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Cyclopolymers as Liquid Membrane Carriers

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Introduction

The synthesis and characterization of unnatural multivalent receptors, for the binding of organic compounds or metal ions, have been recently reported, and one of the essential prerequisites is the three-dimensional disposition of the binding sites in a highly preorganized manner.[1,2] More recently, multivalent systems have been built around well-defined polymeric architectures, such as dendrimers.[3] Cyclopolymerization procedures are very useful for achieving a high degree of structural control within the polymer backbone of a macromolecular structure.[4] Mathias and co-workers have shown that the cyclopolymerization of bisacrylic monomers, obtained by alkylation of malonate esters with acrylic substituents, yields regular, un-cross-linked polymeric structures in which the repeating units are exclusively six-membered rings.[4c] In these systems, the polymer chains grow orthogonally to the substituents on the malonate functionality as a result of the geometrical constraints of the quaternary carbon atom of the disubstituted malonate moiety. Crown ethers containing a malonate functionalities have been initially synthesized and studied by Bradshaw, Izatt, and co-workers.[5] We have recently used them since they give easy access to a variety of derivatives by straightforward chemical modification of the reactive CH_2 functionality as building blocks for novel organic materials.[6]

Smid and co-workers have synthesized and characterized a series of polymers containing well-known (e.g., dibenzo-18-crown-6 derivatives) crown ethers and determined, through extraction and/or affinity experiments, their relative ability of binding alkaline metal ion.[7] Furthermore, polymers containing similar crown ethers have already been proposed in the literature for a variety of purposes, such as sensors[8] or functional materials.[9] In our design strategy, the combination of a cyclopolymerization approach and of malonate crown ethers could give rise to interesting, compact structures in which the ethylene glycol portions of the compounds are held facing each other (Figure 1), reducing the high number of possible conformations inevitably associated with a more flexible acrylic polymer and thus favoring sandwich-like behavior in metal ion binding and transport properties.

Experimental Section

General Experiments. All commercially available compounds were purchased from Aldrich and used as received.

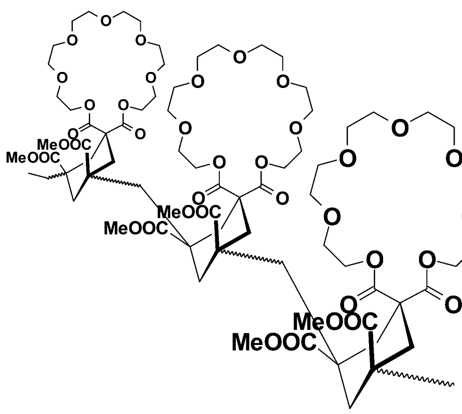

Figure 1. One of the possible conformations of cyclopolymer **7**.

α,α′-Azoisobutronitrile (AIBN) was purchased by Fluka and recrystallized from cyclohexane before use. Compounds **1**,[5a] **2**,[5c] and **3**[10] were prepared as previously described. Toluene (CaH_2), THF (CaH_2), and CH_2Cl_2 (CaH_2) were dried and distilled before use. ^{1}H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker 200 or AMX300 with the solvent residual proton signal or tetramethylsilane (TMS) as a standard. Infrared spectra were recorded on a Perkin-Elmer 881 using NaCl disks or by using a diffuse reflectance apparatus. Size-exclusion chromatography was carried out on a Perkin-Elmer chromatograph (series 2000) equipped with a DRI detector. Low-polydispersity polystyrene standards (Fluka) were used for the calibration curve, and the mobile phase was tetrahydrofuran (1 mL/min, 50 °C). A bank of four columns with porosities of 500 Å, 1000 Å, 10 000 Å, and mixed was used. Elemental analyses were obtained with a Carlo Erba elemental analyzer model 1106.

Compound 4. A solution of crown ether **1** (0.34 g, 1.3 mmol) in dry THF (50 mL) is cooled to 0 °C, and NaO*t*Bu (0.29 g, 3.0 mmol) is added. The solution is stirred for 5 min, and then the bromide **3** (0.56 g, 3.0 mmol) is added at once. The solution is left stirring at room temperature overnight and then neutralized with NH_4Cl (saturated solution), and the compound is purified by column chromatography (AcOEt/MeOH 9/1) to yield **4** as a viscous oil (0.35 g, 67%). IR (cm^{-1}): 1725 ($\nu_{C=O}$), 1630, 1440, 1350, 950. ^{1}H NMR ($CDCl_3$) $\delta = 6.30$ (s, 2H; $H_2C{=}C-$), 5.80 (s, 2H; $H_2C{=}C-$), 4.2 (m, 4H; $-COOCH_2$-CH_2O-), 3.8−3.6 (m, 18H; $-COOCH_3$ and $-OCH_2CH_2O-$), 2.98 (s, 4H; allylic $-CH_2-$). ^{13}C NMR ($CDCl_3$) $\delta = 169.8$, 167.1, 135.3, 129.1, 70.8, 69.9, 68.2, 64.2, 56.8, 51.6.

Compound 5. A solution of crown ether **2** (0.7 g, 2 mmol) in dry THF (50 mL) is cooled to 0 °C, and NaO*t*Bu (0.43 g, 4.5 mmol) is added. The solution is stirred for 5 min, and then the bromide **3** (0.75 g, 4.5 mmol) is added at once. The solution is left stirring at room temperature overnight and then neutralized with NH_4Cl (saturated ammonium chloride), and the compound is purified by column chromatography (AcOEt/MeOH 97/3) to yield **5** as a viscous oil (0.66 g, 61%). IR (cm^{-1}): 1725 ($\nu_{C=O}$), 1630, 1440, 1350, 950. ^{1}H NMR ($CDCl_3$): $\delta = 6.30$ (s, 2H; $H_2C{=}C-$), 5.80 (s, 2H; $H_2C{=}C-$), 4.2 (m, 4H; $-COOCH_2CH_2O-$), 3.8−3.6 (m, 26H; $-COOCH_3$ and $-OCH_2$-CH_2O-), 2.98 (s, 4H; allylic $-CH_2-$). ^{13}C NMR ($CDCl_3$): $\delta = 169.9$, 167.2, 135.3, 129.3, 70.5, 68.4, 64.8, 57.2, 53.2, 51.7, 34.7.

Thermal Polymerization. The monomer and the initiator (AIBN), dissolved in the solvent at the concentration and relative proportions outlined in Table 1, were deoxygenated with nitrogen for 30 min and then heated at 60 °C (in THF) or 70 °C (in toluene) in a thermostatic bath for 48 h. The solvent was then removed in vacuo, the remaining solid was dissolved in the minimum amount of CH_2Cl_2, and the solution was added dropwise to the nonsolvent (cyclohexane, 20 times

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Table 1. Cyclopolymerization of Monomers 4 and 5 under Free Radical Conditions[a]

entry	monomer	polymer	solvent/[M]/[% initiator][b]	M_n[b]	M_w[b]	PDI[b]	yield (%)
1	**4**	**6**	THF/0.5/2[c]	4 900	13 400	2.8	81
2	**4**	**6**	THF/0.5/1[c]	5 900	15 900	2.7	79
3	**4**	**6**	THF/0.5/2[d]	3 700	9 800	2.6	45
4	**4**	**6**	benzene/0.5/2[d]	9 400	27 400	2.9	45
5	**5**	**7**	THF/0.25/2[c]	10 700	17 800	1.7	92
6	**5**	**7**	toluene/0.25/2[c]	20 900	25 900	1.3	54

[a] Polymerizations were run for 48 h at 60 °C (THF or benzene) or 70 °C (toluene). Polymer purified by precipitation in cyclohexane. [b] As determined by GPC relative to polystyrene standards. PDI = polydispersity. [c] Polymerization carried out with AIBN as an initiator. [d] Polymerization carried out with 2,2-dimethoxy-2-phenylacetophenone as the initiator and conducted at room temperature.

its cosolvent volume). The purified, precipitated polymer sample was filtered and dried.

Photochemical Polymerization. The photochemical initiator (2,2-dimethoxy-2-phenylacetonephenone, Aldrich, 99%, 1−2 mol % with respect to the monomer) was added to the solution of monomer in THF, and the solution was degassed with argon in quartz vials. Photochemical reactions were conducted by irradiation with a multilamps reactor fitted with six 15 W phosphor-coated lamps (maximum emission 310 nm) for 48 h. Workup was conducted as above.

Polymer 6. IR (cm^{-1}): 1730 ($\nu_{C=O}$). ^{1}H NMR (CDCl$_3$): δ = 3.90−4.50 (broad m), 3.40−3.85 (broad), 1.8−2.2 (broad). ^{13}C NMR (CDCl$_3$) δ = 176.0, 174.3, 171.8, 171.2, 170.4, 71.0, 70.2, 68.6, 64.7, 51.8, 43.2, 26.8. Anal. Calcd for $C_{21}H_{30}O_{11}$: C, 55.02%; H, 6.60%. Found: C, 55.24%; H, 6.61%.

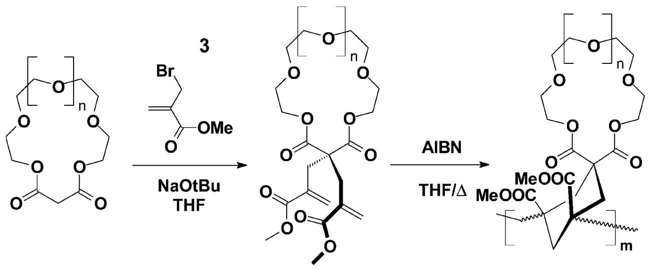
Polymer 7. IR (cm^{-1}): 1730 ($\nu_{C=O}$). ^{1}H NMR (CDCl$_3$): δ = 4.5−3.9 (broad m), 3.85−3.40 (broad), 2.2−1.8 (broad). ^{13}C NMR (CDCl$_3$): δ = 176.4, 174.9, 174.4, 172.0, 171.2, 70.7, 68.9, 68.6, 65.2, 51.8, 43.4, 26.9. Anal. Calcd for $C_{25}H_{38}O_{13}$: C, 54.94%; H, 7.01%. Found: C, 54.96%; H, 6.91%.

Transport Studies. Membrane cells are usually composed of a H_2O upper layer, containing the salt to be trasported, of an organic lower layer, containing the carrier, and from a H_2O receiving phase, where the quantity of salt transported is monitored vs time. Alkaline metal ion picrate salts were synthesized as previously described.[11] The source phase was composed of a 10 mM aqueous solution of a picrate (25 mL), while the receiving phase was distilled water (25 mL). The liquid membrane was a 1 mM solution of the appropriate crown ether host (35 mL) in CHCl$_3$. The same membrane vessel and the same stirring rate (100 rpm) were used throughout this study. Aliquots were taken from the receiving phase (100 μL) at periodic intervals and dissolved in MeCN (1.5 mL), and the absorbance at 380 nm was recorded. By using the molar absorbivity of the picrate salt in MeCN, the quantity of guest transported could be calculated and the initial transport rate (in μmol/h) evaluated through a simple least-squares linear regression. All regressions gave more than satisfactory results ($r^2 \geq 0.98$). The picrate salt absorption coefficient at 380 nm was determined by us and showed small differences from those already published (see Supporting Information).[11] The polymer samples used for the experiments were those obtained in entries 2 and 5, Table 1, which are comparable in terms of molecular weight distributions. A blank experiment, conducted with cesium picrate in the H_2O starting layer and in the absence of carrier in the organic phase, showed no transport at all. Selected experiments were replicated and gave reproducible results (within 5% accuracy).

Results and Discussion

The synthesis of crown ethers **1**[5a] and **2**,[5c] starting from malonyl dichloride and the appropriate poly(ethylene glycol), has been reproduced by us following previously reported procedures. Alkylation of the compounds with methyl 2-(bromomethyl)acrylate (**3**) in the presence NaO*t*Bu as a base in dry THF afforded **4** and **5** in good yields (up to 80%), after separation by flash column chromatography with polar solvents (AcOEt/MeOH) as the eluents (Scheme 1).

Scheme 1. Synthesis of Monomers 4 and 5 and Polymers 6 and 7



1 n = 1
2 n = 3

4 n = 1
5 n = 3

6 n = 1
7 n = 3

The compounds were then subjected to free radical polymerization, either thermally or photochemically induced. The polymerization reaction mixtures, dissolved in the minimum amount of CH_2Cl_2, were purified by precipitation in cyclohexane. The polymers, isolated as white powders, were characterized by means of several techniques, such as ^{1}H NMR and ^{13}C NMR spectroscopies and IR spectroscopy. All these spectroscopic techniques confirmed the total absence of residual vinyl groups signals as a consequence of a highly efficient cyclization step in the cyclopolymerization reaction. Both polymers **6** and **7** were completely soluble in organic solvents such as chlorinated solvents, acetone, and THF. The relative molecular weight distributions were characterized by gel permeation chromatography relative to polystyrene standards and are reported in Table 1. Most of these chromatograms showed bimodal distribution curves, probably as a result of irregular growing steps during the propagation process, and consequently also showed a large polydispersity index (PDI). As shown in entry 6 in Table 1, an unusually low PDI was recorded for the run in which the highest molecular weights were recorded, which is likely a consequence of the fractionation of the polymer molecular weight distribution after purification by precipitation in cyclohexane: high molecular weight chains are probably soluble in this solvent.[12] As a result, the corresponding yield is also much lower than those reported in similar conditions for monomers **4** and **5** (entries 1, 2, 5 vs 6). As expected for free radical polymerization, other conditions equal, polymerizations run in solvents possessing a lower chain transfer coefficient (toluene vs THF) afforded higher average molecular weight distributions (DP) (entries 3 vs 4 and 5 vs 6). Furthermore, the presence of a higher amount of free radical initiator afforded a lower DP (entries 1 vs 2).

The polymerization has also been conducted on selected samples by photochemical means, with less satisfactory results in terms of yields, using an initiator (2,2-dimethoxy-2-phenylacetophenone) used in the photobleaching of a variety of acrylic compounds.[13] ^{1}H NMR

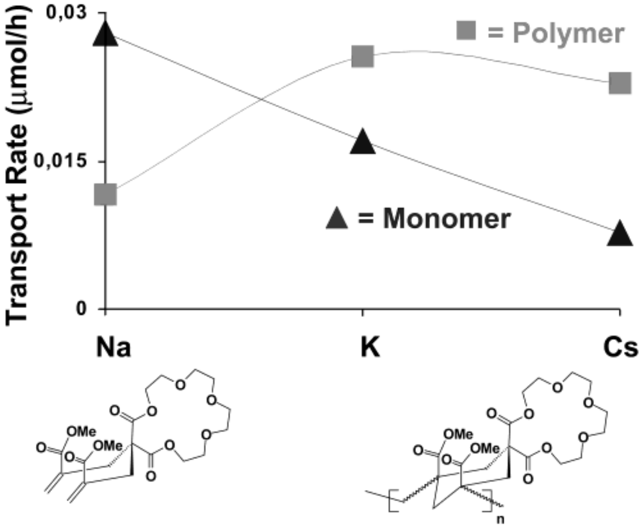


Figure 2. Comparison of the relative transport rates for polymer **6** and monomer **4** for alkaline metal ions.

spectra were found to be superimposable to those obtained by thermal initiation under thermodynamic control, suggesting that also in these cases the repeating ring structure within the polymer backbone is essentially six-membered.[4c] All these data indicate, for bifunctional monomers **4** and **5**, a polymerization behavior similar to that of monofunctional acrylic or methacrylic derivatives. Other conditions equal, the polymerization of monomer **5**, carrying a longer and bulkier oligoethylene glycol portion, gives molecular weights (entry 6, corresponding to an average 38 repeating units) which are definitely higher than **4**, thus showing how the steric hindrance of the substituents as malonate esters is not having any influence on the growing chains during the polymerization process, given the peculiar arrangement of the substituents around the quaternary carbon atom of the malonate moiety as discussed above.

Both monomers and polymers did not show any detectable solubility in H_2O, whereas they were fully soluble in chlorinated organic solvents.[14] To gain insight into the possible differences in binding and recognition phenomena between the monomers and the polymers, we decided to investigate the cation binding properties of these compounds by transport experiments across a lipophilic membrane of the picrate salts of alkaline metal ions.[15] The results are reported in Figures 2 and 3. Given their insolubility in H_2O, their relative ability of transporting picrate salts through a liquid membrane could be considered as a relative measure of their binding ability toward the alkaline metal ions. Lithium pricrate showed negligible transport rates with all the carriers examined and was not included in our evaluation. Furthermore, selected binding data on malonate crown ethers such as **1** have been determined by calorimetric methods, but no data have been reported on any dialkylated derivatives, in which tautomeric forms are not a possibility.

From the comparison of the data reported in Figures 2 and 3, it is evident that there are marked differences between the behavior of the monomer and the corresponding polymer: if adjacent crown ethers on the macromolecular structure were to be completely uncooperative, in a positive or negative way, in terms of binding, one would expect similar, if not identical, trends for the transport experiments. In the case of the monomer **4**, transport rates are higher for the smaller Na$^+$ cation, indicating that this is probably the best fit for the dialkylated malonate crown ether. In the case of the corresponding polymer **6**, this selectivity is shifted toward the potassium ion, whereas the sodium ion has a worse transport rate than in the corresponding monomer. Our possible rationalization is that the conformational rearrangement that the host **4** has to undergo in order to complex efficiently the sodium ion is actually hindered in the highly compact structure of the polymer **6**. In this structure, instead, the transport rates of potassium and cesium ions are enhanced, probably because of cooperative effects between adjacent crown ethers or of polymerization-induced changes in the preferred conformation of the crown ethers, which would alter binding selectivity. A similar explanation could be given to the behavior of the monomer **5**/polymer **7** pair. The dialkylated crown ether **5** showed a very pronounced selectivity toward the potassium ion. This selectivity is completely degraded in the polymer. Again, it is likely that the conformational rearrangement of the long hexaethylene glycol chains necessary for binding is highly hindered in the compact structure of the polymer. Other factors, such as large variations of diffusion coefficients and extraction constants within the polydisperse samples of polymers **6** and **7**, cannot be excluded to be partially responsible for the selectivities observed.

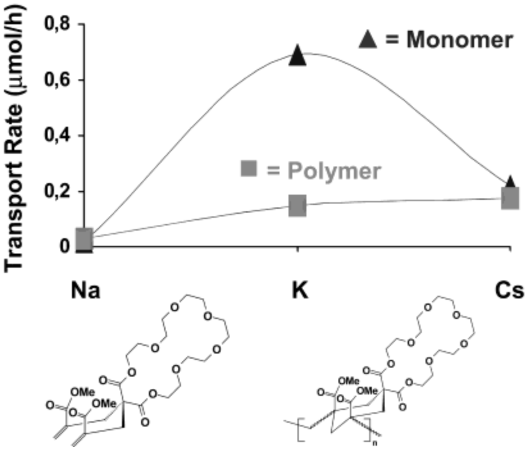


Figure 3. Comparison of the relative transport rates for polymer **7** and monomer **5** for alkaline metal ions.

In conclusion, this study presents the synthesis of novel cyclopolymers bearing oligoethylene glycol substituents in the form of malonate crown ethers embedded within a rigid polymer backbone. Both monomers and polymers show recognition and selectivity behavior for alkaline metal ions as their picrate salts and can be used as liquid membrane carriers for those ions. The ion selectivity is severely modified when the crown ethers are polymerized. The design elements reported in the systems described in this paper could be very useful for future, selected applications in the fields of supramolecular chemistry and polymer science.

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Supporting Information Available: Selected examples of membrane transport curves and of GPC traces for polymer **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) For a review on multivalency in biological systems, see: Mammen, M.; Chio, S.-K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2755–2794.

(2) (a) Rebek, J., Jr. *Acc. Chem. Res.* **1984**, *17*, 258–264. For recent examples, see: (b) Beer, P. D.; Cooper, J. B. *Chem. Commun.* **1998**, 129–130. (c) Perez-Inestrosa, E.; Desvergne, J.-P.; Bouas-Laurent, H.; Rayez, J.-C.; Rayez, M.-T.; Cotrait, M.; Marsau, P. *Eur. J. Org. Chem.* **2002**, 331–344. (d) Kubo, Y.; Sugasaki, A.; Ikeda, M.; Sugiyasu, K.; Sonoda, K.; Ikeda, A.; Takeuchi, M.; Shinkai, S. *Org. Lett.* **2002**, *4*, 925–928.

(3) (a) Roy, R. In *Dendrimers and Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D., Eds.; Wiley: New York, 2002; pp 359–385. (b) Backinowsky, L. V.; Abronina, P. I.; Shashkov, A. S.; Grachev, A. A.; Kochetkov, N. K.; Nepogodiev, S. A.; Stoddart, J. F. *Chem.—Eur. J.* **2002**, *8*, 4412–4423.

(4) (a) Butler, G. B. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 3451–3461. (b) Butler, G. B. In *Encyclopedia of Polymer Science and Engineering*; Kroschwitz, J. I., Ed.; Wiley: New York, 1986; Vol. 4, pp 543–598. (c) Mathias, L. J. *Trends Polym. Sci.* **1996**, *10*, 330–336 and references therein. For recent examples, see: (d) Meagley, R. P.; Pasini, D.; Park, L. Y.; Fréchet, J. M. J. *Chem. Commun.* **1999**, 1587–1588. (e) Kim, T. H.; Dokolas, P.; Feeder, N.; Giles, M.; Holmes, A. B.; Walther, M. *Chem. Commun.* **2000**, 2419–2420. (f) Kim, T. H.; Giles, M.; Holmes, A. B. *Chem. Commun.* **2000**, 2421–2422. (g) Pasini, D.; Klopp, J. M.; Fréchet, J. M. J. *Chem. Mater.* **2001**, *13*, 4136–4146. (h) Kakuchi, T.; Obata, M. *Macromol. Rapid Commun.* **2002**, *23*, 395–406.

(5) (a) Bradshaw, J. S.; Bishop, C. T.; Nielsen, S. F.; Asay, R. E.; Masihdas, D. R. K.; Flanders, E. D.; Izatt, R. M.; Chrisensen, J. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2505–2508. (b) Izatt, R. M.; Lamb, J. D.; Mass, G. E.; Asay, R. E.; Bradshaw, J. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 2365–2366. (c) Bradshaw, J. S.; Scott, T. J.; Jones, B. A. *J. Heterocycl. Chem.* **1980**, *17*, 1317–1318. (d) Lamb, J. D.; Izatt, R. M.; Swain, C. S.; Bradshaw, J. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 479–482. (e) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, *85*, 271–339.

(6) (a) Pasini, D.; Righetti, P. P.; Rossi, V. *Org. Lett.* **2002**, *4*, 23–26. (b) Garlaschelli, L.; Messina, I.; Pasini, D.; Righetti, P. P. *Eur. J. Org. Chem.* **2002**, 3385–3392. (c) Carano, M.; Corvaja, C.; Garlaschelli, L.; Maggini, M.; Marcaccio, M.; Paolucci, F.; Pasini, D.; Righetti, P. P.; Sartori, E.; Toffoletti, A. *Eur. J. Org. Chem.* **2003**, 374–384.

(7) (a) Smid, J.; Sinta, R. *Top. Curr. Chem.* **1984**, *121*, 105–56. (b) Smid, J. *Pure Appl. Chem.* **1982**, *54*, 2129–40. The comparison of binding experiments between the monomeric and polymeric crown ethers showed the presence of cooperativity effects between adjacent crown ethers within the polymer backbone.

(8) Nonokawa, R.; Yashima, E. *J. Am. Chem. Soc.* **2003**, *125*, 1278–1283.

(9) Collie, L.; Denness, J. E.; Parker, D.; O'Carrol, F.; Tachon, C. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1747–1758.

(10) Borrell, J.; Teixidò, J.; Martinez-Teipel, B.; Matallana, J. L.; Copete, M. T.; Llimargas, A.; Garcia, E. *J. Med. Chem.* **1998**, *41*, 3539–3545.

(11) Moore, S. S.; Tarnowski, T. L.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398–6405.

(12) The theoretical limit for a conventional free radical polymerization is 1.5. See Supporting Information for the GPC traces.

(13) Timp, H. J.; Wagner, R.; Paleta, O. *Z. Chem.* **1987**, *27*, 410–411. We explored the possibility of room temperature polymerization, using photochemical initiators, to address the viability of controlling the polymer microstructure with a suitable supramolecular template.

(14) Partition experiments between H_2O and $CHCl_3$ solutions showed no trace of compounds **4**–**7** to be located in the aqueous upper layer after vigorous shaking, as detected by TLC or ^{1}H NMR spectroscopy.

(15) (a) Bradshaw, J. S.; Izatt, R. M. *Acc. Chem. Res.* **1997**, *30*, 338–345. (b) De Santis, G.; Di Casa, M.; Fabbrizzi, L.; Forlini, A.; Licchelli, M.; Mangano, C.; Mocàk, J.; Pallavicini, P.; Poggi, A.; Seghi, B. *J. Coord. Chem.* **1992**, *27*, 39–73. (c) De Santis, G.; Di Casa, M.; Mariani, M.; Seghi, B.; Fabbrizzi, L. *J. Am. Chem. Soc.* **1989**, *111*, 2422–2427. (d) Habata, Y.; Uchida, K.; Sato, Y.; Akabori, S. *J. Membr. Sci.* **1993**, *85*, 175–181. (e) Wright, A. J.; Matthews, S. E.; Fisher, W. B.; Beer, P. D. *Chem.—Eur. J.* **2001**, *7*, 3474–3481. (f) Barnhurst, L. A.; Kutateladze, A. G. *Org. Lett.* **2001**, *3*, 2633–2635.

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