Macrocyclization under Thermodynamic Control. A Theoretical Study and Its Application to the Equilibrium Cyclooligomerization of β-Propiolactone

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Received November 9, 1992

Abstract: A general treatment of macrocyclization reactions occurring under thermodynamic control is presented. The fundamental quantities on which the treatment is based are the effective molarities of the cyclic oligomers and the equilibrium constant for the intermolecular model reaction between monofunctional reactants (K_{inter}). Four typical cases have been considered, namely, addition and condensation of a monomer of the type A–B, addition of A–A, and addition of A–A + B–B. A critical comparison with the classical theory of Jacobson and Stockmayer is presented. It is shown that the phenomenon characterized by the critical monomer concentration (cut-off point) is a limiting phenomenon which would occur only for infinitely large values of K_{inter}. The treatment has been successfully applied to the DOS/DTC-induced cyclooligomerization of β-propiolactone in $CDCl_3$ solution that yields well-behaved ring–chain equilibrates closely adhering to the theoretical model. Best fit of the experimental product distributions to the general equations gave the equilibrium constant (K_{inter}) of the intermolecular model reaction, as well as the effective molarities (EM_i) for the cyclic oligomers from trimer to octamer. The EM_i values decrease in proportion of the −2.5 power of the oligomerization degree, thus providing a strong indication that the oligomeric polylactones are essentially strainless. The extremely low value of K_{inter} (2.5) is responsible for the absence of a cut-off point, which is usually present in ring–chain polymeric equilibrates.

Introduction

Product composition in chemical reactions may be either governed by the relative rates of the competing processes (kinetic control) or by the equilibrium parameters of the system (thermodynamic control). Macrocyclization reactions are no exception. Besides a host of synthetic procedures where irreversible reactions are involved,[1] there are examples where product mixtures consist of unequivocal equilibrium distributions of cyclic oligomers.[2] Furthermore, there is overwhelming evidence that ring molecules occur in a wide range of polymers prepared by ring–chain equilibration reactions.[3]

No doubt, the chemistry of macrocycles has initiated the development of supramolecular chemistry, in which not only monomeric but also oligomeric ring structures play a central role.[4] It appears therefore that there is a great need for quantitative treatments which allow the detailed distribution of all species, both cyclic and linear, to be calculated as a function of the initial reactant concentration under a given set of conditions (chemical nature of end groups, structure and length of the intervening chain, temperature, solvent, catalyst, reaction time, etc.).

The theory of irreversible cyclization is well developed,[5,6] and further refinements are in progress in this group. Mathematical models have been worked out which can serve the purpose of predicting yields and distributions of cyclic oligomers to be obtained under kinetic control. A corresponding treatment of cyclization under thermodynamic control is desirable. A general theory of macrocyclization equilibria has been presented by Jacobson and Stockmayer (JS) as early as 1950.[7] Their theory has been extensively used by polymer chemists to describe the cyclic populations of linear polymeric equilibrates in concentrated solutions.[3,8] To our knowledge, however, it has never been used to describe the distribution of cyclic oligomers to be obtained in dilute solutions, namely, under conditions where according to the theory itself (vide infra) the system is composed of cyclic oligomers only, and the acyclic polymers are virtually absent. Consequently, we have developed an independent treatment of reversible cyclization reactions with the major aim of providing macrocyclic chemistry with a theoretical background to be used for systems where formation of macrocycles occurs under complete equilibration.

In order to apply the theoretical treatment to a real system, we have investigated the reversible cyclooligomerization of β-propiolactone[2b] induced by a catalytic system composed of a 1:1 mixture of 2,2-di-*n*-butyl-1,3,2-dioxastannolane (DOS) and di-*n*-butyltin dichloride (DTC) in $CDCl_3$ at 70 °C. The virtual absence of undesired byproducts renders this reaction an ideal system for the purpose of comparing experiment with theory.

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(7) Jacobson, H.; Stockmayer, W. H. *J. Chem. Phys.* **1950**, *18*, 1600–1606.

(8) Flory, P. J. *Statistical Mechanics of Chain Molecules*; Wiley-Interscience: New York, 1969; Appendix D.

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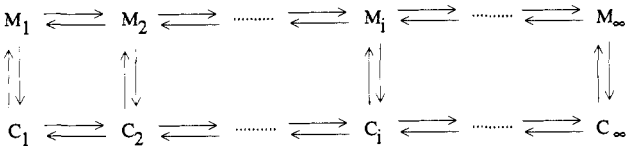
Scheme I



Theoretical Treatment of Reversible Macrocyclization

For simplicity in deriving the following argument, we shall consider a system of identical monomers A–B (M_1) bearing two different functional groups, each capable of reacting with the other only in a reversible addition reaction. The chemical nature of A and B is immaterial to the present treatment. The addition reaction between A and B may rely upon reversible covalent bonding, as well as upon weak noncovalent forces such as hydrogen bonding, charge transfer or stacking interactions, and the like. Actual systems belonging either to this case or to the closely related cases A–A and A–A + B–B treated in Appendix 2, in which A and B are hydrogen bond donor and acceptor groups, can be found in the recent literature.[9] Controlling molecular aggregation via hydrogen bonding is a major trend in supramolecular chemistry.[10]

After equilibration, a system initially composed of bifunctional monomer units M_1 contains in principle an infinite number of cyclics C_i as well as an infinite number of linears M_i, i being the polymerization degree (Scheme I).

At first we will develop a mass balance equation using a formalism somewhat different from that used in JS theory. On the analogy of the definition of the kinetic effective molarity,[11,12] the equilibrium effective molarity (EM_i) is defined as

$$EM_i = \frac{K_{(intra)i}}{K_{inter}} \tag{1}$$

where $K_{(intra)i}$ refers to the ring–chain equilibrium between the acyclic i-mer M_i and the cyclic i-mer C_i (eq 2a–b) and K_{inter} is

$$M_i \rightleftarrows C_i \tag{2a}$$

$$K_{(intra)i} = \frac{[C_i]}{[M_i]} \tag{2b}$$

the equilibrium constant for the intermolecular model reaction between monofunctional reactants (eq 3a–b). The structure of

$$-A + B- \rightleftarrows -AB- \tag{3a}$$

$$K_{inter} = \frac{[-AB-]}{[-A][B-]} \tag{3b}$$

the residues bound to A and B is such as to resemble as closely as possible the part structures linked to the functional groups in the bifunctional monomer A–B.

If the thermodynamics of the reaction between end groups is independent of the length of the chain, the equilibrium constant K_{li} for the general process of linear (l) i-merization in which i molecules of M_1 are converted into M_i (eq 4a–b) is simply related to K_{inter} by eq 5 which clearly shows that i-1 bonds are formed in the i-merization process.

$$iM_1 \rightleftarrows M_i \tag{4a}$$

$$K_{li} = \frac{[M_i]}{[M_1]^i} \tag{4b}$$

$$K_{li} = K_{inter}^{\,i-1} \tag{5}$$

The equilibrium constant K_{ci} for the corresponding process of cyclic (c) i-merization in which i molecules of C_1 are converted into the cyclic oligomer C_i (eq 6a–b) can be visualized as occurring through steps 7a–c. Therefore K_{ci} is simply given by the product of the equilibrium constants for steps 7a–c.

$$iC_1 \rightleftarrows C_i \tag{6a}$$

$$K_{ci} = \frac{[C_i]}{[C_1]^i} \tag{6b}$$

$$iC_1 \rightleftarrows iM_1 \tag{7a}$$

$$iM_1 \rightleftarrows M_i \tag{7b}$$

$$M_i \rightleftarrows C_i \tag{7c}$$

$$K_{ci} = \frac{K_{inter}^{\,i-1} K_{(intra)i}}{K_{(intra)1}^{\,i}} = \frac{EM_i}{EM_1^{\,i}} \tag{8}$$

Combination of eqs 6b and 8 leads to

$$[C_i] = EM_i\left(\frac{[C_1]}{EM_1}\right)^i \tag{9}$$

or

$$[C_i] = EM_i x^i \tag{10}$$

where

$$x = \frac{[C_1]}{EM_1} \tag{11}$$

It is useful to express also $[M_i]$ as a function of x. Combination of eqs 1, 2b, and 10 leads to eq 12. It can be demonstrated that x coincides with the fraction of reacted end groups in the acyclic part of the polymer (Appendix 1).

$$[M_i] = \frac{x^i}{K_{inter}} \tag{12}$$

In the original treatment of JS, the distribution of the linear part of the polymer is of the same form as that in the ring-free case, namely,

$$[M_i] = Ax^i \tag{13}$$

where x is the fraction of reacted end groups in the chain fraction, and A a normalization constant. This is a most probable distribution and is equivalent to assuming that the reactivity between end groups is independent of the length of the chain. It appears therefore that the quantity A, introduced by JS as an

(9) (a) Zimmerman, S. C.; Duerr, B. F. *J. Org. Chem.* **1992**, *57*, 2215–2217. (b) Takasuka, M.; Ezumi, K.; Yamakawa, M. *J. Chem. Soc., Perkin Trans. 2* **1992**, 29–33.

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(11) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1–111.

(12) The kinetic effective molarity, EM(k), is related to the free energy of a cyclic transition state, whereas the thermodynamic effective molarity, EM(t), is related to the free energy of a cyclic product. For small and medium rings there can be significant differences in the strain energy associated with a cyclic transition state and with a cyclic product, therefore there is not a simple relation between EM(k) and EM(t). For large rings (more than 25–30 membered) both the transition state and the product ring can be considered strainless, and therefore $EM(t) = EM(k)/\sigma$, where σ is the symmetry number of the cyclic product which is usually i or $2i$ (see ref 11). It can be viewed as a consequence of the availability of i or $2i$ equivalent bonds for the ring-opening reaction of the cyclic product.

otherwise unspecified normalization constant, has the meaning of the equilibrium constant for dissociation of the model compound –AB–.

The fundamental quantity introduced by JS is the molar cyclization equilibrium constant K_i which refers to the formal ring–chain equilibrium of eq 14a.

$$M_n \rightleftarrows M_{n-i} + C_i \tag{14a}$$

$$K_i = \frac{[M_{n-i}][C_i]}{[M_n]} \tag{14b}$$

Taking into account eq 13, eq 15 was derived.

$$[C_i] = K_i x^i \tag{15}$$

The strong similarity between eqs 15 and 10 is not accidental. In fact, it has already been pointed out[11] that within the usual approximation of reactivity of end groups independent of chain length, the EM_i is both conceptually and operationally identical to the macrocyclization equilibrium constant K_i defined by eq 14b.

A further aspect of the JS theory is that when strainless rings are formed from chain-obeying Gaussian statistics, K_i (EM_i) varies inversely to the $^5/_2$ power of the polymerization degree i as shown in eq 16, where the parameter B has the meaning of the effective molarity that the cyclic monomer would have if it were strainless.

$$K_i = EM_i = Bi^{-5/2} \tag{16}$$

Now let us consider the mass balance equation

$$[M_1]_0 = \underbrace{\sum_{i=1}^{\infty} i[C_i]}_{\text{rings}} + \underbrace{\sum_{i=1}^{\infty} i[M_i]}_{\text{chains}} \tag{17}$$

In general, macrocycles with more than 25–30 ring atoms are virtually strainless, but smaller rings are usually affected by considerable strain,[11] which causes their EM's to be lower than predicted by eq 16.[13] Indicating with r the polymerization degree of the first strainless macrocycle, and taking into account eqs 10, 12, and 16, eq 17 can be written in the form of eq 18.

$$[M_1]_0 = \underbrace{\sum_{i=1}^{r-1} iEM_i x^i}_{\text{strained rings}} + \underbrace{B\sum_{i=r}^{\infty} i^{-3/2}x^i}_{\text{strainless rings}} + \underbrace{\frac{1}{K_{inter}}\sum_{i=1}^{\infty} ix^i}_{\text{chains}} \tag{18}$$

Of course if all the rings are strainless, $r = 1$ and the first summation disappears; in this case B coincides with EM_1. Also note that since the series in the chain fraction diverges for $x \geq 1$, the values of x are confined in the range $0 \leq x < 1$. It should be remarked that the possible occurrence of strained rings was not taken into account in the original JS theory.

(13) The occurrence of ring strain upon closure of the shorter chains is not the sole factor responsible for the lack of adherence to eq 16. Firstly, short chains may not follow Gaussian statistics, which requires appropriate expressions for the density of end-to-end vectors. Secondly, deviations from Gaussian behavior are expected in thermodynamically good solvents because of excluded volume effects (ref 8, p 32). These can have enormous effects on cyclization of long chains, but have found to be unimportant for chains with less than a hundred skeletal bonds (ref 3a, p 47, and references therein cited). Finally, eq 16 is based on the assumption of independence of orientation and proximity of reacting end groups. Orientational correlations are slightly unfavorable for medium-sized chains, but markedly favorable for the shortest chains, which often exhibit EM values exceeding by several orders of magnitude those predicted by any theoretical model where orientational correlation is ignored. EM values of 10^3–10^5 M are not uncommon for 5- and 6-membered rings (Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183–278). Clearly, the cyclic fraction of ring chain equilibria involving the above rings is composed of them only, e.g., pyranose and furanose forms in sugar chemistry.

Using eq 32 (Appendix 1), the mass balance equation takes the useful form of eq 19, which establishes a link between the structural and chemical characteristics of the system at hand, featured by K_{inter}, EM_i's, and initial concentration of monomer $[M_1]_0$. Equations 10, 12, and 19 are all one needs to describe the system in its finest details.

$$[M_1]_0 = \sum_{i=1}^{r-1} iEM_i x^i + B\sum_{i=r}^{\infty} i^{-3/2}x^i + \frac{1}{K_{inter}}\frac{x}{(1-x)^2} \tag{19}$$

In Appendix 2 we report extensions of the above treatment to other typical cases, namely, condensation of A–B, addition of A–A, and addition of A–A + B–B.

The Critical Monomer Concentration

The most remarkable result of the JS theory is the concept of critical monomer concentration (cut-off point). According to the theory, one predicts (and finds in actual systems[3]) that when the extent of reaction p,[14] measured by the fraction of reacted end groups in the system, is equal to 1, there is a critical concentration of the initial monomer $[M_1]_0^*$ below which the system is virtually composed of cyclic species only, and above which the concentration of each cyclic species remains constant and the excess monomer produces acyclic species only.

So far, experimental investigations of the quantitative aspects of macrocyclization equilibria have been mainly concentrated on systems above the cut-off point, in what might be called the polymer chemist's domain.[3] Experimental determinations of limiting values of oligomer concentrations have been carried out with the main purpose of probing the conformation of chains in solution. On the other hand, the organic chemist's interest is mainly focused in the concentration region below critical, where yields of cyclics are maximal. It is apparent that a thorough understanding of this critical phenomenon is needed. A major difficulty in following the JS arguments lies in the fact that p is not only a function of dilution, but also of the chemical nature of the reaction at hand. The present treatment leads to the concept of critical concentration in a very simple way. Since x increases on increasing $[M_1]_0$, and since the limit approached by x is 1, it is apparent from eqs 10 and 12 that on increasing $[M_1]_0$, $[C_i]$ approaches the corresponding EM_i value and $[M_i]$ approaches the value of $1/K_{inter}$. The important difference between the behavior of the cyclic and acyclic fractions is that in eq 18 the series $\sum i^{-3/2}x^i$ unlike the series $\sum ix^i$, is convergent also for $x = 1$. In other words the cyclic fraction, unlike the acyclic one, can contain only a limited amount of monomer units. This amount, which is the limit to which the cyclic fraction converges when x approaches 1, i.e.

$$\left(\sum_{i=1}^{r-1} iEM_i + B\sum_{i=r}^{\infty} i^{-3/2}\right)$$

is by definition the critical monomer concentration. Since $\sum_{i=1}^{\infty} i^{-3/2} = 2.612$,[15] the critical monomer concentration is simply given by eq 20.

$$[M_1]_0^* = 2.612B - \sum_{i=1}^{r-1}(Bi^{-3/2} - iEM_i) \tag{20}$$

Let us make a practical example with the 2-fold aim of illustrating the importance of K_{inter} and showing how our approach can be used to make predictions of chain and ring distributions.

(14) The quantity p, defined as $p = 1 - (\sum[M_i]/[M_1]_0)$, which represents the fraction of reacted end groups in the system, should not be confused with the quantity x which is the fraction of reacted end groups in the acyclic part of the polymer. Here we adopt the same symbolism used by JS in their original paper; however, in subsequent literature very often the fraction of reacted end-groups in the acyclic part of the polymer is indicated with p.

(15) Truesdell, C. A. *Ann. Math.* **1945**, *46*, 144–157.

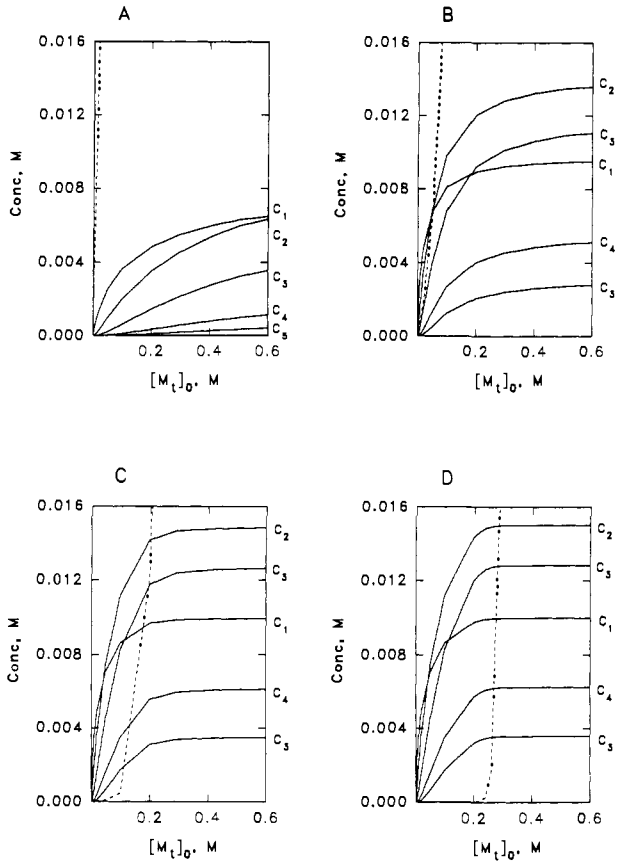


Figure 1. Equilibrium concentrations of cyclic oligomers and weighted chain fraction (dashed line) as a function of total monomer concentration for K_{inter} values of 10 M^{-1} (A), 10^3 M^{-1} (B), 10^5 M^{-1} (C), 10^8 M^{-1} (D). For the EM_i values of this system see text.

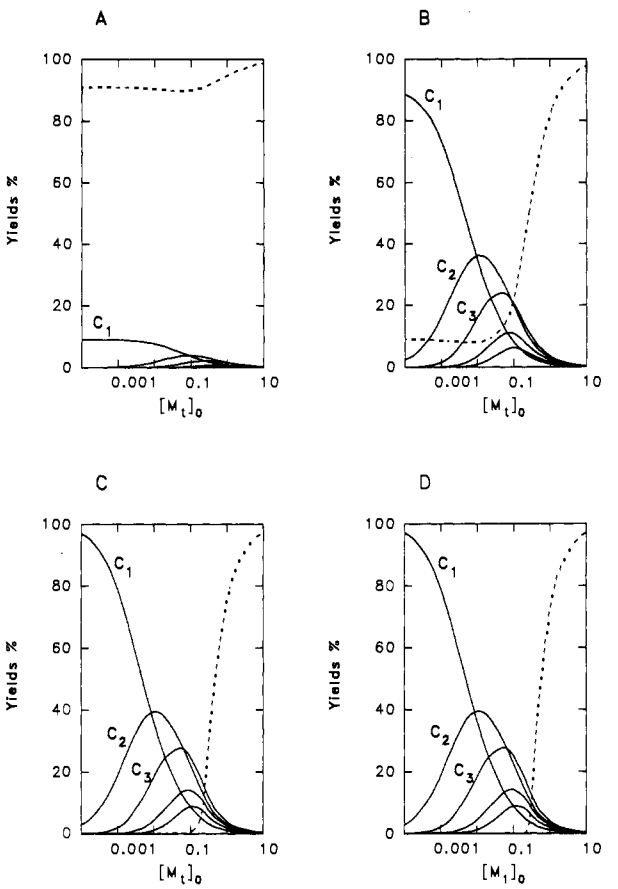


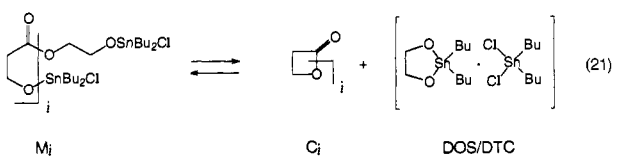
Figure 2. Yields (percent) of cyclic oligomers ($100i[C_i]/[M_1]_0$) and chain fraction (dashed line) as a function of total monomer concentration for K_{inter} values of 10 M^{-1} (A), 10^3 M^{-1} (B), 10^5 M^{-1} (C), 10^8 M^{-1} (D). For the EM_i values of this system see text.

Consider a bifunctional chain leading to a medium-sized monomeric ring C_1 with, say, 10 ring atoms, so that C_2 is 20-membered, C_3 is 30-membered, and so on. The first oligomer that can safely be assumed to be virtually strainless is C_3, which means that EM_3 is solely determined by the loss of conformational entropy suffered by the bifunctional precursor upon cyclization.[11] From the available compilation of averaged entropy data for cyclization (listed in Table 19 of ref 11), the entropy-controlled EM for closure of a chain composed of 29 single bonds is 0.040 M, which after correction for the symmetry number $\sigma = 3$ translates into a EM_3 value of 0.013 M for C_3. This corresponds to a B value of 0.20 M, which was used to calculate the EM values from C_3 onward by means of eq 16. For C_1 and C_2 we assumed EM values of 0.010 and 0.015 M, which correspond to ring strain energies of 2.5 and 0.6 kcal/mol, respectively.[11] For this system eq 20 provides a critical monomer concentration $[M_1]_0^*$ of 0.29 M. Product distributions over a wide range of initial monomer concentrations were calculated from eqs 10, 12, and 19 as indicated in the Computational Procedure for systems characterized by the above set of EM_i values and K_{inter} values of 10, 10^3, 10^5, 10^8 M^{-1}, respectively. The calculated concentration (Figure 1) and yield (Figure 2) profiles show that the appearance of a cut-off point is a limiting behavior which would be observed for infinitely large values of K_{inter}. It is seen that the critical monomer concentration of 0.29 M is the center of a more or less extended region, which begins when the chain fraction is no more negligible and ends when the ring fraction reaches a constant value. The close link between the appearance of a cut-off point and the thermodynamics of the intermolecular reaction is not immediately apparent in the JS paper.[7] It has the important consequence that a large K_{inter} value is beneficial to the yield of cyclic oligomers.

Another point worth considering is that JS did not make any distinction between the case of addition and that of condensation, which is in line with Flory's statement[8] that the chemistry of the reacting groups is immaterial. We point out, however, that the chemistry of the reacting group is immaterial for reaction systems having the same stoichiometry. But condensation, having a stoichiometry different from that of addition, requires a treatment where the molecule eliminated during the reaction course should be taken into account (Appendix 2). Any distinction between the two cases, however, disappears in the limit of infinitely large K_{inter} values.

Cyclooligomerization of β-Propiolactone

β-Propiolactone has been oligomerized in $CDCl_3$ at 70 °C, in the presence of DOS/DTC, to afford equilibrated mixtures of cyclic and linear oligomers (eq 21). The exact nature and dynamic

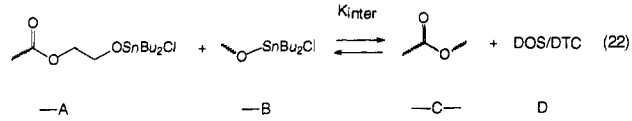


(21)

behavior of the 1:1 adduct between DOS and DTC, which were discussed in a previous paper,[16] are irrelevant to the present treatment.

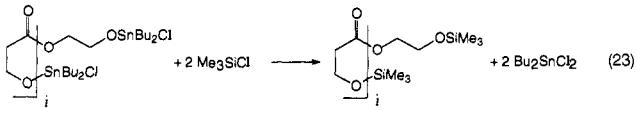
From eq 21 it appears that the cyclooligomerization of β-propiolactone is an example of an A–B condensation as described in Appendix 2. The corresponding intermolecular model reaction can be formulated as follows:

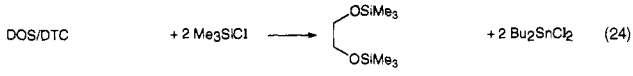
(16) Roelens, S. *J. Chem. Soc., Perkin Trans. 2* **1988**, 2105–2110.



The reaction was run varying the initial monomer concentration in a range wide enough (4.3×10^{-2} to 2.86 M) to cause significant variations of the observed product distributions. The cyclic oligomers from the trimer to the octamer were monitored by ^{13}C NMR spectroscopy directly in the reaction solution with no manipulation of the mixture. This method proved to be particularly convenient,[2b] because the methylene carbon α to the carbonyl gives rise to a signal in the ^{13}C NMR spectrum which is well resolved for each cyclic oligomer up to the octamer, allowing an accurate quantitative measure of the ring distribution. Macrocycles larger than the octamer, together with linear oligomers, are revealed as a partially resolved signal and are taken into account as a whole for the mass balance of the reaction.

The equilibrated reaction mixtures were successively quenched by addition of a stoichiometric amount, relative to DOS/DTC, of chlorotrimethylsilane. Quenching with Me_3SiCl causes fast and clean destannylation without affecting the distribution of products, as shown by the fact that samples analyzed before and after the addition of Me_3SiCl gave strictly the same distribution of cyclooligomers within experimental errors. The stannylated end groups and the residual DOS/DTC were quantitatively converted into dibutyltin chloride and stable trimethylsilyl ethers (eqs 23 and 24) that could be accurately analyzed by ^1H NMR spectroscopy. Such a procedure provided a quantitative measure of the equilibrium concentration of DOS/DTC.





The experimental results are shown in Table I. In runs 1–7 the initial concentration of DOS/DTC ($[DOS/DTC]_0$) was kept almost constant ($(4.6–6.8) \times 10^{-2}$ M), while increasing the initial concentration of β-propiolactone ($[C_1]_0$). However, when $[DOS/DTC]_0$ was less than about 5% of $[C_1]_0$, the absence of free DOS/DTC and increasing amounts of unreacted β-propiolactone in the final mixture revealed incomplete equilibration because of exhaustion of DOS/DTC. These findings are consistent with the view that stannylated chain ends are incapable per se of propagating the cyclooligomerization of β-propiolactone and that DOS/DTC is the active species.[2b] For this reason, experiments at initial concentration of C_1 larger than 7.2×10^{-2} M were run at the constant $[DOS/DTC]_0/[C_1]_0$ ratio of 0.1. Under such conditions complete equilibration was attained.

The first observed oligomer in the distribution is the 12-membered trimeric lactone C_3. No trace of the reactant lactone C_1 and of the dilactone C_2 were detected in the equilibrated mixtures, which indicates that EM_1 and EM_2 are negligibly low. This is not unexpected, as considerable strain energies are likely to be associated with 4- and 8-membered rings.[11] From the data listed in Table I, it is apparent that the ring concentrations C_i have not reached their plateau values. Therefore the EM_i values are not directly measurable as the limiting values approached by the quantities C_i in the high total monomer concentration region.

Now let us consider how the relevant physicochemical parameters of the system at hand can be obtained from the data reported in Table I. Combining eqs 10 and 16, eq 25 is obtained. The numerical value of γ predicted by theory is $^5/_2$, but in actual cases γ can be slightly different from $^5/_2$.[3] Therefore we shall consider γ as a parameter that can be adjusted within limits to improve fit to the data.

$$[C_i] = Bi^{-\gamma}x^i \tag{25}$$

Equation 25 shows that when $x \approx 1$, a plot of $\log[C_i]$ vs $\log i$ would yield a straight line with intercept B and slope $-\gamma$. When x is appreciably smaller than 1, a plot of $\log[C_i]$ vs $\log i$ would still be reasonably linear over a limited range of i values,[17] but the numerical values of the intercept and slope are not of immediate significance. A plot of $\log[C_i]$ vs $\log i$ for the experiment run at the highest monomer concentration (run no. 10 in Table I) is shown in Figure 3. The good linearity of the plot strongly suggest that all of the rings from C_3 onwards closely adhere to eq 25, thus providing a good indication that ring strain and/or other factors[13] that can cause more or less marked deviations from eq 25 do not play a significant role in the system at hand.

A least-squares procedure is now needed to obtain the parameters B, γ, and x. It should be noted that while B and γ are constant quantities, x depends on the experiment we are considering. Therefore there will be as many curves represented by eq 25 as the number of the experiments, each curve having a different x value. These curves can be viewed as orthogonal sections of a hypersurface represented by eq 26.

$$[C_{ij}] = B(\sum_{k=1}^{10} i_k)^{-\gamma} \prod_{k=1}^{10} x_k^{i_k} \tag{26}$$

The running indices j and k represent the experiment number (up to a total of 10 in the present case). B, γ, and x_k are the parameters to optimize, while i_k are the independent variables. The latter are such that when $k = j$, $i_k = i$, while when $k \neq j$, $i_k = 0$.

Nonlinear least squares treatment of the experimental ring concentrations reported in Table I according to eq 26 afforded the optimized values of B (= 2.26 M, σ = 0.16), γ (= 2.55, σ = 0.20), and x_k (x_1 = 0.396, x_2 = 0.445, x_3 = 0.499, x_4 = 0.622, x_5 = 0.734, x_6 = 0.768, x_7 = 0.803, x_8 = 0.841, x_9 = 0.861, x_{10} = 0.855). It is remarkable that the obtained value of γ is quite close to the theoretical value of $^5/_2$.

Adapting eq 36 to the present case, eq 27 is obtained.

$$[C_1]_0 = B\sum_{i=3}^{\infty} i^{-(\gamma+1)}x^i + \frac{x[DOS/DTC]_0}{K_{inter}(1-x)^2 + x(1-x)} \tag{27}$$

By introducing into it the values of $[C_1]_0$, $[DOS/DTC]_0$, B, γ, x_k, 10 values of K_{inter} are obtained, which on average give K_{inter} = 2.5, σ = 1.8. We have thus found numerical values of the physicochemical parameters required for a complete description of the system, namely, B, γ, and K_{inter}. With these parameters we can recalculate by means of eq 27 a new set of x values, and with this new set, we can calculate by eq 25 the ring distribution and by eq 35 the equilibrium concentration of DOS/DTC. These data are collected in Table I. It should be noted that the good agreement between the experimental and calculated equilibrium concentrations of DOS/DTC provides an independent check of the reliability of the model, since the experimental values of [DOS/DTC] have not been used in the optimization procedure. The close adherence of calculated to experimental ring distributions (Figure 4) shows that the DOS/DTC-induced oligomerization of β-propiolactone is a well-behaved ring–chain equilibrium system, closely adhering to the theoretical equations. It is remarkable that a complete description in quantitative terms of such a complex system of ring–chain equilibria requires only two

(17) This occurs because over a limited range of i values there is a satisfactory linear relationship between i and $\log i$.

Table I. Equilibrium Product Distribution: Comparison of Theory and Experiment[a]

run no.	$[C_1]_0$	$[DOS/DTC]_0$	x^b	f^c	[DOS/DTC]	$[C_3]$	$[C_4]$	$[C_5]$	$[C_6]$	$[C_7]$	$[C_8]$
1	43.0	53.0	*0.369*	*0.634*	41.0	8.50	1.60	0.23	0.07		
					43.1	*6.87*	*1.22*	*0.25*	*0.06*		
2	66.0	47.0	*0.433*	*0.709*	36.0	12.0	2.70	0.51	0.14		
					36.1	*11.1*	*2.31*	*0.57*	*0.15*		
3	95.0	47.0	*0.487*	*0.738*	33.0	17.0	4.00	0.87	0.29		
					34.2	*15.7*	*3.68*	*1.01*	*0.31*		
4	220	54.0	*0.616*	*0.752*	33.0	33.0	10.0	2.80	1.00	0.35	
					33.1	*32.0*	*9.45*	*3.30*	*1.28*	*0.53*	
5	470	68.0	*0.736*	*0.714*	33.0	55.0	18.0	6.80	3.10	1.30	
					32.4	*54.4*	*19.2*	*7.99*	*3.69*	*1.83*	
6	570	58.0	*0.775*	*0.739*	26.0	62.0	23.0	9.00	4.80	2.00	0.93
					24.6	*63.6*	*23.7*	*10.4*	*5.06*	*2.64*	*1.46*
7	720	46.0	*0.822*	*0.768*	17.0	71.0	27.0	12.0	7.00	3.40	2.00
					16.3	*75.9*	*30.0*	*13.9*	*7.20*	*3.99*	*2.34*
8	990	95.0	*0.837*	*0.608*	37.4	81.0	34.0	15.0	8.70	3.70	1.90
					31.5	*80.0*	*32.1*	*15.2*	*7.98*	*4.51*	*2.68*
9	1900	189	*0.877*	*0.404*	54.3	86.0	37.0	19.0	10.0	5.70	3.80
					49.6	*92.1*	*38.8*	*19.2*	*10.6*	*6.27*	*3.91*
10	2860	286	*0.892*	*0.294*	72.4	86.0	34.0	16.0	10.0	5.70	
					67.3	*96.9*	*41.4*	*20.9*	*11.7*	*7.04*	

[a] All concentration in 10^{-3} mol L^{-1}. Figures printed in italics are calculated, the others are experimental. [b] Fraction of reacted end groups in the acyclic fraction. [c] Fraction of cyclics calculated as $(\sum_i i[C_i])/[C_1]_0$.

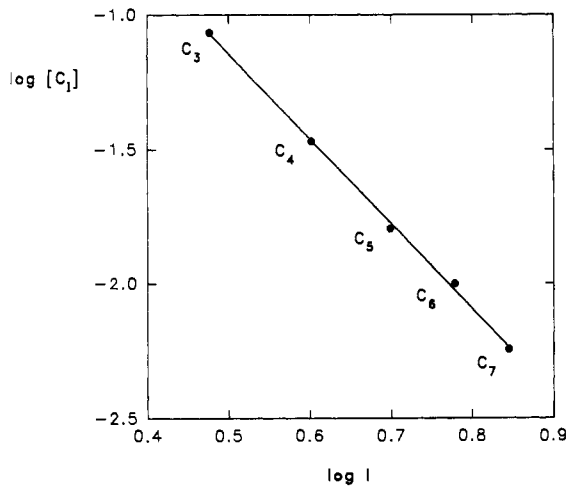


Figure 3. Plot of $\log[C_i]$ vs $\log i$. Data from run no. 10 in Table I. The slope of the line is −3.2.

adjustable parameters, namely K_{inter} and B since γ turned out to be practically coincident with the theoretical value of $^5/_2$.

From eq 16 and the optimized B value of 2.26 M, the following EM_i values (in M units) are calculated: $EM_3 = 0.137$, $EM_4 = 0.066$, $EM_5 = 0.037$, $EM_6 = 0.023$, $EM_7 = 0.016$, $EM_8 = 0.011$. These figures have clearly the meaning of the concentrations of cyclic species extrapolated to infinite monomer concentration. They are graphically shown in Figure 4 as the limiting values of the concentration profiles when x approaches 1.

The close adherence of the EM_i values to a theoretical equation which holds for the ideal case where strainless rings are formed from chains obeying Gaussian statistics strongly suggests that all of the oligomeric polylactones, including the 12-membered trilactone are strainless rings. Similar conclusions were drawn by Ito et al.[18] in a study of equilibrium cyclic oligomer formation in the anionic polymerization of ϵ-caprolactone. This view is further confirmed by the finding that the EM_i data from the present work, when corrected for symmetry, coincide within a factor of 2 with the values expected on the basis of the available compilation of averaged EM data (listed in Table 19 of ref 11) for closure of strainless rings from chains composed of r skeletal bonds.[19]

The adverse effect of the very low K_{inter} value on yields of cyclic species is well illustrated by the fractions f of initial monomer converted into cyclic species at equilibrium (Table I), which are significantly smaller than 1 in all cases. The critical monomer concentration, calculated from eq 20 as 2.85 M, turns out accidentally to coincide with the highest concentration used in the experiments. It appears, therefore, that the concept of critical monomer concentration is of little or no utility whenever the chemical reaction on which polymerization is based is inherently little exoergonic (low K_{inter}).

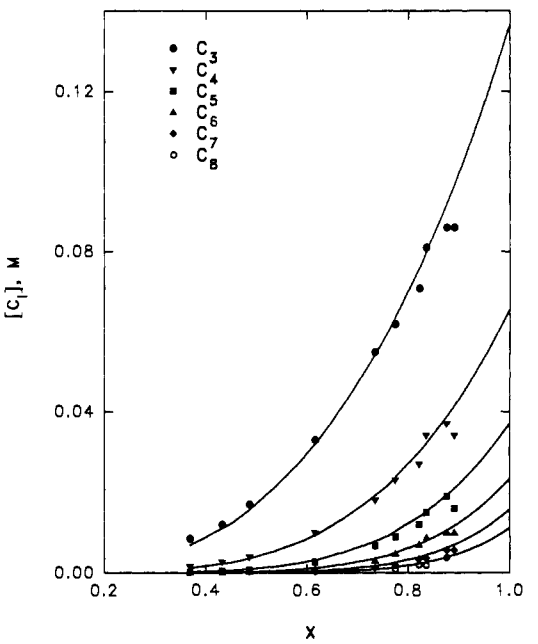


Figure 4. Plot of molar concentration of oligomeric polylactones as a function of reacted end groups in the acyclic fraction, x. The curves are calculated and the points are experimental.

Experimental Section

Materials and Instruments. β-Propiolactone (2-oxetanone) C_1 was a commercial sample (Fluka, puriss.) and was used without purification.

(18) Ito, K.; Hashizuka, Y.; Yamashita, Y. *Macromolecules* **1977**, *10*, 821–824.

(19) For a chain composed of single bonds only, the number r is $ni - 1$ where n is the ring size of the cyclic monomer. In the bifunctional precursors of C_i there are $i - 1$ OC–O bonds (the additional OC–O bond is formed during the process of ring closure) that cannot be considered as essentially single. Since it is known (Blom, C. E.; Gunthard, Hs. H. *Chem. Phys. Lett.* **1981**, *84*, 267) that the E form of methyl acetate is 8.5 kcal/mol higher in energy than the Z form, the OC–O bond is practically frozen and consequently does not significantly contribute to the entropy loss upon cyclization. Thus in the present case ($n = 4$) $r = 3i$.

2,2-Dibutyl-1,3,2-dioxastannolane was prepared according to a known procedure[20] and purified as described previously.[21] Dibutyltin dichloride (EGA Chemie) was used as received. Chlorotrimethylsilane (Carlo Erba RPE) was purified by distillation over quinoline. $CDCl_3$ (Merck, 99.8%) stored on Ag foil and activated 13X molecular sieves was used for NMR analysis. NMR spectra were obtained at 7.05 T. ^1H NMR data were acquired with digital resolution 0.001 ppm, PW < 30°, 3.8-s acquisition, 10-s repetition rate.

Oligomerization Procedure. Experiments were carried out in $CDCl_3$ in 10-mm NMR tubes, equipped with screw-cap tops, to be directly followed by NMR spectroscopy. Samples were prepared by adding into the tube the appropriate volume of a mother solution of DOS/DTC 0.05 M in $CDCl_3$ to the weighted amount of C_1. A mother solution of DOS/DTC was prepared by mixing equimolar amounts of 2,2-dibutyl-1,3,2-dioxastannolane and dibutyltin dichloride. Samples were allowed to react in a thermostatic bath at 70.0 °C for a time long enough to ensure complete consumption of starting material and equilibration of the mixture. This required 65–74 h for all the runs. Analytical concentrations were corrected to take into account the volume increase of the solvent at 70 °C. At complete equilibration, the reaction was quenched with the appropriate volume of a mother solution of Me_3SiCl 1.0 M in $CDCl_3$ and submitted to NMR analysis. Samples of the experiments at constant $[DOS/DTC]_0/[C_1]_0$ ratio were prepared dissolving in $CDCl_3$ the weighted reagents into 5-mm screw-capped NMR tubes. These mixtures were quenched by adding the stoichiometric amount relative to DOS/DTC of neat Me_3SiCl.

Analytical Methods. ^{13}C NMR analysis was conducted under broadband proton noise decoupling by integration of the resolved CH_2CO signals with respect to the total signal of all the β-propiolactone derivatives, providing the equilibrium concentration of each cyclooligomer. Depending on concentration, spectra were accumulated as much as to reach a S/N ratio sufficient for accurate integration. To ensure correct integration, T_1 values of the CH_2CO signals were measured and found to range between 0.5 s for the polymer and 1.1 s for the first cyclic oligomer (trimer) of the distribution. Spectra were thus acquired with a repetition rate of 6–10 s, a pulse angle of ca. 30°, and a digital resolution of 0.002 ppm. Equilibrium concentration of free DOS/DTC and end groups have been measured by integration of the corresponding CH_2O signals in the ^1H NMR spectra recorded after quenching at $\delta = 3.60$ (s) and $\delta = 3.80$ (app. t), respectively. Identification of cyclic oligomers up to the octamer has been done by FAB-MS spectrometry combined with ^{13}C NMR spectroscopy and has been described elsewhere.[2b]

Computational Procedure. Equation 19 in the form $F(x) = 0$ can be solved, for $0 \le x \le 0.9999$, by the Newton–Raphson method.[22] A computer program has been written in which the input data are K_{inter}, the EM's of the strained rings, B, and $[M_1]_0$. Starting with a trial x value, the program iterates until x becomes constant within the desired accuracy (0.001%). Application of the Newton–Raphson method to eq 19 requires two series to be evaluated, namely $\sum i^{-3/2}x^i$ and $\sum i^{-1/2}x^i$. The program evaluates the two series simply summing up the appropriate number of terms, which increases on increasing x (10^3 terms for $0 \le x \le 0.9$; 10^4 terms for $0.9 < x \le 0.999$; 2×10^5 terms for $0.999 < x \le 0.9999$). Unfortunately since the latter of the two series diverges for x approaching 1,[15] the Newton–Raphson method cannot be extended to x values higher than 0.9999. For $0.9999 < x < 1$ we found it convenient to use an iterative method based on eq 28 which is a rearranged form of eq 19.

$$x = 1 - \sqrt{\frac{x/K_{inter}}{[M_1]_0 - \text{rings}}} \tag{28}$$

This method, which is safe only when $[M_1]_0 > [M_1]_0^*$, requires the evaluation of only the former series (6×10^6 terms for $0.9999 < x \le 1$). After having obtained the value of x, the program evaluates $[C_i]$ and $[M_i]$ up to the desired polymerization degree by eqs 10 and 12.

Nonlinear least squares calculations were carried out by the program SigmaPlot (v. 4.0) by Jandel Scientific.

(20) Considine, W. J. *J. Organomet. Chem.* **1966**, *5*, 263–266.
(21) For a general preparation and purification of dioxastannolanes, see: Luchinat, C.; Roelens, S. *J. Am. Chem. Soc.* **1986**, *108*, 4873–4878.
(22) Margenau, H.; Murphy, G. M. *The Mathematics of Physics and Chemistry*, 2nd ed.; Van Nostrand Company: Princeton, 1962; p 492.

Appendix 1

Here it is demonstrated that the fraction of reacted end groups in the acyclic part of the polymer coincides with x or, in other words, that eq 29 holds.

$$x = 1 - \frac{\sum_{i=1}^{\infty}[M_i]}{\sum_{i=1}^{\infty} i[M_i]} \tag{29}$$

Substituting eq 12 into eq 29, eq 30 is obtained.

$$x = 1 - \frac{\sum_{i=1}^{\infty} x^i}{\sum_{i=1}^{\infty} ix^i} \tag{30}$$

The two series appearing in eq 30 are convergent only when $0 \le x < 1$. In this interval of x, eqs 31 and 32 hold.[23]

$$\sum_{i=1}^{\infty} x^i = \frac{x}{1-x} \tag{31}$$

$$\sum_{i=1}^{\infty} ix^i = \frac{x}{(1-x)^2} \tag{32}$$

Substituting eqs 31 and 32 into eq 30, the thesis follows.

Appendix 2

Condensation of A–B. Let us consider the equilibration of a chain A–B undergoing a condensation reaction between the functional groups A and B with elimination of a molecule D. The intermolecular model reaction is defined as follows:

$$\text{-A} + \text{B-} \rightleftarrows \text{-C-} + \text{D} \tag{33a}$$

$$K_{inter} = \frac{[\text{-C-}][D]}{[\text{-A}][\text{B-}]} \tag{33b}$$

Since $K_{inter}/[D]$ coincides with the definition of K_{inter} given in the case of addition (eq 3b), eqs 12 and 19 can be adapted to the case of condensation simply by substituting $K_{inter}/[D]$ for K_{inter}. Let us indicate these new equations (not shown) as eq 12 bis and eq 19 bis, respectively.

Two typical cases must be considered, depending on the nature of the reactants. In the first case the reactants are the cyclic monomer C_1 and D, present at the initial concentration $[C_1]_0$ and $[D]_0$, respectively. Since the amount of D molecules which is consumed in the process of equilibration ($[D]_0 - [D]$) is equal to the amount of linear chains given by eq 34, it is easy to obtain eq 35. Equation 34 is obtained by considering eq 12 bis and eq 31.

$$\sum_{i=1}^{\infty}[M_i] = \frac{[D]_x}{K_{inter}(1-x)} \tag{34}$$

$$[D] = \frac{K_{inter}(1-x)}{K_{inter}(1-x)+x}[D]_0 \tag{35}$$

(23) Note that the left-hand sides of eqs 31 and 32 are the Maclaurin series expansion of the corresponding right-hand sides.

Substituting eq 35 for [D] in eq 19 bis, and considering that the mass balance is referred to $[C_1]_0$, one obtains eq 36.

$$[C_1]_0 = \sum_{i=1}^{r-1} iEM_i x^i + B\sum_{i=r}^{\infty} i^{-3/2}x^i + \frac{x[D]_0}{K_{inter}(1-x)^2 + x(1-x)} \quad (36)$$

In the second case the reactant is the acyclic monomer M_1. This situation is equivalent to that of the first case in which $[C_1]_0 = [D]_0$. Therefore eq 36 is modified by substituting $[M_1]_0$ for both $[C_1]_0$ and $[D]_0$.

Addition of A–A. Here the treatment for the equilibration of a symmetrical monomer A–A is considered. A choice must be made between the three equilibria reported in eqs 37–39 as the intermolecular model reaction.

$$R\text{–}A + A\text{–}R \rightleftarrows R\text{–}AA\text{–}R \quad (37)$$

$$R\text{–}A + A\text{–}R' \rightleftarrows R\text{–}AA\text{–}R' \quad (38)$$

$$A\text{–}A + A\text{–}A \rightleftarrows A\text{–}AA\text{–}A \quad (39)$$

While eqs 37 and 38 refer to reactions between monofunctional reactants whose nonreacting part structures are equal or different, respectively, eq 39 refers to a reaction between bifunctional reactants. The constants for the equilibria 37–39, because of the different symmetry numbers of the species involved, are in the ratio 0.5:1:2. Choosing the constant of eq 39 as K_{inter}, eqs 10, 12, and 19 remain unaltered, the only difference is that the EM of a given ring (and hence B in eq 16) is just half of that of a ring of the same size obtained from A–B. This depends on the different symmetry numbers involved in the corresponding intermolecular reference reactions. This choice has the further advantage of maintaining the equality between EM_i and K_i (see eq 14).

The choice of either eq 37 or eq 38 as the reference reaction involves a different value of the EM's (eq 1) and the introduction of a constant factor in the definition of x, as well as in the right-hand sides of eqs 10, 12, and 19.

Addition of A–A + B–B. Here the treatment for the equilibration of an equimolar mixture of two symmetrical monomers, A–A and B–B is considered.

Let us indicate with M_i^A, M_i^B, and M_i the acyclic oligomers A–(AB–BA–)$_{i-1}$A, B–(BA–AB–)$_{i-1}$B, and A–A(B–BA–A)$_{i-1}$B–B, respectively, and with C_i the cyclic oligomers.

While in the case A–B the symmetry number of C_i is i, in the present case it is $2i$. Therefore the EM of a given ring (and hence the B value in eq 16) is just half of that of a ring of the same size prepared by the A–B reaction.

The distribution of M_i and C_i is still given by eqs 10 and 12. The distribution of M_i^A ($=M_i^B$) is easily obtained considering the equilibrium represented in eq 40a whose constant is equal to $4K_{inter}$ (consider that the symmetry number of both M_i^A and M_i^B is 2).

$$M_i^A + M_i^B \rightleftarrows M_{2i-1} \quad (40a)$$

$$4K_{inter} = \frac{[M_{2i-1}]}{[M_i^A][M_i^B]} \quad (40b)$$

Considering that $[M_i^A] = [M_i^B]$, and taking into account eq 12, eq 40b becomes

$$[M_i^A] = \frac{x^{i-0.5}}{2K_{inter}} \quad (41)$$

Combining eqs 10, 12, 16, 31, 32, and 41, the mass balance equation takes the form of eq 42.

$$[M_1^A]_0 = \sum_{i=1}^{r-1} iEM_i x^i + B\sum_{i=r}^{\infty} i^{-3/2}x^i + \frac{\sqrt{x}}{2K_{inter}(1-\sqrt{x})^2} \quad (42)$$

It can be easily demonstrated that the fraction of reacted end groups in the acyclic part of the polymer in this case does not coincide with x but with $\sqrt{x}$.

Acknowledgment. The authors are grateful to MURST for financial support of the part of work carried out in Rome.