Formation of Macrocyclic Ethers by Free Radical Cyclization: Effects of Chain Length, Substituents, and Solvents

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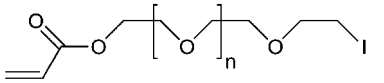
Free radical reduction by tributylstannane of ω-iodopolyoxaalkyl acrylates derived from tri-, tetra-, penta-, hexa-, and heptaethylene glycols gives mixtures of uncyclized reduction products and macrocyclic ethers formed by endo cyclization. The rate constants for cyclization of the intermediate radicals at 80 °C in benzene were determined under carefully defined conditions to be 15×10^4, 13×10^4, 5.1×10^4, 10×10^4 and 3.6×10^4 s^{-1}, for formation of the 12-, 15-, 18-, 21- and 24-membered rings, respectively. These values indicate that the presence of oxygen atoms in the chains increases the rate by a factor of 10−30 by comparison with the previously reported cyclization of alkenyl species. The rate constants at 80 °C in benzene and the endo/exo ratio for reductive cyclizations of the methacrylate, crotonate, cinnamate, maleate, and fumarate esters of 8-iodo-3,6-dioxaoctanol have been determined. The reduction of the 8-iodo-3,6-dioxaoctyl acrylate in solvents of varying polarity indicated that the cyclization rate has a relatively low solvent dependence.

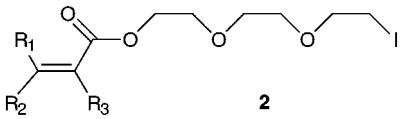
Introduction

Over the two past decades free radical cyclizations have become increasingly important in organic synthesis. About 10 years ago, Porter and co-workers[1] examined the utility of such reactions for the preparation of macrocycles. In an extension of this seminal work we found that the cyclization of ω-unsaturated polyoxaalkyl radicals containing a terminal activated double bond afforded macrocyclic ethers.[2] Later we demonstrated the synthetic potential of this approach.[3] In the present work we use the tin hydride method[4] to determine the rate constants for cyclization of the ω-unsaturated polyoxaalkyl radicals generated from **1a**−**f**, **2a**−**e**, and **3** and hence identify some of the factors affecting the outcomes and kinetics of the cyclization process.



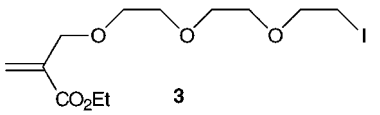
1

a n = 0 **b** n = 1
c n = 2 **d** n = 3
e n = 4 **f** n = 5



2

	R^1	R^2	R^3
a	H	H	Me
b	H	Me	H
c	CO_2Et	H	H
d	H	CO_2Et	H
e	H	Ph	H



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Results and Discussion

Kinetic Methods. The reactions expected to ensue when the substrates **1a**−**f** undergo a chain reaction with tributylstannane (Bu_3SnH) are illustrated in Scheme 1.

Steady-state treatment[4] gives a rate expression (eq 1) where CH represents the cyclized product and RH the uncyclized product and $[Bu_3SnH]_0$ and $[Bu_3SnH]_f$ are the initial and final concentrations, respectively, of tributylstannane. Integration leads to eq 2.

$$d[CH]/d[RH] = k_c/k_H[Bu_3SnH] \quad (1)$$

$$[CH]_f = k_c/k_H\{\ln([Bu_3SnH]_0 + k_c/k_H) - \ln([Bu_3SnH]_f + k_c/k_H)\} \quad (2)$$

These equations are only valid if there is no other process consuming any of the radicals $Bu_3Sn^{\bullet}$, **4**, and **6** involved in the reaction, such as their addition to the activated double bond of any other molecule. This was verified when we found a good material balance (>90%),

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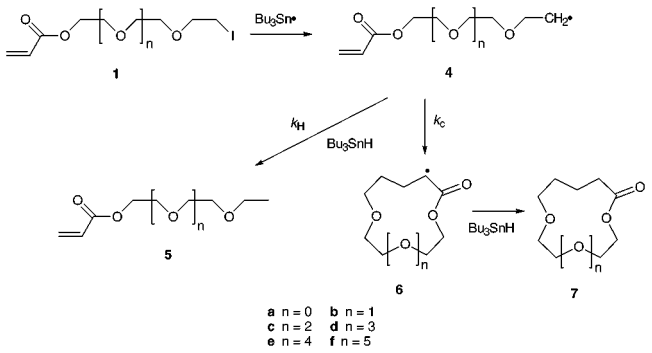
Scheme 1



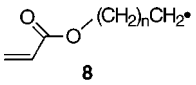
namely $[\mathbf{1}]_0 = [\mathbf{1}]_f + [\mathbf{5}]_f + [\mathbf{7}]_f$ and $[Bu_3SnH]_0 = [Bu_3SnH]_f + [Bu_3SnI]_f$.

The validity of our kinetic measurements depends on the assumption that the cyclization is not reversible under the conditions used. The absence of strain energy in some 12−24-membered macrocycles[5] tends to indicate that the initially formed cyclic radicals **6** should behave like their linear analogues. It has previously been shown that the adducts formed by the free radical additions of esters to alkenes,[6] initiated by di-*tert*-butyl peroxide at 160 °C, do not readily undergo breaking of the C−C bond to produce an unsaturated ester and an alkyl radical. Similarly, the fact that the thermal degradation of poly(methyl methacrylate) to produce methyl methacrylate becomes significant only above 300 °C[7] also suggests that the cyclizations described herein are irreversible, as does our observation that values of k_c/k_h are invariant with $[Bu_3SnH]$. The high yields previously reported for some radical macrocylizations[1,3] favor the same conclusion. Unfortunately, we were unable to prepare the precursors required to determine directly whether the radical **6b** will undergo β-fission at a significant rate. Some of the unsuccessful methods attempted included treatment of **7b** with lithium diisopropylamide and iodine,[8] reduction of **1b** with zinc according to Meyer's procedure[9] followed by iodine or bromine addition, and the reaction of **1b** with *O*-neopentyl *S*-triphenylstannyl xanthate following Zard's method.[10]

Kinetic Effects of Chain Length. The reductions of iodides **1a**−**f** with tributylstannane were performed with equal amounts of the reactants at two different concentrations (0.05 and 0.025 M). The reactions were stopped after 30−80% completion to optimize the precision of the product analysis. The amounts of the reactants, Bu_3SnH and **1**, and the reaction products, Bu_3SnI, **5**, and **7**, were accurately determined by GC to verify the material balance (>90%).

The reaction of **1a** with Bu_3SnH gave only the single open chain reduced product **5a** even under the very low stannane concentration maintained when a solution (4×10^{-3} M) of Bu_3SnH in benzene was added by syringe pump at a rate of 0.0033 mL/min to a solution (4×10^{-3} M) of **1a** in benzene. Clearly the cyclization of the radical **4a** to give a nine-membered ring is too slow to compete with hydrogen-atom transfer under these conditions. As has been previously noted,[1,11] homolytic generation of medium-sized rings from unsaturated iodoalkyl acrylates is very difficult. Conversely, reactions of the iodides **1b**−**f** with Bu_3SnH afforded mixtures of the corresponding cyclized (**7b**−**f**) and uncyclized (**5b**−**f**) reduction products. Substitution of the value of k_H, the rate constant for hydrogen transfer from Bu_3SnH to a primary alkyl radical,[12] into the values of k_c/k_H determined from eq 2 gave the rate constant k_c for the various cyclizations. The results are given in Table 1 together with values of k_c for the analogous all-carbon systems calculated from Porter's results.[1]

The data in Table 1 show that the rate constants for cyclization of the ω-unsaturated polyoxaalkyl radicals **4b** and **4c** are about 30 and 10 times greater, respectively, than those for the comparable ω-alkenyl species **8b** and **8c**. The presence of an oxygen atom in the chain has



8

a n = 6 **b** n = 7
c n = 10 **d** n = 11
e n = 15

previously been shown to increase the rate of the cyclization of 5-hexenyl-like radicals.[13] This was attributed to lowering of the strain energy of the cyclization transition structures by the replacement of a carbon atom by an oxygen.[14] Apparently the presence of the oxygen atoms in the chains of **4b**−**f** has a similar effect on the strain energies of their cyclization transition structures.

Bowry[15] recently proposed the existence of a correlation between the rate constants for intramolecular hydrogen transfers and the distance between the hydrogen and the radical center. The availability of numerous rate constants for homolytic macrocyclizations from Porter's work[1] and our own experiments prompted us to check such an approach for intramolecular homolytic addition. If the radical has a zigzag conformation for the alkyl chain[16] and a *Z* conformation for the acrylic moiety,[17] the "theoretical" values of $[C{=}C]_{eff}$ can be calculated by following the Bowry approach from the distance d between the free radical center and the terminal carbon of the double bond as $[C{=}C]_{eff}^{theory} = 1/[(6.023 \times 10^{23})4\pi d^3/3]$. The data in Table 1 show that the correlation between the experimental rate constants for cyclization of the all-carbon systems and the theoretical values of $[C{=}C]_{eff}$ is

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Table 1. Radical Cyclization Rate Constants at 80 °C and Theoretical[a] Values of $[C{=}C]_{eff}$

(acryloyloxy)polyoxaalkyl radicals				(acryloyloxy)alkyl radicals			
radical	ring size	k_c (10^4 s^{-1})	$[C{=}C]_{eff}$ (M)	radical	ring size	k_c[b] (10^4 s^{-1})	$[C{=}C]_{eff}$ (M)
4b	12	15 ± 4	16.8	**8a**	11	0.28	20.5
4c	15	13 ± 1	8.2	**8b**	12	0.48	15.4
4d	18	5.1 ± 0.8	4.6	**8c**	15	1.2	7.5
4e	21	10 ± 2	2.8	**8d**	16	1.5	6.1
4f	24	3.0 ± 0.6	1.9	**8e**	20	2.1	3.0

[a] See ref 15. [b] Calculated from data in ref 1.

the reverse of that expected. Indeed, as the ring size is *increased* from 11 to 20, the experimental rate constants *increase* by a factor of about 8 while the theoretical values of $[C{=}C]_{eff}$ *decrease* by a factor of about 7. For the polyoxaalkyl radicals the correlation is somewhat better, although the high degree of uncertainty in the rate constants makes an accurate assessment impossible. Nevertheless, with the exception of the cyclization of radical **4e** the rate constant does decrease with decreasing theoretical values of $[C{=}C]_{eff}$. Perhaps the anomalous value of the rate constant for **4e** reflects the formation of a favorable helical conformation of the polyoxaalkyl chain, as suggested by Dale.[18]

In a preliminary examination of the temperature dependence of cyclization values of k_c in benzene or methylcyclohexane for the radicals **4c** and **4d** were measured over the temperature range −40 to 120 °C. Trial experiments showed that at 80 °C the cyclization rate constants were identical in the two solvents. Unfortunately, there was some variability in the values of the rate constants for cyclization, especially at higher temperatures. The Arrhenius coefficients determined by a least-squares correlation in the usual way were $\log(A/s^{-1}) = 8.8 \pm 0.2$, $E_{act} = 6.1 \pm 0.3$ kcal/mol for **4c** and $\log(A/s^{-1}) = 8.1 \pm 0.2$, $E_{act} = 5.7 \pm 0.4$ kcal/mol for **4d**. Comparison of these data with those ($\log A = 8.22$, $E_{act} = 3.9$ kcal/mol) reported by Citterio[19] for the *intermolecular* addition of a primary alkyl radical to methyl acrylate shows that the preexponential terms are much the same. However, the cyclization activation energies are significantly higher. Possibly this reflects the development of some ring strain in the formation of the cyclization transition structure. Preliminary force field calculations support this hypothesis.[20]

Substituent Effects. Five unsaturated esters, **2a**−**e**, of 8-iodo-3,6-dioxaoctanol bearing various substituents on the double bond and the iodo ester **3** were prepared by standard methods and treated with Bu_3SnH in the usual way in order to determine the influence of the substituents on the rates and regioselectivity of cyclization.

The exo/endo ratios for the cyclization of radicals derived from **2a**−**e** and **3** are summarized in Table 2. As expected for a mechanism involving irreversible cyclization, the exo/endo ratios of products derived from **2c**−**e** were invariant for reactions conducted at various stannane and substrate concentrations. Except in the case of **2b**, the regioselectivities of these intramolecular additions are in good agreement with those previously reported for the intermolecular addition of alkyl radicals to the corresponding unsaturated ethyl or methyl esters.[21−26] Cyclization of **2b** represents an intramolecular analogue of intermolecular addition to a crotonic ester. For the addition of cyclohexyl radical to methyl crotonate Giese and co-workers[25,26] identified the products resulting from addition at each terminus of the olefinic bond. However, in the case of **2b** only endo cyclization occurs, possibly because the radical center in **2b** is less sterically demanding than cyclohexyl radical. Also, formation of the smaller ring by exo cyclization may incur more strain energy than endo cyclization.

Table 2. Regioselectivity and Rate Constants of Cyclization at 80 °C in Benzene for Radicals from Various Precursors (RI)

	cyclization yields		k_c (10^4 s^{-1})	
RI	endo (%)	exo (%)	endo	exo
1b	100	0	15 ± 4	
2a	100	0	7.0 ± 1.1	
2b	100	0	0.66 ± 0.10	
2c	43	57	0.60 ± 0.09	0.82 ± 0.10
2d	58	42	9.4 ± 2.2	6.9 ± 1.8
2e	10	90	0.29 ± 0.07	2.6 ± 0.06
3	100	0	14 ± 4	

The data in Table 2 indicate that the fumarate **2d** gives a rather low endo/exo cyclization ratio (1.4). This is much lower than the ratio (endo/exo = 4.9) previously reported for the analogous compound ethyl 8-iodooctyl fumarate, bearing an all-carbon chain.[1] Presumably this reflects differences in the strain energy between the two modes of cyclization by comparison with its all-carbon analogue arising from the presence of the oxygen atoms in **2d**, but a test of this hypothesis awaits the results of further force-field calculations. Interestingly, the isomeric unsaturated esters **2c** and **2d** give somewhat different ratios of the regioisomeric products **10c** and **11c**. This is probably due to the steric effects in the starting materials discussed below.

The cyclization rate constants for the radicals generated from the iodides **2a**−**e** and **3** were conducted in the usual way with two different concentrations (0.05 and 0.025 M) of both reactants in stoichiometric amounts. Equation 2 can still be used for the calculation of rate

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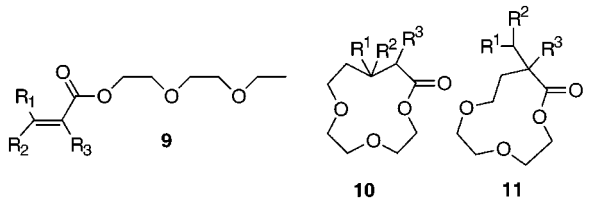

	R^1	R^2	R^3
a	H	H	Me
b	H	Me	H
c	CO_2Et	H	H
d	H	CO_2Et	H
e	H	C_6H_5	H

constants, but in this case $[CH]_f$ represents the *total* final experimental concentration of cyclic products while k_c is the sum of the two cyclization rate constants $k_c^{exo} + k_c^{endo}$. The individual cyclization rate constants can then be obtained by simple proportion using the observed exo/endo ratio. The results are included in Table 2.

The data in Table 2 show that the radicals formed from **2b**,**c**,**e**, which bear substituents on the ω-terminus of the double bond, all have lower cyclization rate constants than those derived from the ω-unsubstituted precursor **1b**. The effects of double-bond substitution on the rates of *intermolecular* radical addition to acrylates and related compounds have been quite extensively studied. The difference between the rate constants for addition of alkyl radicals to the double bond of methacrylic and acrylic esters has been reported to be rather small, with the methacrylates being the more reactive.[19,21,22] For example, Citterio et al.[19] found that the rate constant for the addition of 5-hexenyl radicals to methyl methacrylate at 69 °C is only 1.3 times greater than that for the addition to methyl acrylate. For the analogous cyclizations of **2a** and **1b** the ratio is reversed but is also small. The difference between the cyclization rate constants of the radicals formed from **2a** and **3** is interesting, since both species are methacrylic esters. Possibly the former is the less reactive because of the extra rigidity imposed on the chain by the presence of the unsaturated ester linking group.

Giese[24−26] has studied the kinetics of intermolecular radical reactions somewhat analogous to the cyclizations of **2b**,**d**,**e**. For example, he found that the rate of addition of cyclohexyl radicals to the 3-position of methyl crotonate is 90 times slower than is the equivalent reaction with methyl acrylate, while for ethyl cinnamate the retardation (110 times) is even greater. The same general trend is observed for macrocyclization (compare the data for **2b**,**e** with that for **1b** in Table 2), although it is much less pronounced, presumably because the primary radicals involved in the cyclizations are less susceptible to steric effects than is the secondary cyclohexyl radical used by Giese. However, there is a marked difference between the rate of endo cyclization of the radicals derived from the fumarate **2d** and that of addition of cyclohexyl radicals to dimethyl fumarate. The latter reaction is about 5 times more rapid than the addition to methyl acrylate, whereas the former is considerably slower than the analogous process involving **1b**. This is probably another case where the extra rigidity imposed on the chain by the ester linking group increases the strain energy of the cyclization transition structure for the radicals derived from **2d** by comparison with those derived from **1b**.

Table 3. Solvent Dependence[a] of the Relative Rate Constants for Cyclization of Radical 4b

solvent	E_T^N	yield of 7**b** (%)	k_c/k_H (10^{-2} M)
dioxane	0.164	36 ± 1	1.05 ± 0.01
benzene	0.111	38 ± 1	1.15 ± 0.06
THF	0.207	37 ± 3	1.12 ± 0.15
propan-2-ol	0.546	44 ± 1	1.55 ± 0.03
DMF	0.404	47 ± 1	1.81 ± 0.03
methanol	0.762	49 ± 2	2.0 ± 0.2

[a] Values of E_T^N from ref 31.

The observation that cyclization of the radicals generated from **2d** is more rapid than the analogous reaction of **2c** is in good agreement with results obtained by Bader[23] and Giese[24], respectively, for the addition of methyl radicals to dimethyl fumarate and dimethyl maleate and of cyclohexyl radicals to the analogous diethyl esters. In both cases the more stable *E*-isomer was found to be the more reactive. This was believed to indicate that steric and polar interactions between the two ester groups in the *Z* isomer prevent the system from adopting a planar configuration. Presumably the relative rates of cyclizations of **2c**,**d** are subject to similar effects.

Solvent Effects. The influence of solvent polarity on the rate constants of radical reactions was first reported by Walling and Wagner.[27] In another example of a solvent effect Salikhov and Fischer[28] showed that the rate constant for the addition of *tert*-butyl radicals to acrylonitrile increases proportionally to solvent polarity from 2.8×10^6 M^{-1} s^{-1} in tetradecane to 10.2×10^6 M^{-1} s^{-1} in acetonitrile. In contrast, Beckwith and co-workers[29] showed that the rate of cyclization of hexenyl radicals and related species is essentially insensitive to the polarity of the medium. These observations, and the demonstration that crown ethers undergo conformational change[30] in different solvents, prompted us to study the cyclization of **1b** in solvents of varying polarity. The reactions were performed under standard conditions at 80 °C, with initial concentrations of tributyltin hydride and **1b** of 0.05 M in dioxane, benzene, THF, 2-propanol, methanol, and DMF.

The yields of **7b** at about 80% conversion are given in Table 3 together with the relative rate constants k_c/k_H and values[31] of the solvent polarity parameter E_T^N. The data show that qualitatively the solvent polarity has only a minor effect on the yield of **7b**, which increases from 37% in nonpolar solvents (dioxane, benzene) to about 48% for more polar solvents (methanol, DMF). Linear regression analysis shows that the data fit reasonably well to the linear correlation $\log k_c/k_H = 0.426E_T^N - 2.02$ ($r = 0.953$). The positive gradient indicates that the rate constant for cyclization, k_c, increases with solvent polarity more rapidly than does k_H, the rate constant for hydrogen atom transfer from the stannane. This is as expected because the polar contributions to the transition structure for cyclization, which involves the addition of a

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nucleophilic primary alkyl radical to an electron-deficient double bond, should be greater than those for hydrogen transfer involving the attack of a nucleophilic alkyl radical on the relatively nonpolar Sn−H bond. Recent work[32] on the reduction of β-iodoalkyl esters supports this hypothesis, since k_H was found to increase only very slightly with solvent polarity. A plot of the reported rate constants, k_H,[32] for hydrogen transfer to a nucleophilic primary alkyl radical against E_T^N gives the relationship $\log k_H = 0.130E_T^N + 6.79$ ($r = 0.999$). If we assume that our values of k_H show a similar dependence on E_T^N (0.130), we obtain after normalization of the value of k_H in benzene[12] $\log k_H = 0.130E_T^N + 6.12$. Combination of this correlation with that given above for $\log(k_c/k_H)$ gives $\log k_c = 0.556E_T^N + 4.10$.

The effect of solvent polarity on the rate constant for cyclization of the radical **4b** is much larger than that determined earlier for the cyclization of hexenyl-like radicals.[29] This is to be expected, because cyclization of hex-5-enyl radicals and related species without electron-attracting substituents should involve negligible stabilization of the transition structure by polar effects. On the other hand, the comparison of these results with those of Salikhov and Fischer[28] shows the effect of solvent polarity on cyclization to be qualitatively similar to that for the addition of *tert*-butyl radical to the acrylonitrile double bond, although the plot of the rate constants versus E_T^N for the latter gave a poor correlation coefficient. This provides further evidence for the lack of any significant change in the conformation of the dioxaoctyl chain of the radical when a nonpolar solvent is replaced by a polar one.

Conclusion

The results discussed above indicate that ω-(acryloyloxy)polyoxaalkyl radicals of the general type **4** undergo endo cyclization sufficiently rapidly to compete efficiently with hydrogen transfer from tributylstannane at modest concentration to afford 12-, 15-, 18-, 21-, and 24-membered macro-heterocycles but the reaction fails for the formation of 9-membered rings. The rate constants for cyclization are larger than those previously recorded for analogous radicals with all-carbon chains,[1] presumably because the presence of oxygen atoms reduces the strain energy engendered in formation of the cyclic transition structures. The regioselectivity of cyclization of 8-(1-alkenoyloxy)-3,6-dioxaoctyl radicals with vinylic substituents and the magnitudes of the corresponding rate constants can be rationalized in terms of the competing electronic and steric effects of the substituents. The effect of solvent polarity on the rate of cyclization of 8-(propenoyloxy)-3,6-dioxaoctyl radical is similar to that observed for the addition of *tert*-butyl radical to the acrylonitrile double bond;[28] this appears to indicate an absence of conformational modification of the radical with the solvent.

Experimental Section

NMR spectra were recorded in $CDCl_3$ with $Si(CH_3)_4$ as an internal standard on a 200 MHz or a 250 MHz spectrometer. Microanalyses were performed by the CNRS at Vernaison. GC was conducted on a capillary column (DB1 type, dimethylpolysiloxane, 0.25 μm × 0.25 mm × 10 m)) with N_2 carrier gas.

All solvents were distilled over drying reagents before use. Organic extracts were dried over $MgSO_4$. Acryloyl, cinnamoyl, methacryloyl, crotonoyl, oxalyl, and methanesulfonyl chlorides, di-, tri-, and tetraethylene glycols, 3-oxapentan-1-ol, 3,6-dioxaoctan-1-ol, ethyl iodide, sodium iodide, pyridine, triethylamine, diethyl fumarate, 2,3-dihydropyran, *p*-toluenesulfonic acid (PTSA), bis(tributyltin) oxide, polymethyl-hydrogenosiloxane, 1-chloro-3,6-dioxane, and 3-oxapentyl acrylate (**5a**) were commercially available compounds. Tributylstannane,[33] pentaethylene glycol,[34] (*Z*)-3-(ethoxycarbonyl)propenoyl chloride,[35] (*E*)-3-(ethoxycarbonyl)propenoyl chloride,[35] 3,6,9,12-tetraoxa-12-(2-tetrahydro-pyranyl)dodecan-1-ol,[3] ethyl 2-(bromomethyl)propenoate,[36] and 3,6,9,12-tetraoxa-12-(2-tetrahydropyranyl)dodecan-1-ol[3] were prepared as previously described. The iodo precursors of the cyclic compounds were prepared as previously described,[3] except for **1a** and **2c**.

Values of k_c/k_H were obtained by Newton's method with an iterative computer program. k_c is given as the mean of at least 10 values, with the error corresponding to σ. Activation parameters are given with a confidence level of 95%.

5-Hydroxy-3-oxapentyl Acrylate. A mixture of acryloyl chloride (13.6 g, 0.15 mol), diethylene glycol (31.8 g, 0.3 mol), and triethylamine (16.2 g, 0.16 mol) in dry THF (100 mL) was stirred at room temperature for 16 h and then filtered and concentrated. The residue was dissolved in $CHCl_3$, and the organic phase was successively washed with 5% aqueous hydrochloric acid, 5% aqueous sodium bicarbonate, and brine and dried. The solvent was removed under reduced pressure, and the residue was chromatographed over silica gel (ether) to afford 5-hydroxy-3-oxapentyl acrylate[37] (13.4 g, 56%) as a pale yellow oil; ^{1}H NMR δ 2.83 (1H, s), 3.50−3.70 (6H, m), 4.25 (2H, t, J = 4.7 Hz), 5.78 (1H, dd, J = 10.3, 1.5 Hz), 6.08 (1H, dd, J = 17.3, 10.3 Hz), 6.36 (1H, dd, J = 17.3, 1.5 Hz); ^{13}C NMR δ 61.5, 63.5, 68.9, 72.4, 128.0, 131.1, 166.1.

5-Mesyloxy-3-oxapentyl Acrylate. A mixture of pyridine (9.5 g, 0.12 mol), 5-hydroxy-3-oxapentyl acrylate (16 g, 0.10 mol), and methanesulfonyl chloride (12.6 g, 0.11 mol) was stirred under nitrogen at 0 °C for 4 h and then acidified with 5% aqueous hydrochloric acid to pH 1. The aqueous phase was extracted twice with $CHCl_3$, and the combined organic phases were washed with brine, dried, and concentrated to give the mesylate, which was used without any further purification: ^{1}H NMR δ 3.00 (3H, s), 3.49−3.69 (4H, m), 4.20 (2H, t, J = 4.7 Hz), 4.28 (2H, t, J = 4.4 Hz), 5.75 (1H, dd, J = 10.4, 1.6 Hz), 6.05 (1H, dd, J = 17.4, 10.4 Hz), 6.32 (1H, dd, J = 17.4, 1.6 Hz).

5-Iodo-3-oxapentyl Acrylate (1a). A stirred solution of 5-(mesyloxy)-3-oxapentyl acrylate (23.8 g, 0.10 mol) and sodium iodide (18 g, 0.12 mol) in dry acetone (150 mL) was heated under reflux for 14 h. The solvent was then removed under reduced pressure, and the residue was dissolved in a minimum amount of water and extracted with $CHCl_3$. The organic phase was then dried and concentrated. Chromatography (ether/pentane, 1:1) of the residue gave 5-iodo-3-oxapentyl acrylate as an oil (18.9 g, 70%): ^{1}H NMR δ 3.21 (2H, t, J = 6.7 Hz), 3.68−3.75 (4H, m), 4.28 (2H, t, J = 4.7 Hz), 5.79 (1H, dd, J = 10.3, 1.5 Hz), 6.11 (1H, dd, J = 17.3, 10.3 Hz), 6.40 (1H, dd, J = 17.3, 1.5 Hz); ^{13}C NMR δ 2.6, 63.4, 68.6, 71.7, 128.1, 131.2, 166.0. Anal. Calcd for $C_7H_{11}IO_3$: C, 31.13; H, 4.11; I, 46.99. Found: C, 31.20; H, 4.08; I, 46.74.

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(*Z*)-8-Hydroxy-3,6-dioxaoctyl 3-(Ethoxycarbonyl)propenoate. A solution of (*Z*)-3-(ethoxycarbonyl)propenoyl chloride[35] (0.11 mol) in THF (150 mL) was added to a stirred mixture of triethylene glycol (33.0 g, 0.22 mol) and pyridine (9.5 g, 0.12 mol) in THF (100 mL) under nitrogen. The solution was stirred for 16 h, filtered, washed with ether, and concentrated. The residue was worked up and chromatographed (ether/methanol, 95/5) as described for 5-hydroxy-3-oxapentyl acrylate to afford (*Z*)-8-hydroxy-3,6-dioxaoctyl 3-(ethoxycarbonyl)propenoate (11.5 g, 38%) as an oil: ^{1}H NMR δ 1.15 (3H, t, J = 7.1 Hz), 3.12 (1H, s), 3.43−3.61 (10H, m), 4.09 (2H, q, J = 7.1 Hz), 4.19 (2H, t, J = 4.8 Hz), 6.12 and 6.15 (2H, AB system, J_{AB} = 11.9 Hz); ^{13}C NMR δ 13.7, 60.9, 61.2, 63.8, 68.4, 69.9, 70.2, 72.3, 129.2, 129.9, 164.9.

(*Z*)-8-(Mesyloxy)-3,6-dioxaoctyl 3-(ethoxycarbonyl)-propenoate was prepared as described above for 5-(mesyloxy)-3-oxapentyl acrylate.

(*Z*)-8-Iodo-3,6-dioxaoctyl 3-(ethoxycarbonyl)propenoate (2c) was prepared from (*Z*)-8-(mesyloxy)-3,6-dioxaoctyl 3-(ethoxycarbonyl)propenoate as described for 5-iodo-3-oxapentyl acrylate (**1a**) (60%). Anal. Calcd for $C_{12}H_{19}IO_6$: C, 37.32; H, 4.96; I, 32.86. Found: C, 37.21; H, 4.72; I, 33.03.

3,6,9-Trioxaundecan-1-ol. A mixture of ethyl iodide (7.8 g, 0.05 mol), triethylene glycol (15 g, 0.1 mol), and ground potassium hydroxide (3.1 g, 0.055 mol) in THF (100 mL) was stirred for 4 h at room temperature, and the solvent was then removed under reduced pressure. The residue was dissolved in the minimum amount of water and extracted with CH_2Cl_2. The combined organic phases were washed with 5% aqueous hydrochloric acid and brine and dried. After concentration of the solution, the residue was purified by chromatography (ether/methanol, 96:4) to afford 3,6,9-trioxaundecan-1-ol[38] (5.3 g, 60%). ^{1}H NMR δ 1.06 (3H, t, J = 7.1 Hz), 3.20 (1H, s), 3.37 (2H, q, J = 7.1 Hz), 3.44−3.72 (12H, m).

Similar methods were used for the preparation of **3,6,9,12-tetraoxatetradecan-1-ol**[38] (65%) and **3,6,9,12,15-pentaoxaheptadecan-1-ol**[39] (50%).

3,6,9,12,15,18-Hexaoxaeicosan-1-ol.[39] A solution of 3,6,9,12-tetraoxa-12-(2-tetrahydropyranyl)dodecan-1-ol[3] (8.3 g, 30 mmol), 1-chloro-3,6-dioxaoctane (4.6 g, 30 mmol) and ground potassium hydroxide (1.7 g, 30 mmol) was heated to 90 °C. When the reaction was complete (GC), acetone (100 mL) was added, and the mixture was filtered and concentrated. Chromatography of the residue gave 1,4,7,10,13,16,19-heptaoxa-1-(2-tetrahydropyranyl)heneicosane (4.5 g, 38%): ^{1}H NMR δ 1.08 (3H, t, J = 7.0 Hz), 1.36−1.72 (6H, m), 3.39 (2H, q, J = 7.0 Hz), 3.43−3.55 (24H, m), 3.58−3.70 (2H, m), 4.45 (1H, t, J = 3.4 Hz); ^{13}C NMR δ 14.9, 18.9, 24.9, 30.0, 61.5, 66.0, 66.2, 69.9, 70.0, 98.5.

A solution of the foregoing THP ether (2.0 g, 5 mmol) and *p*-toluenesulfonic acid (0.9 g, 5 mmol) in methanol (35 mL) was heated at 70 °C for 12 h. The solvent was then removed under reduced pressure, and the residual 3,6,9,12,15,18-hexaoxaicosan-1-ol was used without purification: ^{1}H NMR δ 1.10 (3H, t, J = 7.0 Hz), 3.10 (1H, s), 3.45−3.68 (24H, m), 3.38 (2H, q, J = 7.0 Hz); ^{13}C NMR δ 14.9, 61.7, 66.1, 69.8, 69.9, 70.1, 70.2.

3,6-Dioxaoctyl Acrylate (5b). Treatment of 3,6-dioxaoctan-1-ol with 1.0 molar equiv of acryloyl chloride (2.7 g, 30 mmol) and 1.1 equiv of triethylamine in dry THF for 16 h gave the crude ester, which was dissolved in CH_2Cl_2, successively washed with 5% aqueous hydrochloric acid, 5% aqueous $NaHCO_3$, and brine, and dried. The solvent was removed under reduced pressure, and the residue was chromatographed over silica gel (ether/pentane, 40:60) to afford 3,6-dioxaoctyl acrylate (60%) as a pale yellow oil: ^{1}H NMR δ 1.08 (3H, t, J = 7.0 Hz), 3.40 (2H, q, J = 7.0 Hz), 3.46−3.55 (4H, m), 3.62 (2H, t, J = 4.7 Hz), 4.19 (2H, t, J = 4.7 Hz), 5.71 (1H, dd, J = 10.3, 1.5 Hz), 6.03 (1H, dd, J = 17.4, 10.3 Hz), 6.30 (1H, dd, J = 17.4, 1.5 Hz); ^{13}C NMR δ 14.9, 63.4, 66.3, 68.8, 69.6, 70.4, 128.1, 130.7, 165.8. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.09; H, 8.68.

Similar methods were used for the preparation of the following. **3,6,9-trioxaundecyl acrylate (5c)**[40] (60%). Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.97; H, 8.78%. **3,6,9,12-Tetraoxatetradecyl acrylate (5d)** (40%). Anal. Calcd for $C_{13}H_{24}O_6$: C, 56.51; H, 8.75. Found: C, 56.91; H, 8.56. **3,6,9,12,15-Pentaoxaheptadecyl acrylate (5e)** (43%). Anal. Calcd for $C_{15}H_{28}O_7$: C, 56.23; H, 8.81. Found: C, 56.02; H, 8.71. **3,6,9,12,15,18-Hexaoxaeicosanyl acrylate (5f)** (50%). Anal. Calcd for $C_{17}H_{32}O_8$: C, 56.03; H, 8.85. Found: C, 56.25; H, 8.69. **3,6-Dioxaoctyl 2-methylpropenoate (9a)**[41] (50%). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.50; H, 8.63. **(*E*)-3,6-Dioxaoctyl but-2-enoate (9b)** (30%), prepared with potassium carbonate instead of triethylamine. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.32; H, 8.81. **(*Z*)-3,6-Dioxaoctyl 3-(ethoxycarbonyl)propenoate (9c)** (50%). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.12; H, 7.70. **(*E*)-3,6-Dioxaoctyl 3-(ethoxycarbonyl)propenoate (9d)** (50%). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.50; H, 7.60. **(*E*)-3,6-Dioxaoctyl 3-phenylpropenoate (9e)** (40%). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.94; H, 7.68.

Ethyl 2-Methylene-4,7,10-trioxadodecanoate. Triethylamine (3.6 g, 36 mmol) was added to a solution of ethyl 2-(bromomethyl)propenoate[36] (5.8 g, 30 mmol) and 3,6-dioxaoctan-1-ol (4.8 g, 36 mmol) in CH_2Cl_2 at 0 °C. The mixture was then warmed to room temperature, stirred for 30 min, and finally heated to reflux for 24 h. This solution was then washed with 5% aqueous hydrochloric acid and brine, dried, and concentrated. Chromatography of the residue afforded ethyl 2-methylene-4,7,10-trioxadodecanoate: ^{1}H NMR δ 1.09 (3H, t, J = 7.0 Hz), 1.18 (3H, t, J = 7.2 Hz), 3.41 (2H, t, J = 7.0 Hz), 3.47−3.56 (8H, m), 4.10 (2H, q, J = 7.2 Hz), 4.12 (2H, t, J = 1.5 Hz), 5.78 (1H, q, J = 1.5 Hz), 6.17 (1H, q, J = 1.5 Hz); ^{13}C NMR δ 13.9, 14.9, 60.4, 66.4, 69.0, 69.6, 70.0, 70.3, 70.5, 125.2, 137.1, 165.5. Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.47; H, 9.04.

Determination of Cyclization Kinetics. A solution of the iodo compound (0.50 mmol) and a suitable GC reference compound (0.35 mmol) in benzene was made up to 5.0 mL in a standard flask, and a sample (1.0 mL) was placed in a Schlenk tube. A 0.10 M solution of Bu_3SnH in benzene was similarly prepared, and a 1.0 mL sample in a small tube was carefully placed in the Schlenk tube. The contents of the Schlenk tube were degassed by three freeze−thaw cycles, heated to the desired temperature for 5 min, and then mixed. After a suitable time (10−60 min) the mixture was analyzed by GC. Reactions at different concentrations were conducted by appropriate accurate dilution of the reactant solutions.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectral data for compounds **5c**−**f** and **9a**−**e** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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