wall agitator and a helical ribbon agitator. Measurements for this reactor demonstrated that the agitator power climbs substantially as the polymer thickens and reaches its gel point. The gel point is estimated to be reached at a reaction conversion of approximately 90%. Data from this pilot unit indicated that the energy input to the reactor from mechanical mixing was 1.9 W/kg of reaction mass prior to the gel point and 20 W/kg of reaction mass after the gel point. Fortunately, by the time the gel point has been reached, the chemical reaction is substantially complete. An analysis of the data indicated that the reaction could be scaled to a 1200-L reactor. Figure 7 shows the required amount of heat that would have to be removed from a commercial scale 1200-L double-planetary mixer reactor.

Conclusions

The successful scale-up of a polymerization was supported by careful determination of the end point of the reaction using an analytical method employing a bromide-specific electrode. This analytical method was then applied to modeling the polymerization by determining the rates of reaction, activation energy, and heat of reaction.

The model was substantiated by applying the various constants to a semiproduction scale polymerization, with excellent agreement between the model and the actual polymerization.

Combining the heat of reaction, heat of mixing, and potential heat removal showed that the polymerization can be scaled up to a commercial scale 1200-L reactor.

Experimental Section

All chemicals were purchased and used without further purification. Methanol, dimethylacetamide (DMAC), Na_2-

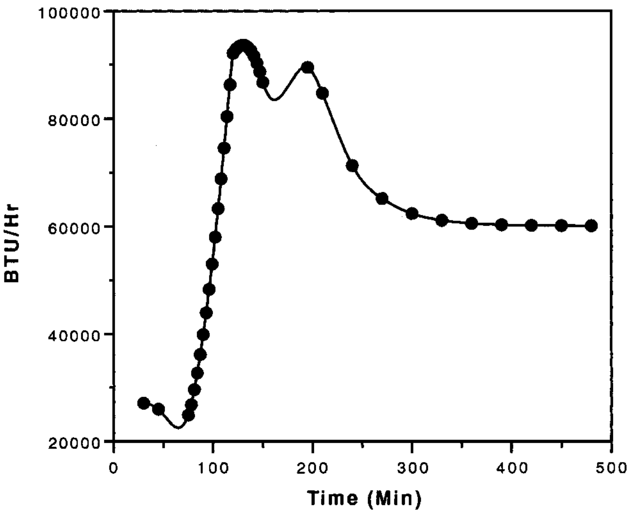

Figure 7. **Total heat flow during the polymerization of DMP 504 in a commercial scale 1200-L reactor.**

CO_3, H_3PO_4, Na_2HPO_4, NaOH, and hydrochloride acid were from EM Science; hydroxypropylcellulose (HPC) Klucell LF grade from Aqualon; dibromodecane (DBD) from Palmer Research; and hexamethylaminediamine (HMDA) from E. I. du Pont de Nemours.

General Reaction Procedure for the ContraLab Reactor. (1) Prepare a solution of 202 mL of DMAC and 202 mL of methanol.

(2) Charge the reactor with 250 mL of the DMAC/methanol solution, and then add 42.3 g of HPC, 45 g of HMDA, and 19.7 g of Na_2CO_3. Stir this mixture at 50 °C for 30 min in order to ensure that the HPC and HMDA are in solution.

(3) Cool the reactor to 20 °C.

(4) Prepare the following solution in an agitated flask using the remaining DMAC/methanol solution (approximately 189 mL) and 130 g of DBD. Slight heating is required for the DBD to go into solution. Once the DBD is dissolved, cool the resulting solution to ambient temperature.

(5) Control the reaction temperature at 20 °C with the ContraLab computer, and add the solution containing the DBD over a 15-min period while maintaining high agitation.

(6) Heat the resulting reaction mass to the test temperature over a 30-min period. Sample the reaction mass at the end of the 30-min period and determine the extent of reaction.

(7) Hold the reaction mass at the test temperature until it becomes too thick to stir. Sample the reaction mass every 30 min and analyze to determine the extent of reaction.

Procedure for the Double-Planetary Mixer. Charge 60 g (0.516 mol) of HMDA, 26.4 g of Na_2CO_3, 56.3 g of HPC, 187.2 g of DMAC, and 158.4 g of methanol as described in Table 4. Heat to 50 °C and hold for 1 h to dissolve the HMDA and HPC. Cool to 40 °C and add 161 g (0.569 mol) of DBD dissolved in 39.6 g of methanol and 46.8 g of DMAC over 30 min. Rinse the addition funnel with 5 mL of methanol/5 mL of DMAC. The temperature profile is followed as shown in Table 4.

(A double-planetary mixer/reactor (also called a change can mixer) consists of a jacketed vertical reaction vessel with mixing blades entering the top of the vessel. The double blades move in a planetary motion such that they sweep through the entire volume of the reactor while closely approaching the wall and bottom surface of the vessel. See ref 6 for a picture and additional description.)

Table 4. **Typical reaction in the 1-qt double-planetary reactor**

Ingredients

60 g (0.515 mol) of hexamethylenediamine (HMDA)
161 g (0.569 mol) of 1,10-dibromodecane (DBD)
198 g of methanol
234 g of dimethylacetamide (DMAC)
26.3 g (0.248 mol) of Na_2CO_3
56.3 g of hydroxypropylcellulose (HPC)

Dissolve DBD in 46.8 g of Dimethylacetamide and 39.6 g of Methanol

time	rpm	temp (°C)	comments
9:50		40	charged HMDA, Na_2CO_3, and HPC
9:92		40	charged 187.2 g of DMAC and 158.4 g of methanol
9:54	90	40	begin agitation
9:56	90	40	set temperature to 50 °C
10:05	90	50	hold at 50 °C for 30 min
10:35	90	50	set temperature to 40 °C, cooling
11:10	90	40	start DBD solution feed
11:25	90	40	half of DBD solution fed
11:40	90	40	finished adding DBD solution
11:41	90	40	rinse DBD solution feed lines with 5 mL of DMAC/5 mL of methanol, set temperature to 45 °C
11:45	90	45	set temperature to 50 °C
11:50	90	50	set temperature to 55 °C
11:55	90	55	set temperature to 60 °C
12:00	90	60	sampled and set temperature to 65 °C
12:05	90	65	set temperature to 70 °C
12:10	90	70	set temperature to 75 °C
12:15	90	75	set temperature to 80 °C
12:20	90	80	sampled and set rpm to 30
12:50	30	80	sampled (polymer had gelled)
1:20	30	80	sampled
2:20	30	80	sampled
3:20	30	80	sampled, held for additional 10 h

Bromide Analysis Method. The following materials were used: Orion bromide-specific electrode and a double-junction reference electrode, an Orion ion analyzer or similar pH meter with millivolt display, a 0.1000 M aqueous sodium bromide stock solution (7990 ppm) of H_3PO_4 and Na_2HPO_4, and a Waring blender.

The following standards were prepared using volumetric pipets and glassware:

(A) 50.00 mL of stock solution diluted to 100.00 mL with 0.10 M Na_2HPO_4 (3995 ppm).

(B) 50.00 mL of A diluted to 100.00 mL with 0.050 M Na_2HPO_4 (1998 ppm).

(C) 50.00 mL of B diluted to 100.00 mL with 0.05 M Na_2HPO_4 (999 ppm).

(D) 50.00 mL of C diluted to 100.00 mL with 0.05 M Na_2HPO_4 (499 ppm).

(E) 50.00 mL of D diluted to 100.00 mL with 0.05 M Na_2HPO_4 (250 ppm).

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(6) Perry, R. H.; Green, D. W.; Maloney, J. O. *Perry's Chemical Engineers' Handbook*, 7th ed.; McGraw-Hill: New York, 1997; pp 18−25.

(F) 100.00 mL of 0.050 M Na_2HPO_4 (blank).

Sample preparation involved the following steps:

(1) Fill a 100-mL graduated cylinder with 0.050 M H_3PO_4. Weigh the filled cylinder, and charge the contents to a Waring blender.

(2) Add a reaction mass sample of known weight (4−7 g) to the blender and blend for 4−5 min at high speed.

Note: The amount added depends on an estimation of the extent of the reaction that has occurred. Early samples (10−20% completion) should be 5−6 g, while later samples (80−90% complete) should be 0.5−1 g, with proportional adjustment in between.

To generate the standard curve, calibrate the meter following the instructions for the meter, using standards A, B, C, and F. Be sure that each standard is at the same temperature and is well stirred. Rinse the electrodes well with distilled water and wipe between samples. After calibration, check the standard curve by recording the measure values for each of the standards in the following order: F, D, C, B (low to high). Each standard should be within 5% of the actual value.

The following steps must be followed for sample measurement:

(1) Rinse the electrode well and equilibrate in the blank solution.

(2) Measure and record the amount (ppm) of bromide in each sample by immersing the electrodes in the sample and allowing the electrode to equilibrate. (Normally, the value oscillates within 10 ppm at equilibrium. The electrode drift is 3 mV/min or less). The temperature must be the same as used for the standards.

(3) If the sample is significantly below the standard curve, a standard addition technique may be used, or the instrument may be recalibrated using standards B, C, D, and F or C, D, E, and F. Also, a lower standard may be used to check the linearity of the curve below the calibration factor.

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