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SYNTHESIS AND ION-BINDING PROPERTIES OF POLYMERIC PSEUDOCROWN ETHERS: A MOLECULAR DYNAMICS STUDY

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ABSTRACT

A novel method for producing inexpensive polymeric pseudocrown ethers *in situ* during free-radical polymerizations was investigated using molecular dynamics simulations. This scheme is based upon a template ion and exploits the tendency of oligomeric ethylene glycol diacrylates to form intramolecular cycles during polymerization. In the scheme, a template ion is used to induce the poly(ethylene glycol) diacrylates (PEGDA) to assume cyclic structures before polymerization with a comonomer. Experimental studies demonstrated that certain salts that were insoluble in nonpolar solvents were solubilized upon the addition of oligomeric poly(ethylene glycol) (PEG) due to complexation. Further evidence of cation binding by oligomeric PEG was obtained by ^1H NMR studies of PEG and its complexes with metal salts. To optimize the template ion synthesis approach, molecular dynamics simulations were performed on PEGDA containing between two and ten ethylene glycol repeating units, with and without the presence of cations. Simulation results indicated that the presence of the templating cation significantly decreased the mean end-to-end distance, thereby bringing the unsaturated endgroups into close proximity. The PEGDA ligand that resulted in the most effective templatization for Na^+ contained four ethylene glycol repeating units. Simulation times greater than 50 ps had little effect on the results for ligands containing 7 or fewer ethylene glycol repeating units.

INTRODUCTION

Since the pioneering work of Pedersen (1,2) cyclic oligomers of ethylene glycol known as crown ethers have been extensively studied for their unique ion-binding properties. Pedersen demonstrated the ability of crown ethers to form stable complexes with metal cations and to solubilize inorganic salts in nonpolar solvents. This ion-binding ability arises from the electron lone pairs on the oxygen atoms of the cyclic ether (3,4), with the most stable complexes formed with ions that fit snugly in the macrocyclic cavity thereby interacting optimally with all donor oxygens. Since Pedersen's work on crown ethers several related compounds have been synthesized and studied, including cryptands (5-7), which are tricyclic ligands; coronands (8,9), in which nitrogen, sulfur or phosphorous replace oxygen as the electron donor; podands (8,10), which are open-chain analogs of the cyclic ligands; and podandocoronands (8) which combine the structural properties of podands and coronands. Several reviews on the synthesis and ion-binding of multidentate macrocyclic compounds (11-13) and host-guest chemistry (14,15) provide an excellent overview of the area of supramolecular chemistry that has burgeoned since Pedersen's efforts in 1967.

The unique ion-binding properties of macrocyclic ligands make them attractive for a variety of applications, most notably phase transfer catalysis. However these compounds are generally synthesized in low yields and through relatively long reaction sequences (10,16) making them rather expensive. For this reason investigators developed schemes for attaching these ligands to polymeric supports thereby allowing the ligands to be efficiently retrieved and recycled. Methods for incorporating macrocyclic ligands either into the polymeric backbone or as pendant side groups (10,17-19) have been reported. Synthetic methods which have been used to produce macrocycle-containing polymers include condensation of di-functional macrocycles with appropriate comonomers, free-radical polymerizations of vinyl crown ethers, and substitutions of macrocycles for leaving groups on existing polymer chains. Macrocycle-containing polymers have been used in a variety of applications in analytical and preparative chemistry including anion and cation separations, column and thin layer chromatography, salt conversions, and phase transfer catalysis (10,13,17,18,20-22). Macrocyclic ligands attached to polymeric chains may exhibit different ion-binding characteristics than the corresponding monomeric species. Interactions which affect the affinity and selectivity of polymer-bound macrocycles can arise from the polymer backbone, the point of attachment, neighboring ligands, or other pendant groups.

In this contribution, a novel method for producing inexpensive polymeric pseudocrown ethers *in situ* during free-radical polymerizations will be investigated using molecular dynamics simulations. Our synthetic scheme is based upon a template ion and exploits the tendency of oligomeric ethylene glycol diacrylates to form intramolecular cycles during the polymerization. Oligo(ethylene glycol) diacrylates undergo free radical polymerizations by virtue of their carbon double bonds. If a growing radical chain reacts with both double bonds within a few propagation steps, a cyclic "pseudocrown ether" will be formed. The probability of this occurrence depends upon the conformation of the dimethacrylate molecule as well as the concentration of double bonds in the proximity of the free radical. This probability will be fairly small for bulk polymerizations and somewhat higher for dilute solution polymerizations. However, if the polymerization is carried out in a nonpolar solvent with a small concentration of a solubilized ion, the ion will bind with the oligo(ethylene glycol) diacrylate, inducing it to assume a cyclic conformation which brings the unsaturated end groups in close proximity (Figure 1). This template effect brought on by the complexed ion should dramatically increase the probability of primary cyclization and should, therefore, increase the pseudocrown ether yield. Compared to the traditional scheme in which a polymeric chain is functionalized with a preexisting crown ether, our scheme offers safety advantages (since crown ethers are not produced until they are polymer-bound) and is less expensive.

This novel synthetic scheme for polymeric pseudocrown ethers builds upon previous research on the ion-binding properties of noncyclic oligo(ethylene glycol)s and polyglycol dimethyl ethers (glymes). The complex stability for alkali cations with glymes exhibits an increase with increasing chain length for relatively small chains (23) but levels off at a threshold value which depends upon the size of the cation. Ethylene oxide oligomers have been reported to form 1:1 and 4:1 complexes with mercuric chloride (24), and the structures of the resulting complexes have been elucidated. Various studies have shown that poly(ethylene glycol) (PEG) and glymes of various chain lengths may be used as a cosolvent phase in heterogeneous reaction systems, due to their ability to bring into contact reagents from aqueous and organic phases, and as agents for phase-transfer

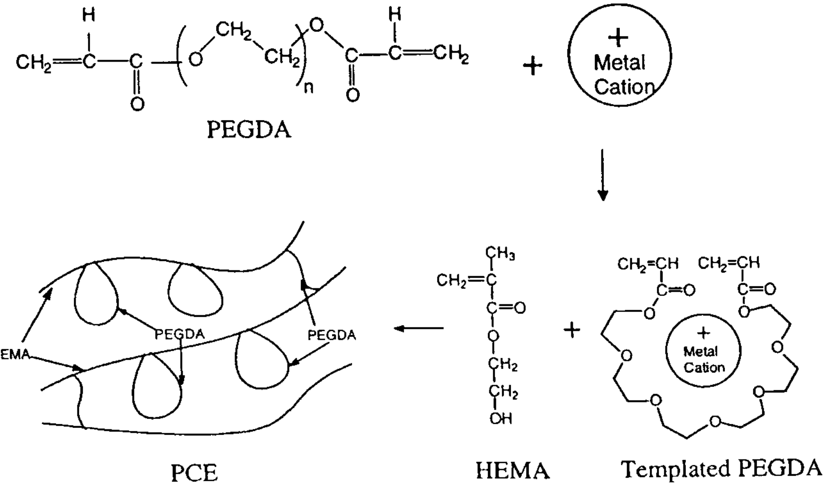

FIGURE 1. Novel synthesis scheme for the production of polymeric pseudocrown ethers.

catalysts in organic syntheses (25-28). This research also builds upon previous work on polymeric pseudocrown ethers. Warshawsky et al. (29) first synthesized polymeric pseudocrown ethers by reacting chloromethylated polystyrene resins with oligomeric ethylene glycols. In their method, the alcohol moieties on the ethylene glycol reacted with the chloromethyl groups by a nucleophilic substitution reaction to produce pseudocrown ethers with varying ring sizes. The resulting polymeric pseudocrown ethers were found to bind various alkali and transition metal ions.

The conformations of macrocyclic ligands and their complexes with ions have been studied using molecular modeling techniques. For example, a molecular mechanics study of 18-crown-6 and its alkali complexes (30) demonstrated that the lowest energy conformers possessed the C_i symmetry, as verified by X-ray crystallography. Wipf et al. (30) have used molecular mechanics simulations to explain the temperature-dependent dipole moment of 18-crown-6 and to investigate the stability of its complexes with Na^+ and K^+. A distance geometry approach was adopted by Weiner et al. (31) to study the geometry of ring systems including 18-crown-6 using both the MM2 and AMBER force fields. Molecular mechanics has also been used to estimate complexation energies and to provide insight into host-guest interactions of alkali cations with anisole spherands (32). Computer simulations illustrated that for some ligands, steric strain involved in wrapping the ligand around the ion is comparable to the free energy of complexation (33). Kollman and collaborators (34) have used a host of simulations methods, including distance geometry, molecular mechanics, and molecular dynamics, to investigate complexes of spherands, crown ethers and porphyrins. These studies revealed that the simulations yielded satisfactory binding energies in good agreement with experimental values. Finally, molecular mechanics and molecular dynamics studies of cation complexes of a cyclic urea-anisole spherand (35) have yielded valuable information about host-guest preorganization.

In this contribution we will describe a series of molecular dynamic simulations of various oligomeric ethylene glycol diacrylates in the presence and in the absence of cationic species. The goal of this modeling effort is to provide an underlying molecular understanding which will allow the development of an efficient reaction scheme which maximizes the yield of the polymeric pseudocrown ether. Clearly the number of ethylene glycol repeating units in the diacrylate is important because the optimal ligand must effectively envelop the cation in order to bring the unsaturated endgroups in close proximity. Therefore, simulations were performed for ligands containing between two and ten ethylene glycol repeating units, with and without the presence of a cation. A series of simulations were performed to investigate the effects of simulation time and boundary conditions. The molecular modeling studies were complemented by experimental investigations of ion solubilization in organic solvents using PEG. In addition, ^{1}H NMR studies were performed to confirm the complexation of the cations with the PEG.

EXPERIMENTAL

Molecular Modeling

Molecular dynamics (MD) simulations were performed on a Silicon Graphics IRIS 4D/220GTX workstation using the molecular modeling software POLYGRAF (36). These MD simulations were performed on PEGDA containing between two and ten ethylene glycol repeating units with and without the presence of a cation (Na^+ or Al^{3+}). The molecular structures were built using the polymer builder and were energy minimized before further MD calculations. Molecular mechanics (energy minimization) calculations were based on the DRIEDING force field parameters, and the steepest descent algorithm was used to perform the minimization. The Gasteiger algorithm was used to charge equilibrate the structures. Canonical TVN MD simulations were performed on the oligomers for a period ranging from 50 to 200 ps and the molecular trajectories were stored over the entire run. The trajectory file was written at every 0.1 ps, and the temperature for all the runs was kept at 300 K. The 200-ps simulations were performed on a single PEGDA molecule within a periodic cell with an external pressure of 1 atm at 300 K with and without the cation (sodium). Plots of total energy versus time and of end-to-end distance (ETED) versus time were generated from the simulations. In addition, the time-averaged values of the above two parameters were calculated.

Ion-Binding Studies of Oligomeric PEG and PEGDA

A series of ion-binding and solubility studies were performed in various solvents. The objective of the studies was to identify ion/ligand/solvent systems in which an initially insoluble ion was solubilized by the PEG ligand. This would ensure that the ligand and the cation complexed with one another. Metal salts that were investigated include cuprous, nickel, lead, tin and chromium chlorides, while the solvents in which the studies were carried out include chloroform, methylene chloride, carbon tetrachloride, and dioxane. All salts were dried in an oven at 60°C for 4 days and stored in a desiccator before use. PEG with an average molecular weight of 300 daltons (Polysciences Inc., Warrington, PA) was chosen as the representative oligomer for these solubility studies. In these experiments, 1 wt % of salt was added to solvent in a 20-ml glass vial. The contents of the vial were then mixed thoroughly in a vortex mixer for about 10 min. If the salt was not soluble in the solvent, then about 10 wt % PEG 300 was added to the vial and the vial agitated for about 15 min. The solubilization of the salts (if any) upon the addition of the PEG 300 was noted.

NMR Studies

^1H NMR spectroscopy was used to characterize binding by the PEG 300 by comparing PEG 300 spectra collected in the absence and in the presence of the cations. These studies were performed in deuterated chloroform and deuterated methylene chloride, and the salts under study were tin chloride and chromium chloride. The NMR spectra were taken on a Varian 300 instrument at the Max T. Rogers NMR facility at Michigan State University. All samples had a concentration of 0.1 wt % in the deuterated solvent. The salt-containing samples were prepared by dissolving 0.1 wt % saturated PEG 300 in the NMR solvent. All spectra were taken at 25°C and were obtained by signal averaging 64 scans. The $CHCl_3$ residual peak at 7.24 ppm in $CDCl_3$ was used as a chemical shift reference.

RESULTS AND DISCUSSION

Ion-Binding Studies with Oligomeric PEG

Results from the ion solubility studies are shown in Table 1. In each case shown in the table, the ion was insoluble before the addition of the PEG. A table entry of "Y" indicates that the addition of the PEG solubilized the metal salts. This solubilization indicates that the ligand and cation are complexed with one another. Similar ion-binding properties were observed for the diacrylates and dimethacrylates of PEG. Since the pseudocrown ether synthesis should be carried out in a solvent in which the PEGDA is soluble but the salt is insoluble unless it is complexed with the PEGDA, chloroform and methylene chloride are good choices for the synthesis solvent.

NMR Studies

^{1}H NMR spectra of PEG 300 in deuterated chloroform are shown in Figure 2. The spectrum in Figure 2a was collected in the absence of any metal salts, while that in Figure 2b was obtained in the presence of chromium chloride. In these spectra, the singlet peak located at 3.6 ppm corresponds to the PEG backbone methylene protons (CH_2) while the end group hydroxyl protons appear at 2.2 ppm in Figure 2a and at 2.7 ppm in Figure 2b. Therefore, the presence of chromium chloride bound by PEG 300 induces a shift in the location of the peak corresponding to the end-group hydroxyl protons. A similar shift was observed in deuterated

TABLE 1. SOLUBILITIES OF SALTS UPON THE ADDITION OF PEG 300

Solvents Salts	$CHCl_3$	CH_2Cl_2	CCl_4	Dioxane
CuCl	Y	Y	Y	---
$NiCl_2$	Y	Y	---	---
$PbCl_2$	---	---	---	---
$SnCl_2$	Y	Y	Y	Y
$CrCl_3$	Y	Y	partial	---

methylene chloride and when tin chloride was substituted for chromium chloride. These shifts may be attributed to complexation of the metal ion with the PEG ligand. The ion may withdraw electron density from the donor oxygen atoms, resulting in inductive deshielding of local (hydroxyl) protons. Similar shifts in NMR peak position induced by metal salts have been reported in the literature. For example, ^{11}B and ^{13}C NMR spectroscopy studies on crown ethers revealed that the chemical shift of a ligand was shifted to a higher field in the presence of an ion as compared to that of the uncomplexed host (37). Proton NMR chemical shifts induced by ionic association on a poly(ethylene oxide) chain have been observed, and the effect of counter ions on the magnitude of the downfield shift has been studied (38,39).

Molecular Dynamics Simulations

A series of simulations were performed to elucidate the effect of the presence of a cation on the conformation of a PEGDA ligand. To determine the effect of the ligand size, simulations were performed on PEGDA containing between two and ten ethylene glycol repeating units with and without the presence of a cation (Na^+ or Al^{3+}). The first set of experiments was carried out for a duration of 50 ps. For these simulations, the total system energy as a function of time fluctuated about the mean value typically with a standard deviation less than 5% of the mean. Therefore, all of the individual conformations had nearly the same energy and are equally probable. The PEGDA end-to-end distance (distance between unsaturated

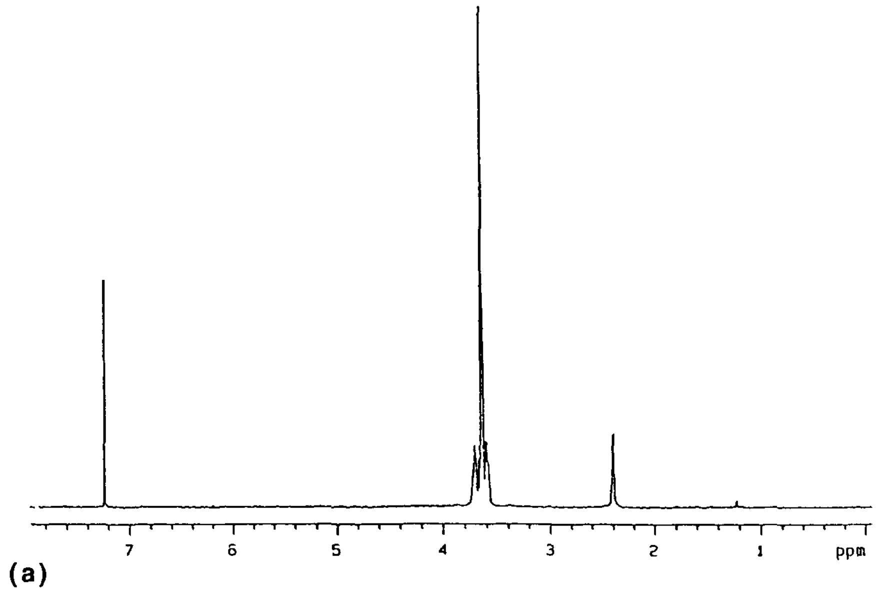

FIGURE 2a. ^{1}H NMR spectrum of PEG 300.

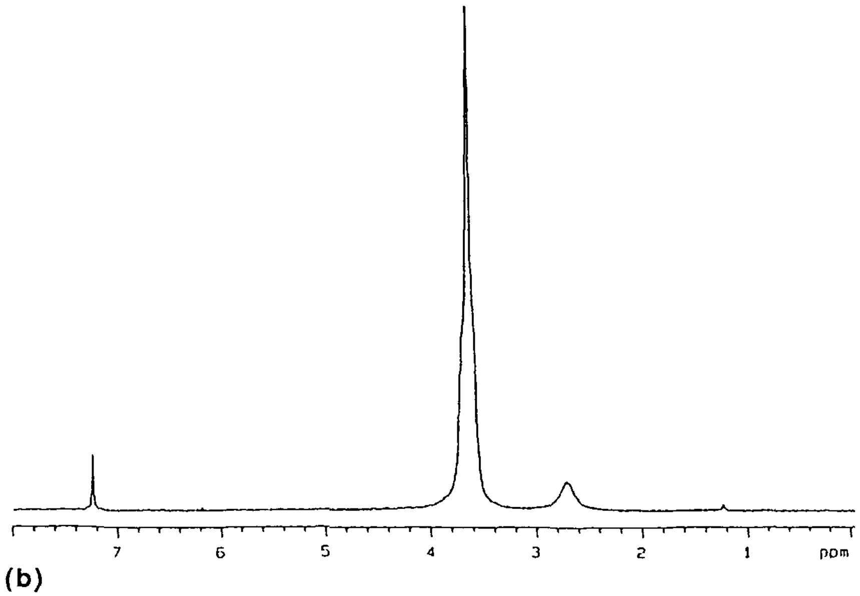

FIGURE 2b. ^{1}H NMR spectrum of PEG 300 with $CrCl_3$.

end groups), which is a parameter useful in determining whether the ion causes any templatization, was also plotted as a function of time for all the simulations. This value also fluctuated with a standard deviation as large as 20% of the mean.

Figure 3 contains a plot of simulation results for the mean end-to-end distance (ETED) as a function of the number of EG repeating units in the PEGDA chain. The figure illustrates that the addition of a sodium ion results in a decrease in the mean ETED for all of the PEGDA chain lengths. Similar trends were observed when the sodium ion was replaced with an aluminum ion. This suggests that there is indeed a propensity for cyclization owing to the presence of a cation since the oligomer tends to template around the cation thereby decreasing the mean ETED. The effect of the ion is illustrated in Figure 4, which contains a pictorial representation of one of the conformations adopted in the presence of a sodium ion. This figure indicates that the PEGDA assumes a crown ether-like conformation around the ion with the unsaturated end groups in close proximity. The results shown in Figure 3 also suggest that there exists an optimum PEGDA chain length since the PEGDA ligand containing four EG repeating units exhibits the lowest ETED and therefore the maximum templatization. This result is in agreement with studies on size-match selectivity reported in the literature. For crown ethers, it has been reported that maximum complexation is achieved when the size of the cavity is comparable to the ionic diameter. For Na^+, the crown ether *tert*-butylcyclohexyl-15-crown-5 with 5 donor oxygens has been found to provide the required size match selectivity (40). For PEGDA, our simulations indicate that the end group acrylate carbonyl oxygens participate in the ion binding, making the PEGDA with $n = 4$ the optimal ligand to bind with sodium.

To investigate the effect of simulation time, MD runs were performed for 50, 100, and 200 ps. In general, MD simulations of greater duration allow a larger number of conformations to be sampled and therefore provide more reliable averaging. However, the inevitable cost of longer simulations is greater computational requirements (in our studies a 50-ps simulation takes a few hours, whereas the 200-ps runs require days to complete). Therefore, it is important to determine the minimum simulation time which provides reliable results. The effect of simulation time on the mean ETED of PEGDA in the presence of a sodium ion is illustrated in Figure 5. The figure illustrates that for PEGDA ligands containing seven or fewer EG units, the simulation results are very repeatable; however, the simulations exhibit greater variations for larger ligands. This interesting behavior

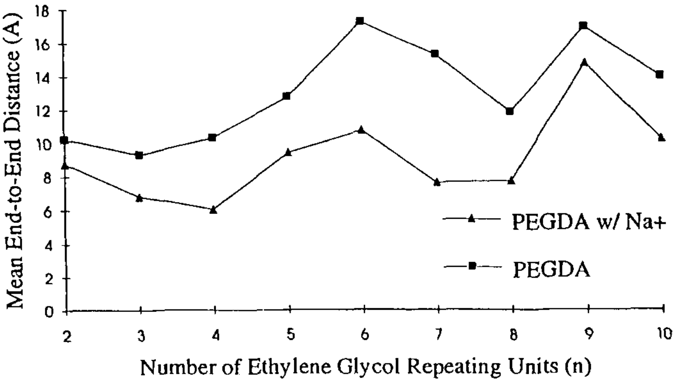

FIGURE 3. MD 50 ps simulation results for the mean end-to-end distance of PEGDA with different number of EG repeating units.

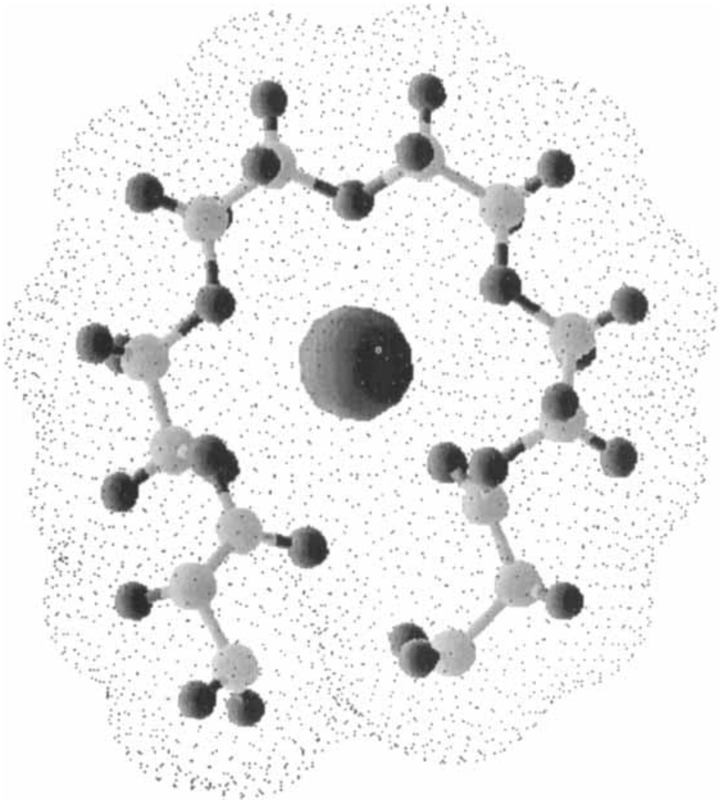

FIGURE 4. Pictorial representation of a PEGDA (n = 4) conformation templated around a Na^+ ion.

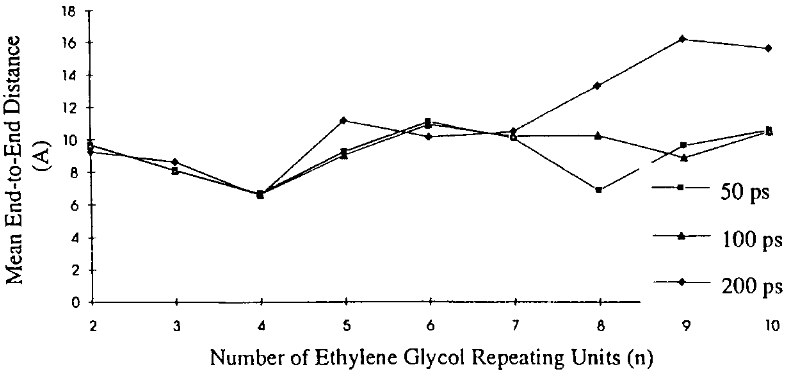

FIGURE 5. Effect of different simulation times on the mean end-to-end distance for PEGDA with Na$^+$ with various numbers of EG repeating units.

suggests that the simulation time has an effect only for relatively long ligands in which the length of the oligomer becomes considerably greater than that required to encompass the ion. For shorter ligands, the ion imposes an overwhelming constraint on the conformations adopted by the ligand due to binding interactions. For the longer ligands, the ion interacts only with a portion of the chain, placing milder constraints on the end-to-end distance.

Differential and cumulative distributions for the PEGDA end-to-end distance from the 200-ps simulations are plotted in Figures 6 and 7, respectively. The points in Figure 6 correspond to the simulation data, while the curves represent Gaussian fits to the data. Both figures clearly illustrate that the presence of the sodium ion shifts the end-to-end distance to lower values while increasing the dispersion slightly. The cumulative distributions shown in Figure 7 may be used to estimate the fraction of the (equally probable) conformations with an end-to-end distance below a give value. By the ergodic theorem, this will correspond to the fraction of PEGDA ligands in the system with an end-to-end distance below this threshold value. Therefore, the simulations can provide information about the fraction of "templated" ligands which could lead to the formation of pseudocrown ethers upon reaction.

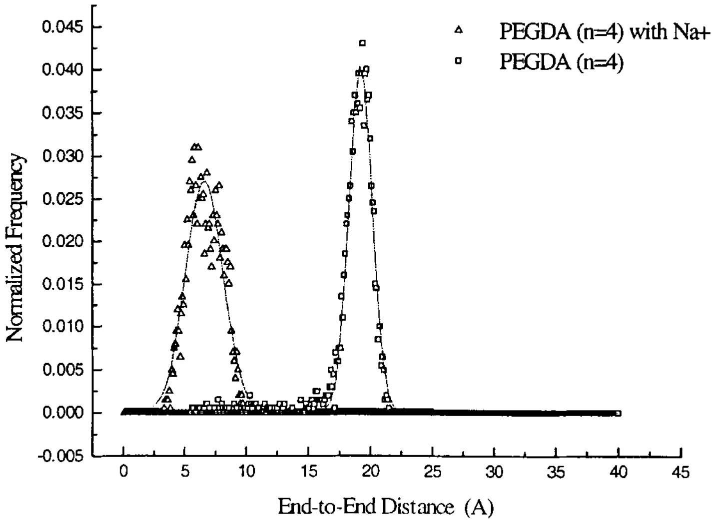

FIGURE 6. Normalized frequency distribution of end-to-end distance for PEGDA (n = 4) with and without Na^+.

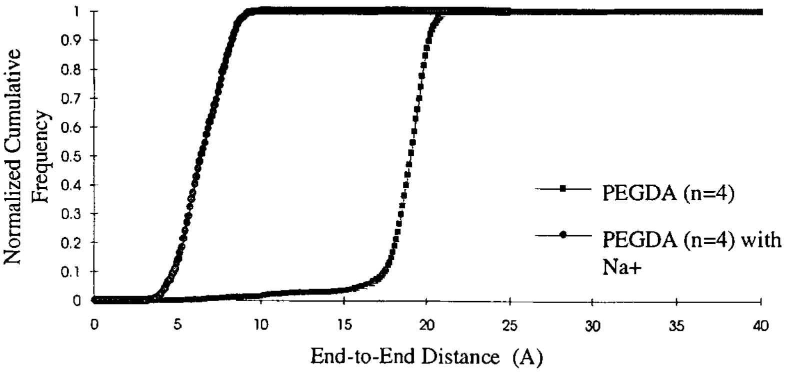

FIGURE 7. Cumulative frequency distribution of end-to-end distance for PEGDA (n = 4) with and without a Na^+ ion.

CONCLUSIONS

In conclusion, we have presented a novel scheme to synthesize polymeric pseudocrown ethers *in situ* during a free-radical polymerization. This scheme is based upon a template ion and exploits the tendency of oligomeric ethylene glycol diacrylates to form intramolecular cycles during polymerization. Compared to traditional schemes in which a polymeric chain is functionalized with preexisting crown ethers, our scheme offers safety advantages and is less expensive. It will thus be possible to economically synthesize polymers with unique ion-binding capabilities appropriate for applications such as phase-transfer catalysis, ion chromatography, and metal ion removal from waste streams. Preliminary experimental studies demonstrated that certain salts that were not soluble in nonpolar solvents, such as chloroform and methylene chloride, were made soluble upon the addition of oligomeric PEG 300. Further evidence of cation binding by oligomeric PEG was obtained by ^{1}H NMR studies of PEG and its complexes with metal salts.

In an effort to optimize the template ion synthesis approach, molecular modeling studies were performed on oligomeric PEGDA containing between two and ten ethylene glycol repeating units, with and without the presence of cations. Simulation results indicated that the presence of the templating cation significantly decreased the mean end-to-end distance, thereby bringing the unsaturated endgroups into close proximity. Although the presence of the cation decreased the ETED for all PEGDA chain lengths, the PEGDA ligand that resulted in the most effective templatization for Na^+ contained four ethylene glycol repeating units. The simulation time had little effect on the results for relatively short PEGDA ligands containing seven or fewer ethylene glycol repeating units. These ligands are highly constrained due to binding interactions with the ion. A higher degree of variation with simulation time was observed for longer ligands in which only a portion of the chain interacts with the ion. These simulations results have affirmed the role of a templating ion in the synthetic scheme. Moreover, the results provide insight into the selection of the templating ion and the PEGDA oligomer that will maximize templatization by bringing the unsaturated end groups into proximity.

ACKNOWLEDGMENTS

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