Macrocyclization under Kinetic Control. A Theoretical Study and Its Application to the Synthesis of Macrocyclic Poly(thiolactones)[1]

Antonella Dalla Cort,*,† Gianfranco Ercolani,*,‡ Anna Laura Iamiceli,† Luigi Mandolini,*,† and Paolo Mencarelli*,†

Contribution from Centro CNR di Studio sui Meccanismi di Reazione and Dipartimento di Chimica, Università La Sapienza, I-00185 Roma, Italy, and Istituto di Chimica Agraria, Università di Catania, Via Valdisavoia 5, I-95123 Catania, Italy

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Abstract: A kinetic model for macrocyclization reactions of bifunctional chains undergoing simple and double ring closure reactions has been proposed. Numerical integration of the proper set of differential rate equations allows yields and distributions of cyclic oligomers to be calculated as a function of initial concentrations of reactants and effective molarities (EM_i) of the rings being formed. In terms of computer time the present model is less demanding than analogous models previously published, in that a high degree of accuracy is obtained without taking into account explicitly linear oligomers with high polymerization degree. The model has been successfully applied to the synthesis of macrocyclic poly(thiolactones) via irreversible reaction of 2,2-dibutyl-1,2,3-dithiastannolane with glutaryl and pimeloyl chlorides. The best fits of the experimental oligomer distributions to the general equations gave the effective molarities from monomer to tetramer in both series.

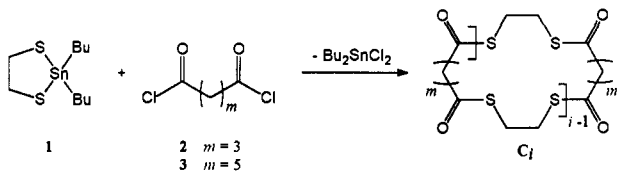
Introduction

The synthesis of macrocycles from acyclic precursors has gained enormous importance over the years,[2] especially by virtue of the development of supramolecular chemistry, in which macrocycles play a central role.[3] This calls for a deeper understanding of the physicochemical aspects involved in macrocyclization processes.

We have recently reported a general treatment of macrocyclization reactions occurring under thermodynamic control,[4] and, for a number of years, we[5] and others[6] have been trying to improve the theoretical modeling of irreversible macrocyclizations.

It has long been recognized that the fundamental physicochemical parameter characterizing intramolecular processes is the effective molarity (EM).[7] A good model would allow not only the prediction of yield distributions of cyclic oligomers when their EMs are known but also the solution of the converse problem, i.e., the recovery of reliable EM values from experimental ring distributions. In spite of longstanding efforts,[6a,b] there has been, up to now, only limited success in the area of macrocyclization reactions occurring under kinetic control. A major reason for this, besides the difficulties in modeling the irreversible macrocyclization, is the paucity of systematic investigations of the effect of reactant concentration on the yield distribution of cyclic oligomers.

Scheme 1



1 2 $m = 3$ 3 $m = 5$ C_i

Here we report a general treatment of macrocyclization reactions occurring under kinetic control that considerably improves upon the treatments previously reported, and that we consider as the culmination of our efforts in this field. In order to apply the theoretical treatment to a real system, we have investigated the irreversible formation of macrocyclic poly(thiolactones) via reaction of 2,2-dibutyl-1,3,2-dithiastannolane (**1**) with glutaryl chloride (**2**) and pimeloyl chloride (**3**), in refluxing $CHCl_3$ (Scheme 1). The virtual absence of undesired byproducts renders this reaction ideally suited for a proper comparison of theory and experiment.

Kinetic Treatment of Irreversible Macrocyclization

Consider a system composed of identical bifunctional chain molecules A–B in which each of the two different end-groups is capable of reacting irreversibly with the other only. We assume, as usual, that the inherent reactivity (k_{inter}) of the functional groups is independent of the size of the molecule to which they are attached. In such a system a formidable competition between inter- and intramolecular processes takes place which leads to a complex reaction mixture. In the absence of side reactions (solvolysis, oxidation, etc.) which may lead to stoichiometric imbalance of the reacting groups as the reaction proceeds, and of complicating phenomena such as precipitation of linear oligomers in the time course of the reaction, *the mixture is eventually composed of cyclic oligomers only*, whose distribution

† Università di Roma.
‡ Università di Catania.
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(1) Part of the results of this work have been the object of a preliminary communication: Dalla Cort, A.; Ercolani, G.; Mandolini, L.; Mencarelli, P. *J. Chem. Soc., Chem. Commun.* **1993**, 538–540.

(2) (a) Rossa, L.; Vögtle, F. *Top. Curr. Chem.* **1983**, *113*, 1–86. (b) Knops, P.; Serdhoff, N.; Mekelburger, H. B.; Vögtle, F. *Top. Curr. Chem.* **1992**, *161*, 1–36. (c) Dietrich, B.; Viout, P.; Lehn, J.-M. *Macrocyclic Chemistry*; VCH: Weinheim, 1992.

(3) (a) Vögtle, F. *Supramolecular Chemistry*; Wiley & Sons: Chichester, 1991. (b) *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Durr, H., Eds.; VCH: Weinheim, 1991.

(4) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. *J. Am. Chem. Soc.* **1993**, *115*, 3901–3908.

(5) (a) Galli, C.; Mandolini, L. *Gazz. Chim. Ital.* **1975**, *105*, 367–376. (b) Ercolani, G.; Mandolini, L.; Mencarelli, P. *Macromolecules* **1988**, *21*, 1241–1246. (c) Ercolani, G.; Mandolini, L.; Mencarelli, P. *Gazz. Chim. Ital.* **1989**, *119*, 209–214. (d) Ercolani, G.; Mencarelli, P. *J. Chem. Soc., Perkin Trans. 2* **1989**, 187–191. (e) Ercolani, G.; Mandolini, L.; Mencarelli, P. *J. Chem. Soc., Perkin Trans. 2* **1990**, 747–752.

(6) (a) Stoll, M.; Rouvé, A.; Stoll-Comte, G. *Helv. Chim. Acta* **1934**, *17*, 1289–1308. (b) Morawetz, H.; Goodman, N. *Macromolecules* **1970**, *3*, 699–700. (c) Gordon, M.; Temple, W. B. *Makromol. Chem.* **1972**, *152*, 277–289. (d) Szwarc, M. *Makromol. Chem.* **1989**, *190*, 567–576. (e) Fastrez, J. *J. Phys. Chem.* **1989**, *93*, 2635–2642.

(7) (a) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183–278. (b) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1–111.

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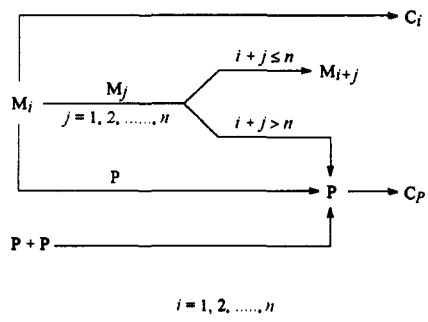
Scheme 2



solely depends on dilution and on the effective molarities of the various acyclic i-mers (EM_i).[8] Clearly, such an ideal behavior is more likely approached by well-behaved real systems in the dilute solutions (0.001–0.1 M) used in the practice of macrocycle synthesis than in the highly concentrated media used in polymerization processes.

A rigorous kinetic treatment for the reaction of a monomer A–B would result in an infinite set of simultaneous differential equations, one for each oligomeric species involved, not amenable to analytical solution. Truncation of this infinite system allows an approximate numerical solution which may be improved as much as desired, just by increasing the number of equations.[5b] However, since the number of equations to take into account dramatically increases on increasing the initial monomer concentration, this approach is computationally demanding to such an extent that its application to even moderately concentrated monomer solutions is not practicable, especially for the evaluation of EMs from experimental ring distributions.

To overcome these difficulties we have previously proposed two complementary truncation modes which have been dubbed the overestimating and underestimating models, respectively.[5d] The two models owe their names to the fact that they provide, respectively, an overestimate and an underestimate of the yields of the cyclic oligomers. In these models, the reactions of the lower linear oligomers up to a prefixed polymerization degree are explicitly taken into account whereas the higher linear oligomers are represented as a whole by an undefined linear polymer P. The two models differ in the behavior which is assumed for P. In the overestimating model P is assumed to undergo only intramolecular cyclization, whereas in the underestimating model P undergoes only intermolecular reactions. Of course these are extreme behaviors; in fact P undergoes simultaneous intra- and intermolecular reactions. A more realistic modeling of the behavior of P would certainly provide a better estimate of the yield distribution of the various cyclic oligomers. Pursuing this goal we arrived at the formulation of the following kinetic model.

Consider the reaction system outlined in Scheme 2, where M_i and C_i represent the acyclic and cyclic i-mers, respectively, P and C_P represent the acyclic and cyclic polymer, respectively, and n is the maximum degree of polymerization explicitly accounted for by the scheme itself. Any reaction between M_i and M_j leads to a linear oligomer M_{i+j} if $i + j \le n$ or to the linear polymer P if $i + j > n$. If follows that $[P] = \sum_{i>n}[M_i]$. The model differs from the previously proposed underestimating model for taking into account the possibility that P cyclizes to yield C_P. Accordingly, the set of differential rate equations pertinent to the underestimating model needs to be modified as follows:

$$d[C_i]/dt' = EM_i[M_i] \qquad i = 1, 2, \ldots, n \qquad (1)$$

$$d[C_P]/dt' = EM_P[P] \qquad (2)$$

$$d[M_i]/dt' = -EM_i[M_i] + \sum_{j=1}^{i-1}[M_j][M_{i-j}] - 2[M_i]\sum_{j=1}^{n}[M_j] - 2[M_i][P] \qquad i = 1, 2, \ldots, n \qquad (3)$$

$$d[P]/dt' = -EM_P[P] + \sum_{i=1}^{n}\sum_{j=n-i+1}^{n}[M_i][M_j] - [P]^2 \qquad (4)$$

the modifications consisting in the addition of eq 2 and of the first term in the right-hand side of eq 4. Note that, for the sake of convenience, the time scale of the set has been adjusted (t'), as usual,[5d] so that k_{inter} and $k_{(intra)i}$ are numerically equal to 1 and EM_i, respectively. This, of course, has no effect on the final ring distribution. In formulating the above rate equations, allowance has been made for the following facts: (i) two molecules of M_i disappear upon $M_i + M_i$ dimerization; (ii) the reactions $M_i + M_j$ with $i \neq j$ and the reactions $M_i + P$ are statistically twice as likely as the reactions $M_i + M_j$ with $i = j$ and the reaction P + P.[5b]

The quantity EM_P is the number average effective molarity of the linear polymer P. According to Kuhn's statistical treatment of chain molecules,[9,10] the EMs for cyclization of oligomeric chains obeying Gaussian statistics and leading to strainless cyclic i-mers are proportional to $i^{-3/2}$.[11] Assuming that the oligomers constituting P show this behavior, one can estimate EM_P by eq 5, where p is the number average polymerization degree of P and A is a constant that coincides with the actual EM_1 value if M_1 is long enough to follow ideal behavior. Clearly, p is not a constant

$$EM_P = Ap^{-3/2} \qquad (5)$$

but a variable quantity that increases on increasing the progress of the reaction. By definition p is given by eq 6, where $[P_w]$ ($=\sum_{i>n} i[M_i]$) is the weighted concentration of P in terms of monomer units. The instantaneous value of $[P_w]$ can be obtained

$$p = \frac{[P_w]}{[P]} \qquad (6)$$

by adding eq 7 to the set of equations 1–4. Equation 7 is obtained

$$d[P_w]/dt' = -pEM_P[P] + \sum_{i=1}^{n}\sum_{j=n-i+1}^{n}(i+j)[M_i][M_j] + 2[P]\sum_{i=1}^{n} i[M_i] \qquad (7)$$

by just taking into account the weight, in terms of monomer units, of all the processes that lead to the formation or to the consumption of P. Thus, the weight is p for the process $P \rightarrow C_P$, $i + j$ for $M_i + M_j \rightarrow P$, and zero for $P + P \rightarrow P$.

Numerical integration of the set of equations 1–4 and 7, taking into account eq 5 and 6, allows the evaluation of the distribution of cyclic oligomers in a given experiment. In order to illustrate the performance of the present model, consider the case of a bifunctional chain M_1 leading to a monomeric ring C_1 with, say, 15 ring atoms, so that C_2 is 30-membered, C_3 45-membered, and so on. While all of the rings from C_2 onward can be considered as virtually strainless and their EMs solely determined by the conformational entropy change upon cyclization, C_1 can still have a certain strain energy. From the available compilation of averaged entropy data for cyclization (listed in Table 19 of ref

(8) The EM of a given bifunctional chain is defined as the ratio k_{intra}/k_{inter} where k_{intra} is the specific rate of cyclization.[7]

(9) Kuhn, W. *Kolloid–Z.* **1934**, *68*, 2–15.

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

(11) In general, these conditions are fulfilled by sufficiently long chains with, say, more than 25–30 skeletal bonds. Note that in the original Kuhn treatment the EM is denoted by the symbol C_{eff} (effective concentration).

Table 1. Percent Yields of C_1–C_5 for a Batchwise Reaction of a Bifunctional Chain Monomer[a]

	exact values	$n = 1$	$n = 2$	$n = 3$	$n = 4$	$n = 5$
C_1	15.7	15.4 (21.4–13.1)	15.6 (18.5–14.5)	15.6 (17.4–15.0)	15.7 (16.8–15.3)	15.7 (16.4–15.5)
C_2	28.2		28.1 (33.9–26.8)	28.2 (31.0–27.7)	28.2 (29.7–28.0)	28.2 (29.1–28.1)
C_3	13.6			13.6 (16.0–13.0)	13.6 (14.9–13.3)	13.6 (14.4–13.5)
C_4	8.6				8.6 (10.1–8.2)	8.6 (9.6–8.4)
C_5	6.0					6.0 (7.1–5.7)

[a] See text for details.

7b), the entropy-controlled EM for closure of a chain composed of 29 single bonds is 0.040 M. This corresponds to an A value of 0.113 M ($=0.040 \times 2^{3/2}$) which can be used to evaluate all the EM_i values with $i > 1$. For C_1 the typical EM value of 0.010 M is assumed.[7b] Computational results for a batchwise experiment with initial monomer concentration of 6×10^{-2} M are reported in Table 1. In the first column of Table 1 are reported the exact values of the yields of C_1–C_5 obtained by an exhaustive kinetic model in which more than 99% of the starting material is transformed in cyclic oligomers. This required explicit consideration of all the oligomers up to a polymerization degree of 50. In the successive columns are reported the yields obtained by the present model and, in parentheses, those obtained by the overestimating and underestimating models, respectively, for a number of n values. As it can be seen, the values obtained by the model outlined in Scheme 1 are virtually exact even for $n = 1$. It should be remarked that, in contrast with the previous models whose predictive power increases on increasing n, with the present model there is no need to increase the value of n, unless one is interested in the yields of the successive cyclic oligomers.

We report, in the supplementary material, the extension of the above treatment to the double ring closure of two symmetrical bifunctional monomers A–A and B–B and, in the following section, an experimental study of a case of double ring closure of two symmetrical monomers leading to poly(thiolactones) along with the application of the corresponding kinetic model to extract EMs from the experimental ring distributions.

Application of the Treatment to the Synthesis of Poly(thiolactones)

We have recently reported an improved procedure for the synthesis of macrocyclic poly(thiolactones) *via* reaction of 2,2-dibutyl-1,3,2-dithiastannolane (**1**) with diacyl chlorides.[12] The irreversible nature of the reaction, previously pointed out by Shanzer and Libman,[13] was fully confirmed by our recent studies on the dramatic effect of the reactant mixing technique on the final ring distribution.[12] We now report a careful scrutiny of product distributions in the reactions of **1** with glutaryl chloride (**2**) and pimeloyl chloride (**3**), respectively (Scheme 1), carried out in boiling $CHCl_3$ under batchwise conditions over a wide range of initial reactant concentrations. HPLC analysis of the reaction mixtures revealed the cyclic oligomers C_i in the range $1 \leq i \leq 7$. Figure 1 shows a typical HPLC chromatogram (UV detector, $\lambda = 230$ nm) of the reaction mixture obtained from a batchwise experiment with equal initial concentrations of **1** and **3** (0.050 M). Column chromatography of the product mixtures led to the isolation of the first three oligomers in each series. In order to calibrate the HPLC traces, the molar absorptivities ϵ_i of the above oligomers were determined in CH_3CN (Table 2). A marked hypochromic effect is apparent in the 9- and 11-membered monomeric rings (C_1, $m = 3$ and $m = 5$, respectively), most likely arising from severe limitations imposed by the medium ring geometries to planarity of the structural unit $-CH_2COSCH_2-$, which is required for the most effective conjugation of the sulfur atom with the carbonyl chromophore.

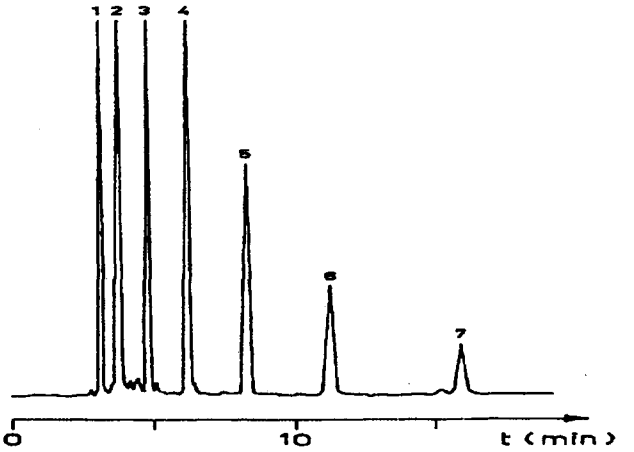


Figure 1. Typical HPLC chromatogram of the reaction mixture obtained in a batch experiment where $[1]_0 = [3]_0 = 0.050$ mol dm^{-3}. The number on each peak indicates the degree of polymerization of the corresponding cyclic oligomer C_i, $m = 5$.

Table 2. Molar Absorptivities of Cyclic Oligomers C_i in CH_3CN, $\lambda = 230$ nm

cyclic oligomers (C_i)	i	$10^{-3}\epsilon_i$	$10^{-3}\epsilon_i/i$
thioglutarates ($m = 3$)	1	2.70	2.70
	2	12.55	6.27
	3	18.40	6.13
thiopimelates ($m = 5$)	1	4.51	4.51
	2	13.13	6.56
	3	20.04	6.68

This hypochromic effect totally disappears in the higher oligomers, as shown by the fact that the molar absorptivities calculated on a monomer unit basis (ϵ_i/i) are virtually independent of i, which means that the individual chromophores in the dimeric and trimeric rings bear contributions to the total absorption which are practically independent of the size of the ring. This observation has important consequences. It provides a sound basis to the assumption that the same ϵ_i/i values determined for the cyclic trimers apply as well to the more elusive higher oligomers. Furthermore, it strongly supports the view that the 18- and 22-membered cyclic dimers (C_2, $m = 3$ and $m = 5$, respectively) are virtually strainless. This is most likely due to the presence of bare sulfur atoms and trigonal carbons, which are expected to relieve considerably the eclipsing and transannular interactions that are major sources of strain in medium rings and still appreciable in the smaller large rings.[7b,14]

Absolute yields of cyclic oligomers, obtained from a comparison of the calibrated HPLC peak intensities with an internal standard, are given in Tables 3 and 4 and graphically shown in Figure 2 and 3. Consistent with expectations, increasing dilution causes a composition shift toward the smallest oligomers. The total yields of cycles with polymerization degree up to 7, reported in the last column of Tables 3 and 4, account for most of the starting materials in the diluted experiments, but not in the concentrated ones. We believe that what is missing is essentially constituted

(12) Dalla Cort, A.; Mandolini, L.; Roelens, S. *J. Org. Chem.* **1992**, *57*, 766–768.

(13) Shanzer, A.; Libman, J. *Synthesis* **1984**, 140–141.

(14) (a) Sicher, J. *Prog. Stereochem.* **1962**, *3*, 202–263. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A*, 3rd ed.; Plenum Press: New York, 1990; Chapter 3.

Table 3. Experimental and Calculated Distributions of Oligomeric Thiolactones C_i in the Reaction of 2,2-Dibutyl-1,3,2-dithiastannolane (**1**) with Glutaryl Chloride (**2**)[a,b]

$[1]_0 = [2]_0$ mol dm^{-3}	% C_1	% C_2	% C_3	% C_4	$\sum_{i=1}^{7}$ % C_i
0.005[c]	20 (20)	44 (48)	20 (20)	7 (7)	93
0.010[d]	10 (12)	46 (47)	23 (23)	10 (10)	97
0.050[e]	4 (3)	35 (34)	19 (19)	12 (12)	86

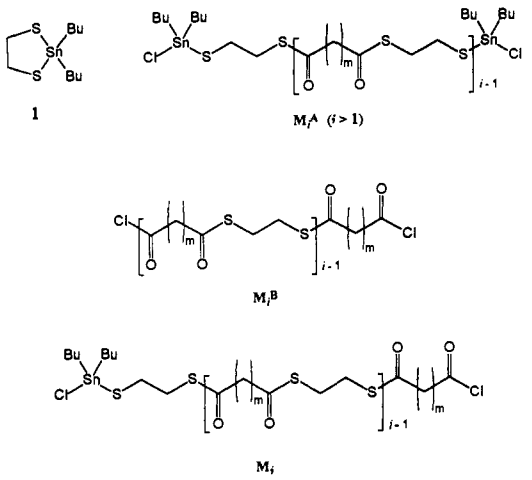
[a] Reactions carried out under batchwise conditions in refluxing $CHCl_3$. [b] Values in parentheses refer to calculated yields. [c] C_5 (2%) was also detected in the HPLC trace. [d] C_5 (6%) and C_6 (2%) were also detected in the HPLC trace. [e] C_5 (9%), C_6 (5%), and C_7 (2%) were also detected in the HPLC trace.

Table 4. Experimental and Calculated Distributions of Oligomeric Thiolactones C_i in the Reaction of 2,2-Dibutyl-1,3,2-dithiastannolane (**1**) with Pimeloyl Chloride (**3**)[a-c]

$[1]_0 = [3]_0$ mol dm^{-3}	% C_1	% C_2	% C_3	% C_4	$\sum_{i=1}^{7}$ % C_i
0.001	91 (88)	8 (10)	-(<1)	-(<1)	99
0.005	65 (62)	28 (28)	6 (7)	2 (2)	101
0.010[d]	42 (46)	34 (34)	13 (11)	6 (4)	99
0.050[e]	14 (15)	26 (26)	12 (12)	6 (7)	68

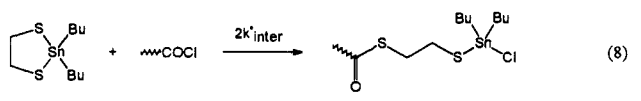
[a] Reactions carried out under batchwise conditions in refluxing $CHCl_3$. [b] Values in parentheses refer to calculated yields. [c] The calculated yields here reported are slightly different from those reported in ref 1. The differences arises from the fact that a less rigorous optimization procedure was adopted in the previous paper. [d] C_5 (3%) and C_6 (1%) were also detected in the HPLC trace. [e] C_5 (5%), C_6 (3%), and C_7 (2%) were also detected in the HPLC trace.

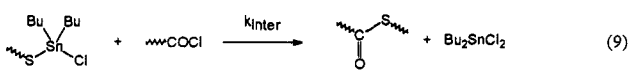
Chart 1



of cyclic oligomers with $i \geq 8$, as no trace of acyclic material was found in the ^{1}H NMR spectra.

It has been suggested that reaction of **1** with COCl groups affords species with a $SSnBu_2Cl$ end-group (eq 8) which is capable of further reacting with a COCl function (eq 9).[12] It appears





therefore that, in the case of the reactions reported in Scheme 1, the reactive species present in solution are those depicted in Chart 1, namely, **1** and linear oligomers having as terminal groups two $SSnBu_2Cl$ functions (M_i^A with $i > 1$), two COCl functions (M_i^B), and one $SSnBu_2Cl$ plus one COCl function (M_i). Among these only the oligomers M_i undergo cyclization to C_i. It should

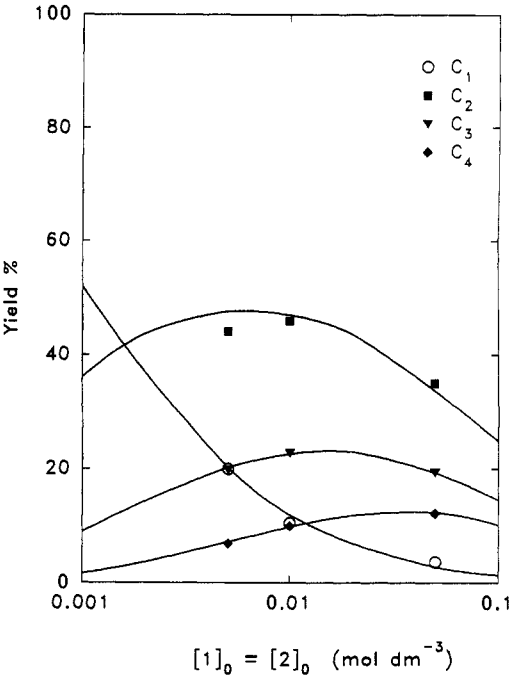


Figure 2. Oligomer distributions of cyclic thioglutarates C_i, $m = 3$, as a function of initial reactant concentrations. The points are experimental (Table 3), and the curves are calculated (see text).

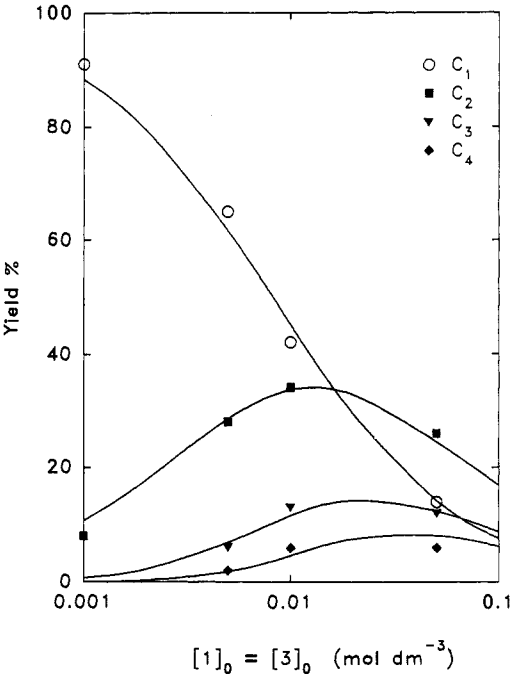


Figure 3. Oligomer distributions of cyclic thiopimelates C_i, $m = 5$, as a function of initial reactant concentrations. The points are experimental (Table 4), and the curves are calculated (see text).

be noted that apart from **1**, which is "anomalous" in that its structure is different from that of M_i^A with $i = 1$, the linear oligomers in Chart 1 are those of a typical A–A + B–B reaction. Therefore, in addition to the rate constant k_{inter}, which refers to the general reaction between $SSnBu_2Cl$ and COCl end-groups (eq 9), the rate constant $2k'_{inter}$ for the reaction of **1** with COCl end-groups (eq 8) should be considered. Here the coefficient 2 is clearly a statistical factor that accounts for the presence in **1** of two equivalent sulfur atoms.

In order to adapt to the present reaction the set of rate equations pertinent to the case A–A + B–B (supplementary material) it is only necessary to multiply the concentration of M_1^A by the ratio k'_{inter}/k_{inter}. This ratio was evaluated as 0.068 by an independent

Table 5. Calculated Effective Molarities[a] of C_1–C_4 for the reactions of **1** with the Diacyl Chlorides **2** and **3**

diacyl chloride	EM_1	EM_2	EM_3	EM_4
2	$2.04 \pm 0.17 \times 10^{-3}$	$1.17 \pm 0.13 \times 10^{-1}$	$6.8 \pm 1.7 \times 10^{-2}$	$5.6 \pm 3.0 \times 10^{-2}$
3	$1.65 \pm 0.08 \times 10^{-2}$	$6.8 \pm 1.0 \times 10^{-2}$	$3.00 \pm 0.95 \times 10^{-2}$	$1.35 \pm 0.68 \times 10^{-2}$

[a] In moles/liter.

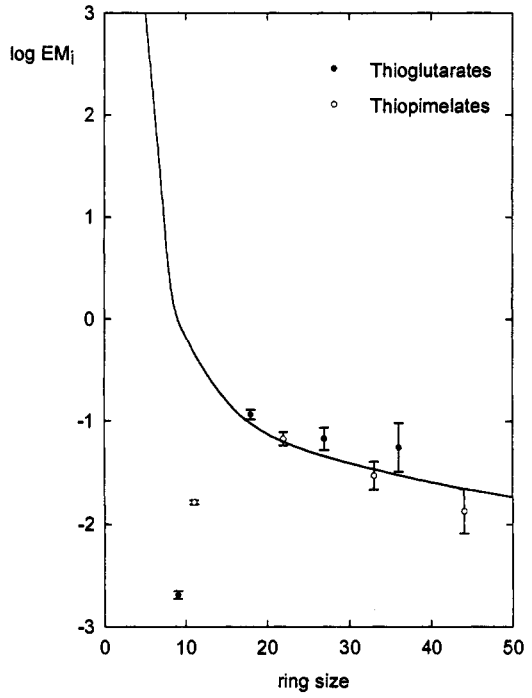


Figure 4. Idealized EM profile for cyclizations leading to strainless rings. The curve is from ref 7b, and the points are from Table 5.

experiment based on the reaction of **1** with propanoyl chloride as model compound (Appendix).[15] The modified set of rate equations indicates that the final ring distribution is a function of the initial concentration of the reactants, of the ratio k'_{inter}/ki_{nter}, of the EM_i values, and of the constant A. It is convenient, for reasons that will be clear later, to lock the value of the constant A to the EM of the first ring which is presumed to be strain-free. Since in both the reactions with **2** and **3** this is the cyclic dimer, we assumed $A = EM_2(2)^{3/2}$.

A nonlinear least-squares procedure based on numerical integration of the modified set of rate equations was carried out with $n = 4$. The input data were the initial reactant concentrations, the k'_{inter}/k_{inter} ratio, and the experimental yields of cyclic oligomers C_i with i from 1 to 4. The EMs were treated as adjustable parameters to improve the fit of calculated to experimental yields. In Table 5 are reported the optimized value of the EMs along with their standard deviations for the reactions of **1** with the diacyl chlorides **2** and **3**. In Tables 3 and 4 are listed the calculated yields of cyclic oligomers, and in Figure 2 and 3 are shown, as solid lines, the calculated ring distributions. The good agreement between calculated and experimental yields confirms the reliability of our kinetic model as well as of the computational procedure.

The log EM_i values with their error bars are reported against ring size in Figure 4 (for the meaning of the curve, see below). It is apparent that the relative error[16] of EM_i increases on increasing i. As it has been already pointed out, the yield of a cyclic oligomer depends strongly on its EM and on the EMs of the lower oligomers but only slightly on the EMs of the higher oligomers.[5c] In the converse problem a symmetrical situation is found, in that the calculated EM of a given ring depends strongly on its yield and on the yields of the lower oligomers but only slightly on the yields of the higher oligomers. It follows that the error of a certain EM_i will mainly depend on the errors associated with the ring yields from C_1 to C_i and, consequently, the precision of EM_i will be higher the lower the i value. This sets a limit to the scope of the present method in that EMs of adequate precision can be obtained for the lower cyclic oligomers only and explains why the computational procedure has been truncated at $i = 4$, with the exclusion of the next higher oligomers, which were clearly detected in the HPLC traces (Tables 3 and 4 and Figure 1). The choice of locking the value of the constant A to the EM of the smallest strainless ring is justified by the fact that this value is expected to be the most precise.

Comparison of the EM data for the formation of macrocyclic poly(thiolactones) with the idealized EM profile for closure of strainless rings, plotted as a line in Figure 4, provides an independent check of the reliability of the EM values derived from yield data, along with a deeper insight into the role of ring strain on the ease of cyclization. To illustrate the meaning of the idealized EM profile, reference is made to eq 10 which is easily

$$EM = \exp\left(-\frac{\Delta H^{\ddagger}_{intra} - \Delta H^{\ddagger}_{inter}}{RT}\right) \exp\left(\frac{\Delta S^{\ddagger}_{intra} - \Delta S^{\ddagger}_{inter}}{R}\right) \quad (10)$$

derived by applying transition-state theory to both intra- and intermolecular reactions.[7b] The second exponential in the right-hand term of eq 10 is the entropy component of the EM, whereas the quantity $\Delta H^{\ddagger}_{intra} - \Delta H^{\ddagger}_{inter}$ in the first exponential may be defined as the strain energy of the ring-shaped transition state. When strainless rings are formed, i.e., when $\Delta H^{\ddagger}_{intra} - \Delta H^{\ddagger}_{inter} = 0$, eq 10 reduces to the simple form of eq 11.

$$EM = \exp\left(\frac{\Delta S^{\ddagger}_{intra} - \Delta S^{\ddagger}_{inter}}{R}\right) \quad (11)$$

The idealized EM profile in Figure 4 was constructed by means of eq 11 and the entropy data, taken from the compilation reported by one of us (Table 19 of ref 7b), which was obtained by averaging and smoothing a large number of experimental entropy data related to several cyclization reaction series. If one considers that an uncertainty of ±2 eu in the above entropy differences corresponds to an uncertainty of about ±0.4 in the calculated log EM, it is seen that the adherence of the EM values obtained for the dimeric, trimeric, and tetrameric poly(thiolactones) to the idealized profile is virtually perfect. This finding is clearly consistent with the view that the transition states leading to the above rings are strainless or very nearly so.

On the other hand, the marked downward deviations found for the 9- and 11-membered monomeric rings are clearly too large to be ascribed to experimental uncertainties. The EMs for closure to the 9- and 11-membered rings are 500 and 28.5 times, respectively, smaller than predicted for strainless rings. These figures can be translated by means of eq 10 into ring strain energies of 4.2 and 2.3 kcal/mol, respectively, which appear quite reasonable values for medium ring transition states.[7b]

Conclusions

A mathematical model has been worked out which can serve the purpose of calculating with high accuracy yields and

(15) Calculated yields turn out to be little sensitive to the value of the k'_{inter}/k_{inter} ratio. For example, when the value of the k'_{inter}/k_{inter} ratio was doubled, calculated percent yields of cyclics were found to be reproducible within ±0.2 on the average. Similar results were obtained when the k'_{inter}/k_{inter} ratio was halved.

(16) From the law of error propagation $\sigma_{log(EM)} = 0.434\sigma_{EM}/EM$.

distributions of cyclic oligomers to be obtained in simple and double ring closure reactions of bifunctional chains under kinetic control as a function of initial concentrations and effective molarities of the rings being formed. Even more importantly, the model can be used to obtain sets of effective molarities as best fit parameters from analysis of precise yield data of oligomers formed in well-behaved macrocyclization reactions. Effective molarities for kinetically controlled ring closure reactions have been classically obtained by direct measurements of rates of cyclization of bifunctional chains and the corresponding non-cyclization reactions.[7] There are cases, however, where determination of effective molarities based on direct kinetic measurements is not possible. Examples of reactions of this kind are provided by the syntheses of macrocyclic poly(thiolactones) described in this work, where the bifunctional chains undergoing cyclization are reactive intermediates and, as such, not amenable to direct kinetic investigation. It appears therefore that the method based on analysis of cyclic oligomer distributions complements the method based on direct kinetic measurements, thus increasing considerably the number of cyclization reactions for which effective molarities can be measured.

Experimental Section

Instruments and Techniques. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian XL-300 spectrometer and are reported in ppm *vs* TMS as δ values. Positive FAB-MS spectra were obtained on a Kratos MS 80 spectrometer. UV spectra were measured from solutions in CH_3CN on a Cary Model 219 spectrophotometer. Melting points were determined on a Büchi 510 apparatus and are uncorrected. GLC analyses were performed on a HP Model 5890 A instrument fitted with a OV 17 column (3% phenylsilicone). GLC–MS analyses were carried out on a HP 5890 gas chromatograph equipped with a 12 m × 0.25 mm silica capillary column with methyl silicon gum and coupled with a HP 5970 MSD. HPLC analyses were performed on a HP 1050 instrument with an UV spectrophotometric detector. The wavelength used for the analyses was 230 nm. The column was a Supelcosil LC-18 DB (25 cm × 4.66 mm), and the eluant was CH_3CN. Retention times and peak areas were measured on a HP recorder.

Materials. 2,2-Dibutyl-1,3,2-dithiastannolane (**1**) was available from previous work.[12] Reagent-grade samples of acyl chlorides were distilled before use.

Cyclic Oligomers C_i (i = 1, 2, and 3; m = 3 and 5). Macrocyclization reactions of **1** with diacyl chlorides **2** and **3** were carried out on a 3-mmol scale as described previously.[12] The macrocycles were isolated from the complex reaction mixtures using column chromatography on silica gel with toluene containing increasing amounts of ethyl acetate from 0 to 20%. The cyclic trimers were not obtained in a pure form, but were contaminated by minor amounts of the corresponding dimers in both cases, as shown by HPLC. Since the molar absorptivities of the dimers were known (Table 2), the molar absorptivities of the trimers could be easily calculated.

1,4-Dithiacyclononane-5,9-dione (C_1, m = 3): mp 98–99 °C; ^1H NMR δ 3.35 (s, 4H), 2.78 (m, 4H), 2.27 (m, 2H); ^{13}C NMR δ 200.36, 45.09, 34.60, 25.87; MS *m/e* 190 (M^+). Anal. Calcd for $C_7H_{10}O_2S_2$: C, 44.21; H, 5.22. Found: C, 43.60; H, 5.50.

1,4,10,13-Tetrathiacyclooctadecane-5,9,14,18-tetrone (C_2, m = 3): mp 142–143 °C (lit.[13] mp 140–145 °C).

1,4,10,13,19,22-Hexathiacycloheptacosane-5,9,14,18,23,27-hexone (C_3, m = 3): ^1H NMR δ 3.11 (s, 12H), 2.62 (t, J = 7 Hz, 12H), 2.02 (quintet, J = 7 Hz, 6H); ^{13}C NMR δ 197.83, 42.45, 28.90, 21.19.

1,4-Dithiacycloundecane-5,11-dione (C_1, m = 5): mp 79–80 °C (lit.[13] mp 75–78 °C).

1,4,12,15-Tetrathiacyclodocosane-5,11,16,22-tetrone (C_2, m = 5): mp 134–135 °C (lit.[13] mp 125–129 °C).

1,4,12,15,23,26-Hexathiacyclotritriacontane-5,11,16,22,27,33-hexone (C_3, m = 5): ^1H NMR δ 3.08 (s, 12H), 2.56 (t, J = 7 Hz, 12H), 1.68 (quintet, J = 7 Hz, 12H), 1.37 (m, 6H); ^{13}C NMR δ 198.58, 43.64, 28.87, 27.90, 25.17; FAB-MS *m/e* 655 $(M + 1)^+$.

4,7-Dithiadecane-3,8-dione (5). Propanoyl chloride (213 μL, 2.46 mmol) was added to a boiling solution of **1** (400 mg, 1.23 mmol) in ethanol-free $CHCl_3$ (10 mL). The mixture was allowed to react for 30 min, cooled, and treated with 2,2′-bipyridyl (191 mg, 1.23 mmol) to complex the Bu_2SnCl_2 formed. Filtration through a small amount of silica gel to remove the complex and concentration in vacuo afforded a virtually quantitative yield of crude **5**, which was purified by elution on silica gel with hexane–EtOAc, 9:1. The purified material was an oil: ^1H NMR δ 3.05 (s, 4H), 2.58 (q, J = 7.5, 4H), 1.18 (t, J = 7.5, 6H); MS *m/e* 206 (M^+).

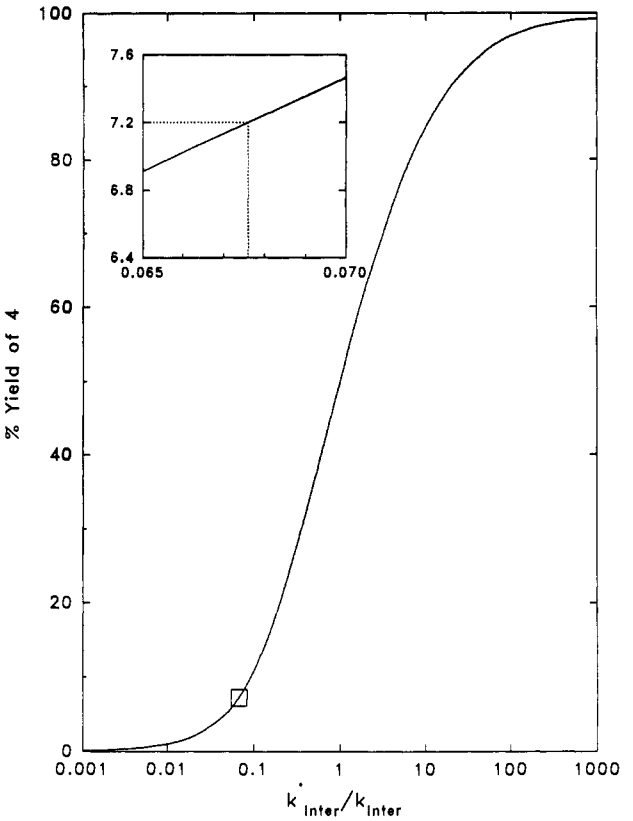
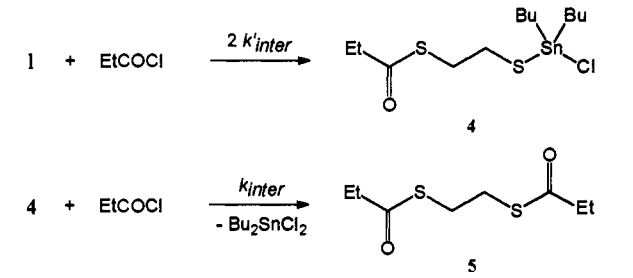


Figure 5. Plot of the calculated yield of **4** against the ratio k'_{inter}/k_{inter}, under the constraint of equal concentration of the reactants. The region of interpolation is shown enlarged in the inset.

Scheme 3



3,6-Dithiaoctane-2,7-dione (7). This compound was prepared from acetyl chloride and **1** according to the same procedure described for the preparation of **5**: mp 67–68 °C; ^1H NMR δ 3.07 (s, 4H), 2.35 (s, 6H); MS *m/e* 178 (M^+).

Distributions of Cyclic Oligomers. Macrocyclizations for distribution studies were carried out under batchwise conditions. The following procedure is typical. **3** (100 mg, 0.50 mmol) was rapidly added to a boiling solution of **1** (165 mg, 0.50 mmol) in ethanol-free $CHCl_3$ (10 mL). The solution was allowed to react for 1 h, cooled, and treated with 2,2′-bipyridyl (78 mg, 0.50 mmol) to complex Bu_2SnCl_2. Filtration on a small amount of silica gel to remove the complex, followed by concentration in vacuo, afforded a crude product that was dissolved in CH_3CN (50 mL) and eventually submitted to HPLC analysis. To determine the absolute yields of cyclic oligomers, a measured portion of the CH_3CN solution was added with known quantities of an authentic sample of cyclic dimer C_2, m = 3, for the series with m = 3, and cyclic monomer C_1, m = 5, for the series with m = 5. The increase in size of the corresponding peak was measured, and the absolute yield was calculated therefrom. The absolute yields of the other cyclic oligomers were calculated from the integrated peak ratios and relative response factors.

Determination of the k'_{inter}/k_{inter} Ratio (Appendix). Propanoyl chloride (54 μL, 0.60 mmol) was added to a boiling solution of **1** (200 mg, 0.60 mmol) in $CHCl_3$ (5 mL). After 10 min acetyl chloride (43 μL, 0.60 mmol) was added, and heating was continued for an additional 10 min. After cooling to room temperature and the usual workup, the mixture was subjected to GLC analysis (internal standard: dodecane). Besides the two peaks due to **5** and **7**, a third peak was detected, with retention time intermediate to those of **5** and **7**, which was shown by GLC–MS to have the mass (M^+ = 192) expected for the unsymmetrical diacylated product $MeCOSCH_2CH_2SCOEt$ (**6**). The yield of **6** was determined as 7.2% by assuming that its response factor is the arithmetic mean of those of **5** and **7**.

Computational Procedure. Numerical integrations of differential rate equations were carried out by a fourth-order Runge–Kutta method with an adjustable step size. Nonlinear least-squares (NLLSQ) fittings were carried out by Gauss's method. Both the routines implementing the Runge–Kutta method and the Gauss method, coded in BASIC, have been adapted from published codings.[17] The NLLSQ program makes use of the Runge–Kutta subroutine to evaluate the concentrations of rings (and hence their yields). In the NLLSQ fittings a simple constant-weight scheme was adopted. All calculations were carried out on a 33-MHz 486-DX IBM-compatible PC.

Appendix

Here we describe the experiment which allowed the evaluation of the ratio k'_{inter}/k_{inter}. The experiment consists in the reaction of an equimolar mixture of **1** and propanoyl chloride. According to Scheme 3, the reaction yields a mixture of **4**, **5**, and unreacted **1** in proportions which depend on the ratio k'_{inter}/k_{inter}.

Analysis by ^1H NMR spectroscopy revealed an approximately equimolar mixture of the diacylated product **5** and unreacted **1**, with no clear-cut evidence of the unsymmetrical intermediate **4**. In order to use a more sensitive analytical tool for the detection of the small amount of **4** possibly formed, the mixture was quenched with 1 molar equiv of acetyl chloride to convert **4** into the unsymmetrical diacylated product $MeCOSCH_2CH_2SCOEt$ (**6**). Analysis of the mixture by GLC showed that, besides the expected symmetrical diacylated products **5** and $MeCOSCH_2CH_2SCOMe$ (**7**), **6** was indeed formed in 7.2% yield. This figure was translated into a k'_{inter}/k_{inter} ratio of 0.068 by interpolation from the plot shown in Figure 5. This plot, which shows the relation existing between k'_{inter}/k_{inter} and the yield of **4** (assumed to coincide with that of **6**), was constructed by numerical integration of the rate equations of Scheme 3 for varying values of the k'_{inter}/k_{inter} ratio under the constraint of equal concentration of the reactants.

Supplementary Material Available: Rate equations for the double ring closure of two symmetrical bifunctional monomers A–A and B–B (4 pages). This material is contained in many 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.

(17) Johnston, M. D., Jr. *Computational Chemistry*; Elsevier: Amsterdam, 1988.