# Two-Dimensional Polymerization of Lipid Bilayers: Effect of Lipid Lateral Diffusion on the Rate and Degree of Polymerization

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ABSTRACT: Hydrated amphiphiles can yield quite complex lyotropic liquid crystals such as the lamellar (bilayer) and nonlamellar phases. Lamellar structures can be solidlike or liquid crystalline. An important characteristic of these lamellar phases is the lateral diffusion of the lipids which increases by ca. $10^2$ at the main phase transition, $T_m$. The rate ($R_p$) and degree ($X_n$) of polymerization were determined for polymerizable lipids in these two phases. A determination of the effect of temperature between 25 and 45 °C on the $R_p$ of redox-initiated polymerization of mono-SorbPC bilayers showed a discontinuity near the $T_m$. The calculated activation energy, $E_a$, and frequency factor, $A$, for the polymerization at temperatures below $T_m$ are 10 kcal/mol and $10^7$, respectively. A similar calculation for the polymerization at temperatures above the $T_m$ gave an $E_a = 24$ kcal/mol and $A = 10^{16}$. The degree of polymerization, relative to poly(methyl methacrylate) standards, for bilayers of mono-SorbPC at temperatures above and below the $T_m$ were $43 \pm 3$ and $51 \pm 4$, respectively. A comparable study of the polymerization of mono-AcrylPC bilayers found $X_n$ of $198 \pm 8$ and $235 \pm 9$, respectively, showing that even in the slow diffusion regime at temperatures below the $T_m$ relatively large polymers can be obtained. When the temperature increase spans the main phase transition, $T_m$, both the rate *and* the degree of polymerization are moderately increased. A most useful aspect of these results is the similarity of polymer size produced by redox polymerizations at temperatures both above and below the $T_m$. These studies in hydrated bilayers provide a clear indication that polymerizable lipids, such as the acryloyl, dienoyl, and sorbyl lipids, could also be usefully polymerized in condensed monolayers or multilayers at surfaces to create polymeric films composed of relatively long chains with high conversion from monomer to polymer.

## Introduction

The organized nature of assemblies of hydrated amphiphiles offers several attractive features for applications in both biological and materials sciences, e.g., catalysis, surface modification, therapeutics, diagnosis, among others. In many cases the potential utility requires a means to enhance the colloidal and/or chemical stability of the self-assembled systems. A useful approach to the stabilization of these assemblies is the formation of the desired assembly from reactive amphiphiles and the subsequent polymerization of the amphiphiles in the assembly.[1,2] Hydrated amphiphiles can yield quite complex lyotropic liquid crystals such as the lamellar (bilayer) and nonlamellar phases.[3−5] Lamellar structures can be solidlike, the so-called $L_\beta$ phase, or liquid crystalline, the so-called $L_\alpha$ phase.[6] The nonlamellar phases include the inverted hexagonal ($H_{II}$) and various bicontinuous cubic ($Q_{II}$) phases. As part of our studies of the polymerization process in the confined geometry of these structures, we have previously compared the rate and degree of polymerization of the $L_\alpha$ and $H_{II}$ phases.[7] Here we compare and contrast the polymerization process in the $L_\beta$ and $L_\alpha$ phases.

An important characteristic of the lamellar phases of hydrated lipids is the lateral diffusion of the lipids in the plane of the bilayer. The lateral diffusion coefficient, $D$, increases with increasing temperature. This monotonic increase in $D$ is punctuated by a significant discontinuity at the main phase transition, $T_m$, of the hydrated lipid.[8] The value of $D$ changes from ca. $10^{-2}$ to ca. 1 $\mu m^2/s$ at this characteristic temperature. To examine the effect of temperature and $D$ on the polymerization of reactive lipids in hydrated bilayers, the polymerization chemistry must be suitable for both phases.

Initiation of polymerization in lipid assemblies can be accomplished by utilizing the same techniques employed in isotropic media. Initiating radicals for chain polymerizations of lipid assemblies can be generated by thermal decomposition, as well as redox reactions. Both redox and photochemical methods of polymerization are less sensitive to changes in temperature than thermal initiation chemistries, because the activation energies are relatively low.[9] Consequently, these initiation methods are desirable for a comparison of polymerizations at different temperatures. However, since the redox polymerization of lipid assemblies generally yields larger polymers than found with photopolymerizations, and it is easier to detect any variable-dependent changes in the degree of polymerization if the polymers are relatively large, we selected redox chemistries for comparative studies of polymerizations in the $L_\beta$ and $L_\alpha$ phases.

When this research was started, the only published results of redox polymerization of lipid bilayer assemblies involved the dienoyl-substituted lipids, e.g., mono-DenPC.[10] The ability of redox-generated hydroxyl radicals to permeate these bilayers was shown by the radical quenching of methylene blue encapsulated in the aqueous compartment of bilayer vesicles.[10] The polymerization of mono-DenPC with various redox-initiating systems has been reported and parallels the well-known observations in isotropic media that the rate of polymerization increases with the oxidant strength.[11,12] Increases in the degree of polymerization are generally proportional to increases in the [oxidant] to [reductant] ratio. Redox reactions that generate hydroxyl radicals

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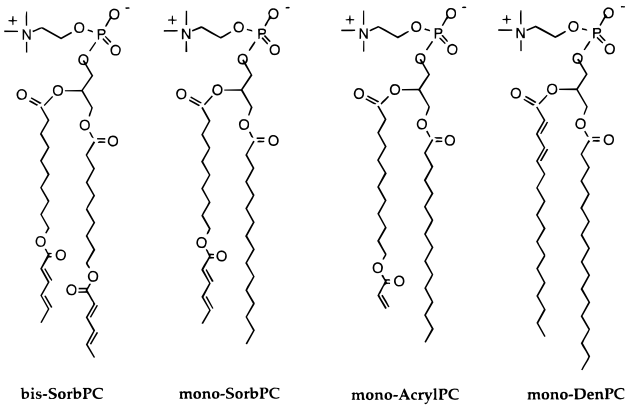
have been applied to polymerization of lipids with reactive groups in the hydrophobic as well as hydrophilic regions of the bilayer.[13,14] More recently, redox chemistry was successfully utilized to initiate the polymerization of nonlamellar cubic and hexagonal phases composed of hydrated reactive lipids.[15−17]

## Results

**Redox Initiated Polymerization of Lipid Bilayers.** First, the initial rates of redox polymerization ($R_p$) of bis-SorbPC bilayers were examined at 30 °C. At this temperature, the bis-SorbPC bilayers are above the $T_m$ and in the fast diffusion regime.[18] The $R_p$ was somewhat dependent on the form of the bilayer vesicles, i.e., large unilamellar vesicles (LUV) polymerized about twice as fast as multilamellar vesicles (MLV). Consequently, most of the subsequent experiments employed LUV. In each case the redox initiator was composed of an oxidant and reductant. The preliminary experiments showed that decreasing the [M]/[O], where [M] is the monomer concentration and [O] the concentration of oxidant, reduced the $R_p$ for both MLV and LUV polymerizations. A decrease in the [O]/[R], where [R] is the concentration of reductant, also reduced the $R_p$ in a manner consistent with classical isotropic redox polymerizations. Moreover, the use of stronger oxidants, $KBrO_3 > K_2S_2O_8$, and/or stronger reductants, L-cysteine > $NaHSO_3$, increased the $R_p$ of bis-SorbPC.




**Effect of Temperature on the $R_p$.** The preliminary study was followed by an analysis of the effect of temperature between 25 and 45 °C on the $K_2S_2O_8$/$NaHSO_3$-initiated polymerization of mono-SorbPC LUV. Because the measured $T_m$ of mono-SorbPC LUV was found to be 34.6 °C, the range of experimental temperatures spanned the sample $T_m$. A previous study showed that at low conversion the AIBN-initiated polymerization at 60 °C of acryloyl-substituted PC (mono-AcrylPC) bilayers exhibit a kinetic dependence on $[I]^{0.5}$and [M].[19] Here the initial $R_p$ of mono-SorbPC LUV at 25 and 45 °C was examined to determine its dependence on [I]. The change of [M] was followed by absorption spectroscopy for samples with different molar ratios of monomer to initiator. Figure 1a shows the loss of mono-SorbPC during polymerization at 25 °C for ratios of [M]/[I] = 5, 10, 20, and 30. The data for similar experiments performed at 45 °C are shown in Figure 1b. These data are summarized in Figure 2 as the log $R_p$ vs log [I] plots that indicate the initial $R_p$ is proportional to $[I]^{0.5}$.

The conversion of mono-SorbPC LUV to polymer at several temperatures is shown in Figure 3. In these experiments the ratio of [M] to [O] was 10. Since the

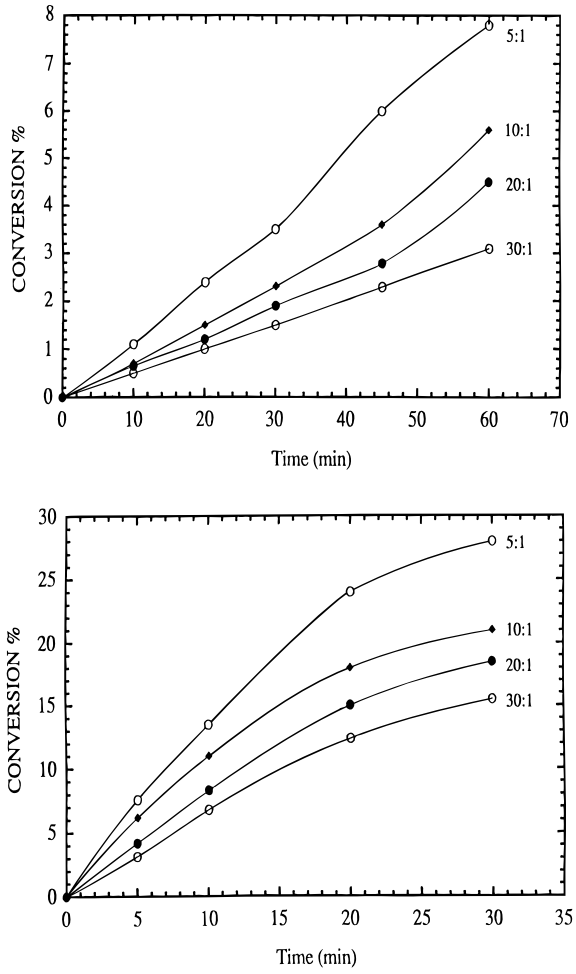



**Figure 1.** Initial conversion of hydrated mono-SorbPC LUV to polymer vs time as a function of the ratio of [M] to [I] at (a, top) 25 and (b, bottom) 45 °C, where [I] is equimolar $K_2S_2O_8$/$NaHSO_3$.

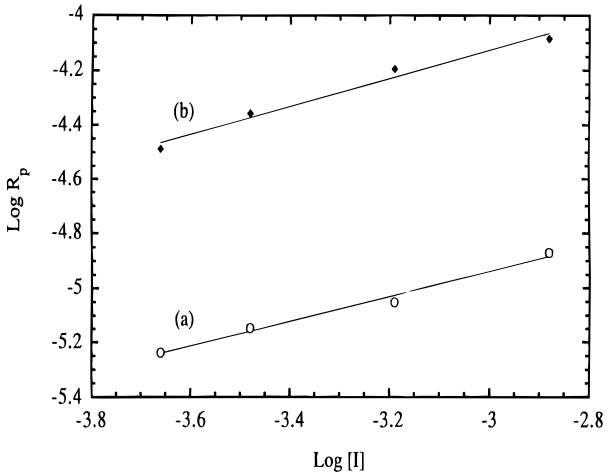



**Figure 2.** Initial rate of polymerization, $R_p$, vs the concentration of initiator, equimolar $K_2S_2O_8$/$NaHSO_3$, for the polymerization of hydrated mono-SorbPC LUV at (a) 25 and (b) 45 °C.

dependence of the initial rate of polymerization on the concentration of initiator is $[I]^{0.5}$, it is reasonable to assume that the initial rate of polymerization follows the equation

$$R_p = k[M][I]^{0.5} \quad (1)$$

as in the cases of polymerization of mono-AcrylPC and

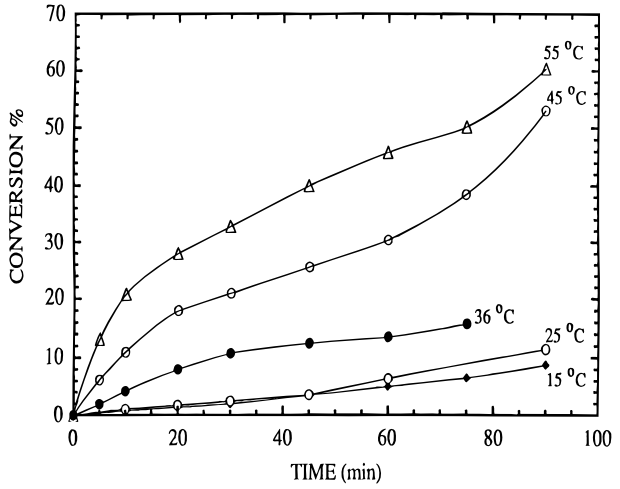



**Figure 3.** Conversion of hydrated mono-SorbPC LUV to polymer vs time as a function of the indicated temperatures. The [M] to [I] was 10, where [I] is equimolar $K_2S_2O_8$/$NaHSO_3$.

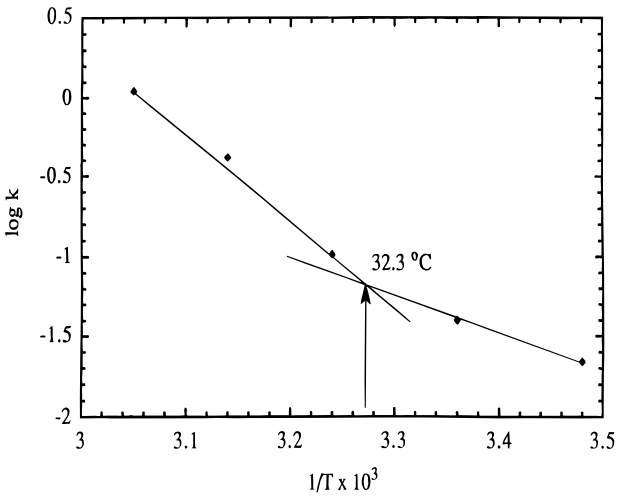



**Figure 4.** Arrhenius plot for the log $k$, rate constant of polymerization, vs $1/T$ for the redox polymerization of hydrated mono-SorbPC LUV.

mono-methacryloyl substituted PC.[19] The experimental data allow the solution of eq 1 for the rate constant, $k$, at different temperatures, where $R_p$ is obtained from

$$R_p = \frac{dc}{dt} = c_0 \frac{dx}{dt} \qquad (2)$$

using $c_0$ as the initial concentration of the monomer, and $x$ is the percentage conversion of the monomer at a specific time. Substitution of eq 2 into eq 1 gives the calculated rate constant at the experimental temperatures.

A plot of log $k$ vs $1/T$ is shown in Figure 4. Normally a plot of the rate of polymerization vs $T^{-1}$ is linear over the full range of temperatures investigated as expected from the Arrhenius equation, unless there is a phase transition within the experimental temperature range. The data for mono-SorbPC are not linear but can be fit by two linear plots (Figure 4) that intersect at 32.3 °C, which is similar to the temperature of the main phase transition, $T_m$, of mono-SorbPC LUV. The calculated activation energy, $E_a$, and frequency factor, $A$, for the polymerization at temperatures below $T_m$ are 10 kcal/mol and $10^7$, respectively. A similar calculation for the polymerization at temperatures above the $T_m$ gave an $E_a = 24$ kcal/mol and $A = 10^{16}$.

**Table 1. Number-Average Degree of Polymerization for Reaction of Mono-AcrylPC with $K_2S_2O_8$/L-Cysteine**

| temp/°C | [M]/[O] | [O]/[R] | $X_n$ |
|---|---|---|---|
| 60 | 1 | 1 | 4−6 |
| 35 | 5 | 5/2 | 235 ± 9 |
| 25 | 5 | 5/2 | 198 ± 8 |

**Table 2. Number-Average Degree of Polymerization for Reaction of Mono-SorbPC with $K_2S_2O_8$/L-Cysteine**

| temp/°C | [M]/[O] | [O]/[R] | $X_n$ |
|---|---|---|---|
| 60 | 1 | 1 | 4−6 |
| 40 | 5 | 5/2 | 51 ± 4 |
| 30 | 5 | 5/2 | 43 ± 3 |

**Effect of Temperature on the Degree of Polymerization.** The degree of polymerization relative to poly(methyl methacrylate) (PMMA) standards was determined for polymers obtained from either mono-AcrylPC or mono-SorbPC bilayers at temperatures above and below their $T_m$. The hydrated lipids were prepared in LUV that usually have a lower $T_m$ than those determined for MLV, because of the curvature energy of LUV. The $T_m$ of the LUV used in these studies were 30.2 and 34.6 °C for mono-AcrylPC and mono-SorbPC, respectively. This compares to the previously reported $T_m$ values of 31.8 and 36.1 °C for extended bilayers (MLV) of mono-AcrylPC and mono-SorbPC, respectively.[18]

Mono-AcrylPC LUV at 25 °C are in a solidlike phase, whereas at 35 °C the hydrated lipids are in a liquid-crystalline phase, i.e., the fast diffusion regime. The data for mono-AcrylPC redox polymerizations are given in Table 1. Mono-AcrylPC was initially treated with $K_2S_2O_8$/L-cysteine, [M]/[O] = 1 and [O]/[R] = 1 at 60 °C, but these conditions produced only oligomers. Complete loss of monomer was observed after 6 h. To generate larger polymers, the concentration of oxidant was reduced with respect to the monomer to a [M]/[O] = 5, and the reductant concentration was reduced to [O]/[R] = 2.5. These conditions produced greater than 70% conversion to poly(AcrylPC) after 48 h at either 25 or 35 °C. The isolated poly(AcrylPC) were transesterified with methanolic HCl to facilitate SEC analysis.[20] The $X_n$ at 25 and 35 °C was 198 ± 8 and 235 ± 9, respectively, showing that even in the slow diffusion regime at temperatures below the $T_m$ relatively large polymers can be obtained. Increasing the experimental temperature to above the $T_m$ produced a moderate increase in polymer size.

A comparable set of experiments was performed with hydrated bilayers of mono-SorbPC at temperatures above and below the $T_m$. The initiator was $K_2S_2O_8$/L-cysteine, and the polymer sizes were estimated as before. The data for these mono-SorbPC polymerizations are summarized in Table 2. The reaction of mono-SorbPC with $NaS_2O_8$/L-cysteine at [M]/[O] = 1 and [O]/[R] = 1 at 60 °C produced oligomers. Larger polymers were obtained when the [M]/[O] = 5 and [O]/[R] = 2.5 at temperatures of 30 and 40 °C. These temperatures span the measured $T_m$ for mono-SorbPC LUV. Greater than 70% conversion to polymer was observed after 48 h at either temperature. The isolated polymers were transesterified with methanolic HCl and then analyzed by SEC. The $X_n$ at 30 and 40 °C were 43 ± 3 and 51 ± 4, respectively.

Both the mono-AcrylPC and mono-SorbPC redox polymerizations produced larger polymers at temperatures above the $T_m$. The $X_n$ of the poly(AcrylPC) was ca. 4 times larger than that for poly(SorbPC). Because

the reactive groups of both lipids are located at the terminus of the lipid tail, the observed difference in $X_n$ cannot be due to differences in location of the reactive groups and is a consequence of the differences in reactivity of the two polymerizable groups. The 4-fold difference in $X_n$ between AcrylPC and SorbPC is similar to the previously reported difference in $X_n$ for the thermal polymerizations of these lipids with AIBN.[20,21]

## Discussion

Although it is well-known that redox polymerizations are less sensitive to temperature than thermally initiated polymerizations, it is important to assess the magnitude of the effect of temperature on the redox polymerization of a single bilayer phase, before considering the effect of a temperature change that spans a phase change. Consequently, we previously examined the polymerization of mono-DenPC at two temperatures above the bilayer $T_m$.[7] LUV of mono-DenPC were prepared and polymerized at 45 and 65 °C using $KBrO_3$/L-cysteine (10/1) and [M]/[O] = 10. The observed rate of polymerization was 30% faster at 65 °C than at 45 °C. The polymer size ($X_n$) determined by SEC was 30% less at 65 °C than at 45 °C, 125 ± 25 and 185 ± 15, respectively. Note that the estimated $X_n$ of 125 for poly(DenPC) formed at 45 °C is ca. 3 times the size of poly(DenPC) reported by Tsuchida et al. for the redox polymerization of mono-DenPC at 35 °C with [M]/[$K_2S_2O_8$] = 20 and [$K_2S_2O_8$]/[$NaHSO_3$] = 1.[10] The observed effects of temperature on both the rate and $X_n$ in the liquid-crystalline, $L_\alpha$, phase are consistent with previous studies of redox polymerizations in solution where increasing temperatures moderately increase the rate and decrease the kinetic chain length.[9]

The observed temperature effect on the rate of a redox polymerization within a single phase, i.e., mono-DenPC, indicates that the overall activation energy ($E_R$) for the rate of polymerization was 3 kcal/mol. These values were obtained from the initial rate of reaction where lamellar phase polymerizations behave in a conventional mode, i.e., bimolecular termination.[19] Under these circumstances $E_R = E_p + {}^1/_2E_d - {}^1/_2E_t$.[9] The estimated value for the activation energy for decomposition ($E_d$) of the initiator was ca. 9 kcal/mol or less. If this is the case, the difference between the activation energy for propagation ($E_p$) and termination ($E_t$) is small. It is likely that a significant contribution to the propagation step is the diffusion of monomeric lipid to the growing radical chain end. A 20 deg increase in the sample temperature has been shown in other lipid bilayers to increase the lipid lateral diffusion coefficient by a factor of 2.[22] This small change seems consistent with the observed moderate increase in rate and should affect both the propagation ($E_p$) and termination ($E_t$) parameters.

When the temperature increase spans the main phase transition, $T_m$, both the rate *and* the degree of polymerization are moderately increased in contrast to the effect of increasing temperature on chain polymerizations in a single phase. Lipids (here monomers) are in the slow diffusion regime, and the lipid hydrocarbon tails are usually in the all-trans-extended conformation when the sample temperature is below the $T_m$, whereas at temperatures above the $T_m$ the lipid lateral diffusion is increased ca. $10^2$-fold and the hydrocarbon tails adopt gauche conformations. Because the reactive acryloyl and sorbyl groups are located at the end of the lipid tails, their average conformation should be different at temperatures above and below the $T_m$. Both the increase in monomer diffusion and change in reactive group conformation could be reflected in the radical chain propagation step as well as the termination step(s). Since the effect of the phase change is an apparent increase in kinetic chain length, the net effect of the increase in diffusion and monomer conformations must be reflected in an increase in propagation relative to termination. Our previous studies of the degree of polymerization of AcrylPC[21] and SorbPC[20] in the liquid-crystalline-like phase concluded that at high conversion to polymer the major termination process was reaction of growing polymer chain with excess radicals from the initiator, AIBN, i.e., primary termination. In those experiments the AIBN and its radical were present in the bilayer interior throughout the course of the reaction. The circumstances are somewhat different with the redox initiators used in this study. The redox pair resides in the water outside the bilayer and reacts to yield products including hydroxyl radicals that can diffuse into the bilayer to initiate and perhaps terminate radical polymer chains. Consequently, the change of bilayer phase with increasing temperature may modulate the permeation of the initiating species into the bilayer and affect the relative rates of propagation and termination.

Analysis of the differences in $R_p$ at temperatures above and below the $T_m$ reveals a significant difference in the frequency factor and the activation energy, as defined in the Arrhenius equation. When the polymerization temperature is greater than the $T_m$, both the frequency factor and the activation energy are greater than when the polymerization was performed below the $T_m$. The net effect is only a moderate increase in the observed rate of the reaction as the reaction temperature is increased above the $T_m$. The data suggest that the frequency of collision becomes more favorable at these higher temperatures, presumably because of the increased lateral diffusion of the lipid monomers above the $T_m$. Kölchens et al. experimentally determined that the lateral diffusion coefficient of mono-ArcylPC changes significantly at the $T_m$.[23] On the other hand, the full effect of the expected increases in $R_p$ due to increased monomer diffusion at temperatures above $T_m$ is offset by the increases in the activation energy. Although several factors might contribute to increased activation energy, the conformational freedom of the lipid tails in the interior of the bilayer may be the primary factor. The reactive group, either sorbyl or acryloyl, must adopt a suitable confomation for the propagation step to proceed. At temperatures below the $T_m$ the lipid tails are in the all-trans extended conformation, and the reactive groups are more likely to approach one another in a favorable conformation for the propagation reaction. However, since the rate of diffusion of the monomeric lipids is slow, the frequency factor for the reaction is reduced.

The difference in polymerization in the slow and fast diffusion regimes may also be influenced by the permeability of the initiating species. At temperatures below $T_m$, the activation energy for the polymerization is 10 kcal/mol, which is close to 12.5 kcal/mol as reported by Ghosh et al. for the redox polymerization of simple monomers.[11] At low temperature, the radicals formed are thought to be mainly $SO_4^{\bullet-}$ and $HSO_3^{\bullet-}$. Ionic species such as these are expected to have relatively low

bilayer membrane permeability, causing a slow rate of polymerization at low temperature. Increasing the bilayer temperature increases the fluidity of the lipid bilayer and may allow radicals easier access to the polymerizable group. In addition, the increase in reaction temperature may significantly increase the formation of •OH radical,[24] which can permeate through the hydrophobic bilayer membrane much more readily than ionic radicals.

Whatever the underlying reasons for the moderate increases in the degree and rate of polymerizations of hydrated bilayers in the liquid-crystalline phase, perhaps the most useful aspect of these results is the similarity of polymer size produced by redox polymerizations at temperatures both above and below the $T_m$. These observations are consistent with the temperature-dependent variation in the reported $X_n$ for poly(DenPC) of 45 and 27 at 35 and 8 °C, respectively.[10] The polymerization at 35 °C was in the $L_\alpha$ phase while that at 8 °C was in the $L_\beta$. Consequently, the polymerization of the chain-substituted lipids, of the type described here or by Tsuchida and co-workers,[10] can yield reasonably long polymer chains in either the slow or fast diffusion regimes. This characteristic of the acryloyl, dienoyl, and sorbyl lipids distinguishes them from the diacetylenic lipids which only form long poly(diacetylenes) in the slow diffusion regime of bilayers or the condensed phase of monolayers or multilayers.[25,26] Our studies in hydrated bilayers provide a clear indication that polymerizable lipids, such as the acryloyl, dienoyl, and sorbyl lipids, could also be usefully polymerized in condensed monolayers or multilayers at surfaces to create polymeric films composed of relatively long chains with high conversion from monomer to polymer. Indeed, a report of the polymerization of a monolayer of mono-AcrylPC on an alkylated surface has already appeared.[27]

## Experimental Section

**Methods and Materials.** Compounds containing UV-sensitive groups were handled under yellow light. UV−vis absorption spectra were recorded on a Varian DMS 200 UV−vis spectrometer. A Microcal Inc., model MC-2, differential scanning calorimeter was used for thermotropic studies. The phase transition temperature was measured at the point of maximum excess heat capacity. Quasi-elastic light scattering (QELS) was performed with a BI-8000-autocorrelator from Brookhaven Instruments, and particle sizes were calculated with the accompanying software. The polymerizable lipids, i.e., mono-SorbPC and mono-AcrylPC, were synthesized as described previously.[20,21,28] Lipid purity was evaluated by thin-layer chromatography (TLC) with chloroform/methanol/water (65:25:4 by volume) and visualized by a UV lamp. Potassium persulfate, sodium bisulfite, and L-cysteine were purchased from Aldrich Chemicals and used as received. The lipids were hydrated in Milli-Q water, Millipore Inc.

**Kinetic Studies.** *Extruded Vesicles.* A desired volume of mono-SorbPC lipid was transferred from stock solution into a vial, and the solvent was evaporated by directing a stream of Ar over the solution to yield a lipid film on the wall of the vial. MilliQ water was added to the lipid to adjust the total lipid concentration lipids to 5 mg/mL. The lipid dispersion was frozen in dry ice/propanol bath, slowly thawed in a water bath, and then vortexed. This freeze−thaw−vortexed cycle was repeated 10 times to form MLV. The dispersion was then extruded 10 times through two 0.1 $\mu$m Nuclepore polycarbonate membrane filters at 40 °C using a Lipex extruder to produce a clear, translucent dispersion of LUV.[29]

*Polymerization.* Typically, an ampule containing vesicles was provided with two syringe needles inserted through a septum. One long syringe needle was connected to an ultrapure argon line directing a stream of the gas into the dispersion in the ampule. Another short syringe needle was used as outlet for the purged gas. The outgassing proceeded for 1 h or longer before initiation of polymerization. Temperatures were regulated by a water bath circulator. Polymerization was carried out at 15, 25, 35, 45, and 55 °C.

The initiator was potasium persulfate (99.998%) with sodium hydrogen sulfate as an activator. A freshly prepared aqueous solution of $K_2S_2O_8$/$NaHSO_3$ was added into the ampule containing the lipid vesicles after the ampule had been equilibrated at a desired temperature. The concentration of the initiator was prepared such that the volume of the added initiator solution was less than 2.5% of the total volume. The polymerization process was followed by sampling the dispersion at desired intervals with a Varian DMS 200 UV−vis spectrophotometer.

**Molecular Weight Determination.** *Polymerizations.* Approximately 5 mg of lipid was evaporated from a stock solution (10 mg/mL in benzene) by freeze-drying. The lipid was then hydrated with deoxygenated MilliQ water at a concentration of 80 $\mu$M through several freeze−thaw−vortex cycles and then extruded to yield LUV. A solution of the redox pair was prepared, and an aliquot was added to the hydrated lipid to give the desired [M]/[I] ratio. Polymerization was performed at the desired temperature under positive argon pressure.

*Size Exclusion Chromatography.* Samples of polylipid were transesterified as described previously.[20] The resulting polymer sizes were determined relative to PMMA standards using an Ultrastyragel linear column. SEC chromatograms were obtained with a Waters Maxima 820 chromatography workstation equipped with a Waters model R401 differential refractometer detector. The data were analyzed with Maxima 820 version 3.31 software.

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