Macromolecules
ARTICLE

Macromolecules **2009**, *42*, 4077–4083 **4077**
DOI: 10.1021/ma900457a

Combinatorial Macrocyclizations under Thermodynamic Control: The Two-Monomer Case

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Received March 2, 2009; Revised Manuscript Received April 14, 2009

ABSTRACT: Dynamic libraries of cyclophane formaldehyde acetals were generated from mixtures of two different monomeric units and quantitatively analyzed for the equilibrium concentrations of the lower cyclic oligomers. Plots of equilibrium concentration versus total monomer concentration exhibited saturation behaviors analogous to those observed in the equilibration of a single monomer. However, unlike the one-monomer case, limiting concentrations in the two-monomer case no longer provide a direct measure of the effective molarity (EM) of the various cyclic oligomers. A theoretical treatment of macrocyclization equilibria occurring in mixtures of two different monomeric units, ^{a}M and ^{b}M, is presented herein. Such a theory is based on the definition of probabilities p_a and p_b of the two monomers at the equilibrium and allows for realistic situations in which a monomer unit of a given type shows structural bias to be incorporated into one or more specific cyclooligomers, thus causing deviations from a purely statistical distribution. The theory allows to translate equilibrium concentrations into EM data.

Introduction

Much evidence has been obtained over the years of macrocycles occuring in a wide range of polymers as a consequence of ring−chain equilibration reactions.[1] A general theory of macrocyclization equilibria was presented by Jacobson and Stockmayer (J−S)[2] almost six decades ago. This theory is concerned with strainless rings in equilibrium with ideal chains characterized by a single repeating unit. The cyclic fraction in ring-chain equilibrates has attracted the attention of many workers in the field of polymer chemistry, mainly because the concentrations of cyclic oligomers, thanks to J−S theory, serve as a measure of the statistical configurations of chain molecules in solution.

In more recent years, J−S theory was adapted to the formation of strained rings as well as reformulated to be easily understandable by nonspecialists.[3] With the recent birth and development of dynamic covalent chemistry,[4] a quantitative knowledge of reaction systems where macrocycles are formed under complete equilibration has gained increasing importance. In many cases, the dynamic libraries (DL) reported in the literature consist of interconverting macrocycles generated by the reversible combination of several kinds of monomeric units. To our knowledge, however, a complete and experimentally tested theory of macrocyclization under thermodynamic control in systems composed of more than one monomer is still lacking.

As a first approach to this problem, we have generated DLs of cyclophane formaldehyde acetals starting from mixtures of two different monomers. In this article, we report on a quantitative investigation of such systems and propose a general theory of macrocyclization equilibria for the two-monomer case, which is fully consistent with experimental data. Extension of the theory to the many-monomer case is also presented.

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Background and Results

We have recently reported that the CF_3SO_3H-catalyzed (TfOH) transacetalation of the formaldehyde acetals of 1,4- and 1,3-benzenedimethanol in chloroform solution generates long-lived DLs of oligomeric cyclophanes (Scheme 1), virtually free from side reactions.[5,6] The concentration-dependent populations of the lower oligomers (Figures 1 and 2) show typical saturation behaviors. According to theory,[3] for values of the equilibrium constant for linear propagation (K_{inter}) that are large enough, the concentration of each cyclic species increases upon increasing the monomer concentration, $[M_1]_0$, until a critical value, $[M_1]_0^*$, is obtained. Above such critical value (cutoff point), the concentration of each cyclic species remains constant and coincides with the effective molarity[7] (EM_i) of the given cyclic oligomer (eq 1)

$$\lim_{[M_1]_0 \to [M_1]_0^*} [C_i] = EM_i \tag{1}$$

Therefore, a quantity that would require, in principle, independent measurements of two equilibrium constants[7] is directly measured as an equilibrium concentration.

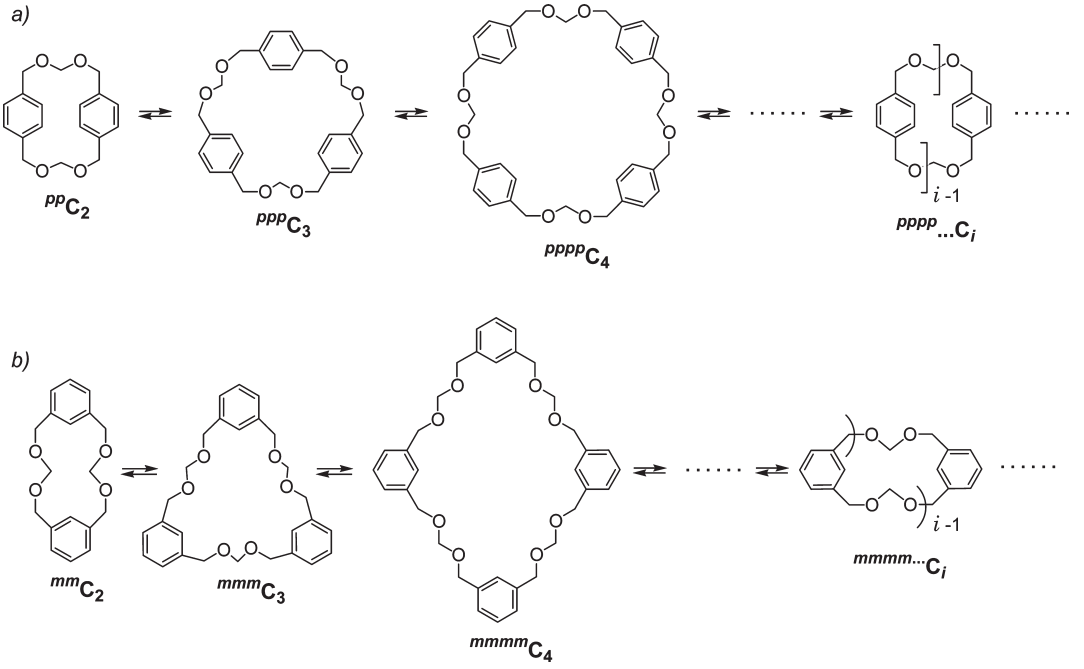
It is important to stress that the cyclic fraction, unlike the acyclic fraction, can contain only a finite amount of monomer units. This amount, which is the limit to which the cyclic fraction converges when the monomer concentration approaches its critical value, provides a definition of the critical monomer concentration ($[M_1]_0^*$) itself, eq 2. In a pictorial representation of a DL of equilibrating macrocycles, the various oligomers, $\mathbf{C}_i$, are viewed as communicating vessels whose capacity is iEM_i.

$$[M_1]_0^* = \sum_{i=1}^{\infty} iEM_i \tag{2}$$

All of the monomeric units added to the system at concentrations below the critical are collected in the vessels. When the critical

Published on Web 05/08/2009

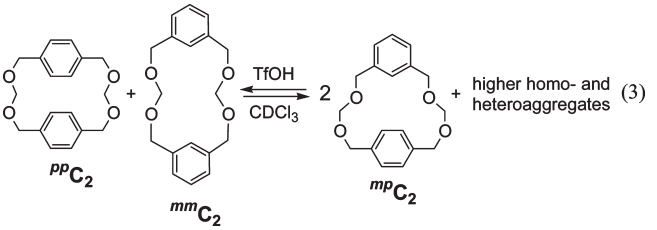
Scheme 1. DLs of (a) *para*- and (b) *meta*-Cyclophane Formaldehyde Acetals



concentration is reached, the vessels fill up, and any excess material overflows into a container of very large (infinite) capacity, representing the acyclic fraction.

A dynamic system composed of two different building blocks offers a higher degree of complexity because heteroaggregates are formed besides homoaggregates. We have reported[6] that a mixture of $^{mm}\mathbf{C_2}$ and $^{pp}\mathbf{C_2}$ cyclophanes generates a DL in which the simplest heteroaggregate is the mixed oligomer, $^{mp}\mathbf{C_2}$, eq 3. Upon increasing the polymerization degree, the number of cyclic heteroaggregates increases dramatically; there are two different heterotrimers, four heterotetramers, six heteropentamers, eleven heterohexamers, and so on.

Therefore, using the same metaphor as above, the number of communicating vessels increases significantly, and this poses a number of questions concerning the amount of monomeric material needed to fill all of the vessels and the relation between equilibrium concentrations and effective molarities of the various cyclic oligomers. Answers to the above questions are crucial, inter alia, to the important goal of translating equilibrium concentrations into effective molarities.



(3)

The following set of experiments, while providing an illustration of the problems encountered in a two-monomer system, gives an at least partial answer to some of the above questions. The cross-ring-opening cyclooligomerization of equimolar mixtures of $^{mm}\mathbf{C_2}$ and $^{pp}\mathbf{C_2}$ in $CDCl_3$ was initiated by the addition of TfOH (0.5 mM). Equilibrium was complete after 5 h in all cases. Portions of ^{1}H NMR spectra in Figure 3 reveal the strong dependence on the composition of the equilibrated mixtures. In the high-concentration domain, a very large fraction of the starting material is in the form of unidentified higher oligomers. Signals of the homodimer $^{mm}\mathbf{C_2}$ and of the heterodimer $^{mp}\mathbf{C_2}$ are clearly visible in all cases, but those of the homodimer $^{pp}\mathbf{C_2}$ are below the detection limit on account of the intrinsically low thermodynamic stability of that ring (Figure 1). Plots of dimer concentration versus total monomer concentration (Figure 4) are quite similar to those shown in Figures 1 and 2. The two profiles in Figure 4 display an undeniable tendency toward saturation, showing that the experiment carried out at the highest concentration closely approaches the cutoff point.[8] Interestingly, the limiting concentration of the homodimer $^{mm}\mathbf{C_2}$, 3.2 mM, is much lower than the corresponding value of 13.4 mM obtained in the one-monomer equilibration experiment (Figure 2), but nothing can be said about the heterodimer $^{mp}\mathbf{C_2}$ because its EM is unknown.

Further insight into the quantitative behavior of two-monomer systems was obtained from the DL generated from a 1:1 mixture of $^{pp}\mathbf{C_2}$ and its deuterated derivative $^{pDpD}\mathbf{C_2}$ (eq 4). Such an experiment was based on the idea that isotopic substitution on the benzene ring would hardly affect the EM values of the various cyclic oligomers with the same *i* value while generating distinct species with different molecular weights. The ^{1}H NMR spectrum of a fully equilibrated 1:1 mixture of $^{pp}\mathbf{C_2}$ and $^{pDpD}\mathbf{C_2}$, is compared in Figure 5 with the corresponding spectrum of a DL generated from $^{pp}\mathbf{C_2}$ alone. In both systems, the total monomer concentration of 100 mM ensures working conditions very close to the cutoff point (see Figure 1). It is apparent that the aliphatic portions of the two spectra are perfectly superimposable, which indicates that the population of the various oligomers is exactly the same in the two systems. The same signals are also displayed in the aromatic regions, but the intensity of each signal in the cross experiment is exactly one-half of the intensity of the corresponding signal in the DL generated from $^{pp}\mathbf{C_2}$ alone.

These results are consistent with a purely statistical distribution of deuterated building blocks among the various oligomers, which is fully confirmed by electrospray ionization time-of-flight mass spectrometric analysis of the reaction mixtures (Figure 6). The distribution of intensities creates a 1:2:1 triplet within the dimers and a 1:3:3:1 quartet within the trimers.[9]

Combination of ^{1}H NMR and mass spectrometric data shows that the limiting concentration of the two homodimers is

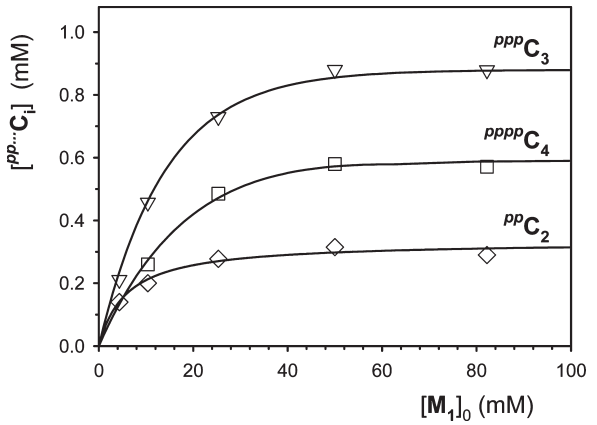


Figure 1. Equilibrium concentration of cyclic oligomers in the acid-catalyzed transacetalation of $^{pp}\mathbf{C_2}$ versus total monomer concentration in $CDCl_3$ at 25 °C. $^{pp}EM_2$ = 0.30 mM; $^{ppp}EM_3$ = 0.90 mM; $^{pppp}EM_4$ = 0.59 mM (data from ref 5).

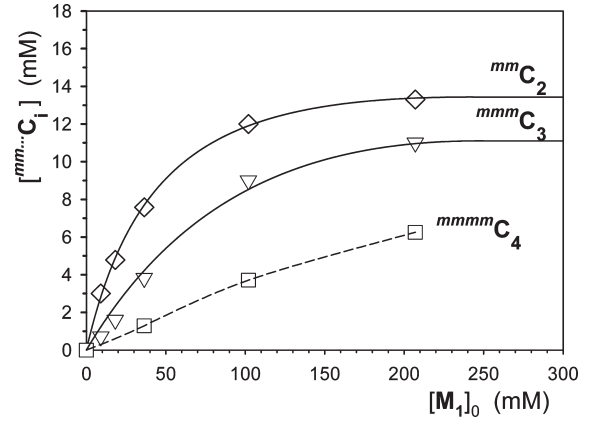
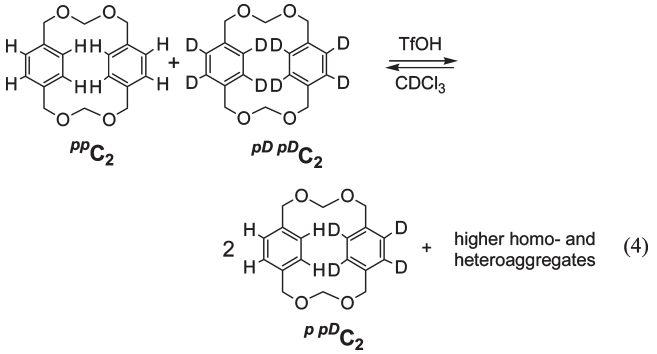


Figure 2. Equilibrium concentration of cyclic oligomers in the acid-catalyzed transacetalation of $^{mm}\mathbf{C_2}$ versus total monomer concentration in $CDCl_3$ at 25 °C. $^{mm}EM_2$ = 13.4 mM; $^{mmm}EM_3$ = 11.0 mM; $^{mmmm}EM_4$ = ca. 6 mM (data from ref 6).

0.075 mM and that of the heterodimer is 0.15 mM. These values are indistinguishable from 1/4 × 30 mM and 1/2 × 30 mM, where 30 mM is the numerical value of $^{pp}EM_2$ (Figure 1). Similarly, the concentration of the two homotrimers (0.11 mM) and that of the heterotrimer (0.33 mM) coincide within experimental errors with 1/8 $^{ppp}EM_3$ and 3/8 $^{ppp}EM_3$ ($^{ppp}EM_3$ = 0.90 mM from Figure 1).



(4)

Going back to the cross equilibration experiment of eq 3 (Figure 4), we note that the limiting concentration of homodimer $^{mm}\mathbf{C_2}$, 3.2 mM, is very nearly 1/4 of the corresponding EM value, 13.4 mM (Figure 2). It is therefore tempting to calculate the EM of the heterodimer $^{mp}\mathbf{C_2}$ to be twice the corresponding limiting concentration of 11.4 or 22.8 mM.

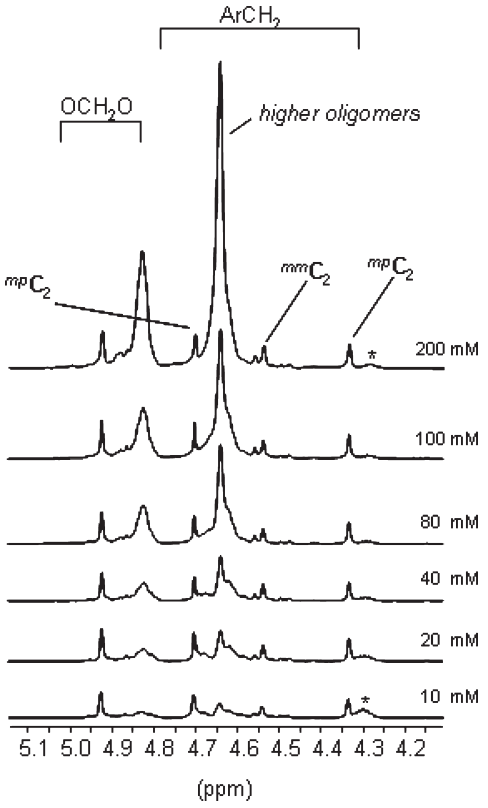


Figure 3. ^1H NMR spectra (OCH_2O and $ArCH_2$ signals) of equilibrated mixtures of para and meta cyclic oligomers obtained from 1:1 solutions of $^{mm}\mathbf{C_2}$ and $^{pp}\mathbf{C_2}$ at the given total monomer concentration ($CDCl_3$, 25 °C, 0.5 mM TfOH). The asterisk indicates partially deuterated nitromethane in the CD_3NO_2 stock solution of TfOH.

Theoretical Treatment

The obtained experimental results prompted us to develop a consistent theoretical treatment. Before considering the theory of combinatorial ring−chain equilibria of two distinct monomers, it is useful to recall the basic tenets of the theory of ring−chain equilibria of a single monomer, M_1, bearing at its ends two functional groups, −X and −Y. The two functional groups are capable of reacting with each other only in a reversible addition reaction, whose equilibrium constant, K_{inter}, is independent of the length of the chain to which they are attached. After equilibration, a system initially composed of monomer units, M_1, contains, in principle, an infinite number of linear as well as cyclic oligomers in equilibrium with each other, whose concentrations are given by eqs 5 and 6, respectively.[3]

$$[M_i] = \frac{x^i}{K_{inter}} \tag{5}$$

$$[C_i] = EM_i x^i \tag{6}$$

In the above equations, x represents the extent of reaction in the linear fraction and EM_i represents the effective molarity of the ith cyclic oligomer.[7]

The extent of reaction, x, is determined by the mass balance equation (eq 7), where $[M_1]_0$ is the initial monomer concentration.

$$[M_1]_0 = \sum_{i=1}^{\infty} iEM_i x^i + \frac{1}{K_{inter}} \frac{x}{(1-x)^2} \tag{7}$$

The two terms in the right-hand side of eq 7 represent the amount of monomer, in concentration units, that at equilibrium has gone into the cyclic and linear fractions, respectively. If the cyclic

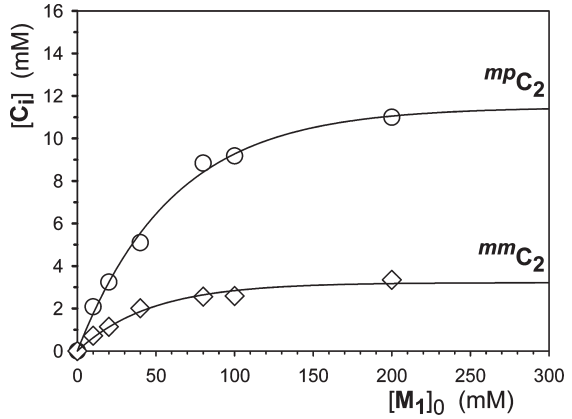


Figure 4. Equilibrium concentration of cyclic oligomers in the acid-catalyzed transacetalation of equimolar mixtures of $^{mm}C_2$ and $^{pp}C_2$ versus total monomer concentration in $CDCl_3$ at 25 °C. Limiting values for $^{mm}C_2$ and $^{mp}C_2$ are 3.2 and 11.4 mM respectively.

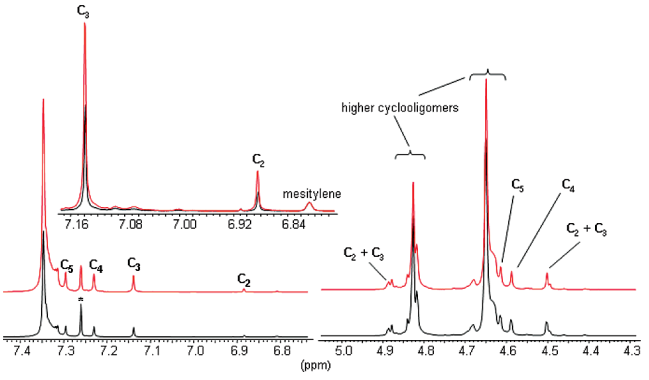


Figure 5. Aliphatic and aromatic regions of the ^{1}H NMR spectra of equilibrates obtained from 50 mM $^{pp}C_2$ (red trace) and from a 25 mM equimolar solution of $^{pp}C_2$ and $^{pDpD}C_2$ (black trace). The total monomer concentration is 100 mM in both cases. Reaction conditions: $CDCl_3$, 25 °C, 0.5 mM TfOH, 0.60 mM mesitylene added as internal standard. The asterisk indicates $CHCl_3$.

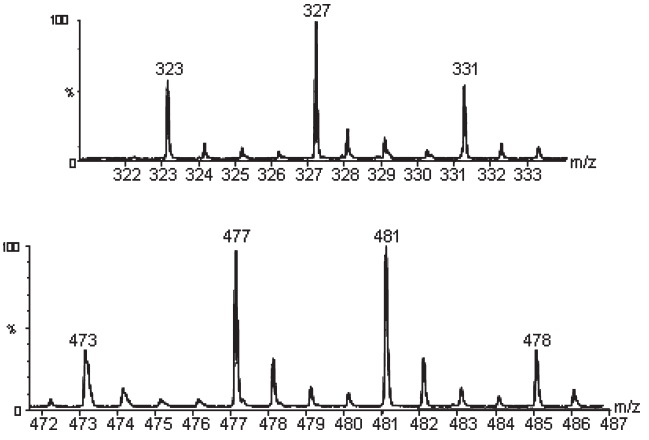


Figure 6. ESI-TOF mass spectrum (dimer and trimer regions) of the equilibrate from a 25 mM equimolar solution of $^{pp}C_2$ and $^{pDpD}C_2$.

oligomers are large enough to be strain free, then their EM_i follows the Jacobson−Stockmayer (J−S) equation (eq 8), where B coincides with the EM of the real or hypothetical strain-free monomeric ring.[2,3]

$$EM_i = Bi^{-5/2} \tag{8}$$

The factor $i^{-5/2}$ in eq 8 may be regarded to be the product of $i^{-3/2}$ and i^{-1}. The former relates to the probability that a Gaussian chain of i repeating units has its ends coincident, and the latter refers to the number of equivalent bonds available for the ring-opening of a cyclic i-mer.

Note that upon increasing $[M_1]_0$, x tends to 1, and according to eq 6, the concentration of each cyclic oligomer approaches a plateau value equal to the corresponding EM value. If the value of K_{inter} is very large, say well above 10^5 M^{-1}, then there is a critical value of the initial monomer concentration ($[M_1]_0^* = \Sigma iEM_i$), below which the system is virtually composed of cyclic species only and above which the concentration of each cyclic species remains practically constant and the excess monomer produces linear polymer only.

Consider now a mixture of two distinct monomers bearing the same functional groups −X and −Y at their ends but differing in the core structure, and indicate them as $^aM_1$ and $^bM_1$, where the left superscript is a letter code to distinguish the two monomers from each other. Indicating the initial concentration of the two monomers as $[^aM_1]_0$ and $[^bM_1]_0$, the initial overall monomer concentration, $[M_1]_0$, equal to the initial overall concentration of either −X or −Y groups, is given by the sum of the two concentrations.

$$[M_1]_0 = [^aM_1]_0 + [^bM_1]_0 \tag{9}$$

Equations 5−8 are still valid if allowance is made for the change of meaning of M_i, C_i, and EM_i as follows. M_i represents the now the whole family of linear i-mers so that $[M_1] = [^aM_1] + [^bM_1]$, $[M_2] = [^{aa}M_2] + [^{ab}M_2] + [^{ba}M_2] + [^{bb}M_2]$, and so on, where the left superscript indicates the sequence of monomeric units along the chain.[10] Note that each family of linear i-mers contains 2^i distinct oligomers differing for the primary structure. Indeed if we envisage a process in which we build a linear i-mer by adding i monomeric units one by one, then the first monomer can be chosen in two different ways, and so can the second, the third, and so on, and thus the total number of possibilities is 2^i. In mathematical jargon, this is the number of permutations with repetitions of i monomeric units from a set of two distinct monomers. Analogously, C_i now represents the whole family of cyclic i-mers differing from each other for the cyclic primary structure, for example, $[C_1] = [^aC_1] + [^bC_1]$, $[C_2] = [^{aa}C_2] + [^{ab}C_2] + [^{bb}C_2]$, and so on, where the first and the last term of the sequence appearing in the left superscript have to be considered to be joined together. Note that apart from the case $i = 1$, the number of distinct cyclic i-mers is smaller than the number of distinct linear i-mers because, in general, a cyclic i-mer, devoid of rotational symmetry, can give i distinct isomeric linear i-mers upon ring-opening, depending on the skeletal bond undergoing fission; for example, $^{ab}C_2$ can generate either $^{ab}M_2$ or $^{ba}M_2$. If a cyclic i-mer has a rotational symmetry axis of order t, then the number of distinct linear i-mers that can be generated is i/t; for example, $^{aa}C_2$ possessing a rotational axis of order two can only give $^{aa}M_2$ upon ring-opening. Now, before considering the new meaning of EM_i, it is convenient to consider the problem of the distribution of the various oligomers within each family. At equilibrium, each oligomer has a given probability of existence that is dictated, among other things, by its composition. Let us define p_a and p_b as the probabilities of the monomer $^aM_1$ and $^bM_1$ at equilibrium by eqs 10 and 11, respectively

$$p_a = \frac{[^aM_1]}{[M_1]} \tag{10}$$

$$p_b = \frac{[^bM_1]}{[M_1]} \tag{11}$$

Of course, because $[M_1] = [^aM_1] + [^bM_1]$, $p_a + p_b = 1$. Now let us envisage a process in which we build a linear i-mer by adding i monomeric units one by one. For simplicity, let us

consider a specific oligomer, say $^{abbab}M_5$; the first monomeric unit of the type a is extracted with a probability p_a, the second of the type b is extracted with a probability p_b, and so on. Because the extractions are independent events, the total probability of $^{abbab}M_5$ is given by the product of the single probabilities, that is, $p_a^2 p_b^3$. From this result, it is apparent that the probability of a linear *i*-mer within its family depends only on the number of monomeric units of each type (its composition) and not on the specific sequence; in other words, isomeric chains have the same probability of occurrence. Note that the whole set of probabilities for a family of linear *i*-mers is given by the binomial $(p_a + p_b)$ raised to the *i*th power; it is evident that this set adds up to 1, as expected. Note also that the probability of each linear oligomer coincides with the mole fraction of the oligomer within the family. In conclusion, the distribution of monomeric units of the type *a* and *b* within each family of the linear fraction is purely statistical. The case of cyclic oligomers is, in principle, more complicated because the mole fraction of a cyclic oligomer within its family depends not only on the intrinsic probability of its cyclic primary structure but also on its effective molarity whenever this is different from those of the other family members. Let us focus first on the evaluation of the intrinsic probability of the cyclic primary structure. As pointed out above, a cyclic *i*-mer devoid of rotational symmetry can give *i* distinct isomeric linear *i*-mers upon ring-opening, and thus the probability of such a cyclic *i*-mer is *i* times that of any of the corresponding linear isomer; for example, the probability of $^{abbab}C_5$ is $i\,p_a^2 p_b^3$. If a cyclic *i*-mer has a rotational symmetry axis of order *t*, then the number of distinct isomeric linear *i*-mers that can be generated is i/t, and thus its probability will be i/t times that of any of the corresponding linear isomers. Of course, the set of intrinsic probabilities of the same family of cyclic oligomers also adds up to 1. The effect of different EMs within a family is best understood by considering a specific example, say, a family of cyclic dimers $^{aa}C_2$, $^{ab}C_2$, and $^{bb}C_2$ having effective molarities $^{aa}EM_2$, $^{ab}EM_2$, and $^{bb}EM_2$, respectively. It is readily apparent on the basis of eq 6 that eq 12 holds.

$$[^{aa}C_2] + [^{ab}C_2] + [^{bb}C_2] = (p_a^2\ ^{aa}EM_2 + 2p_a p_b\ ^{ab}EM_2 + p_b^2\ ^{bb}EM_2)x^2 \quad (12)$$

The three quantities in parentheses in the right-hand term are, in the given order, the limiting values approached by the concentrations of $^{aa}C_2$, $^{ab}C_2$, and $^{bb}C_2$ upon increasing the total monomer concentration to its critical value, that is, when $x \rightarrow 1$.

By comparing eqs 6 and 12, it appears that the overall value of EM_i (in this case EM_2) is just the weighted average of the EMs of the family members with corresponding weights given by the intrinsic probabilities. Accordingly, the critical monomer concentration for the two monomer case is expressed by eq 13

$$[M_1]_0^* = \sum_i i \sum_j \frac{i}{t_{ij}} p_{ij} EM_{ij} \quad (13)$$

where the term ip_{ij}/t_{ij} represents the intrinsic probability of the *j*th member of the family of cyclic *i*-mers and EM_{ij} its effective molarity. From the definition given in eq 12, it also appears that the mole fraction of a given cyclic oligomer within its family is given by the product of its intrinsic probability by the ratio of its EM to the overall EM of the family, for example, the mole fraction of $^{ab}C_2$ is equal to $2p_a p_b\ ^{ab}EM_2/EM_2$. Of course, if all of the members of the family have the same EM value, then the mole fraction of a given cyclic oligomer is simply given by its intrinsic probability.

Now the problem is how to evaluate the values of p_a and p_b. There is no simple and general solution to this problem, however, under certain conditions, some simplifying assumptions are warranted. Let us first consider the case in which the EMs within each family of cyclic oligomers are equal. This is the case that is best approximated by the experiment regarding the equilibration of the two para monomers that only differ for the isotopic substitution (eq 4). In this case the average EM of the family coincides with the EMs of its members, and the mole fraction of a given cyclic oligomer within its family only depends on its intrinsic probability. Under this condition, the distribution of monomeric units of the type a and b within each family of linear as well as cyclic oligomers is purely statistical. Because a monomeric unit of a given type shows no structural bias to be incorporated into one or more specific oligomers, the values of p_a and p_b coincide with the initial mole fractions of the two monomers (eqs 14 and 15).

$$p_a = \frac{[^aM_1]_0}{[M_1]_0} \quad (14)$$

$$p_b = \frac{[^bM_1]_0}{[M_1]_0} \quad (15)$$

On the contrary, if two monomers give rise to families of cyclic oligomers in which the EMs of the members of the same family differ from each other, then one of the two monomers will be preferentially incorporated into the family, causing a deviation of p_a and p_b from eqs 14 and 15. The case is exemplified by the experiments regarding the combinatorial equilibration of the para and meta monomers. Indeed, it has been evidenced by previous experiments in which each of the para and meta monomers has been equilibrated alone that $^{mm}EM_2$ is larger than $^{pp}EM_2$ as a result of differential strain energy of the corresponding cyclic dimers.[5,6] Then, the question arises, "Under what conditions can p_a and p_b significantly deviate from eqs 14 and 15, respectively?" The answer is implicit in the above discussion: "whenever the unbalance caused by the nonstatistical incorporation of the two monomers into the various cyclic families is significant with respect to the amount of monomers incorporated into all of the other oligomers following a purely statistical distribution". In particular, there are two conditions that, when occurring simultaneously, should cause a significant deviation of p_a and p_b from eqs 14 and 15: (i) two monomers with a different number of rotatable single bonds because, apart from possible strain effects in the smaller cyclic oligomers, the EM of each cyclic oligomer mainly consisting of the less conformationally mobile monomeric unit will be systematically larger than the EM of the complementary cyclic oligomer mainly consisting of the other monomeric unit; (ii) a negligible linear fraction because the distribution of monomeric units within the linear fraction is always purely statistical. The second condition occurs when both the value of K_{inter} is very large and the total amount of initial monomer is lower than the critical concentration $[M_1]_o^*$. It is worth pointing out that when the initial monomer concentration is significantly larger than $[M_1]_o^*$, eqs 14 and 15 tend to be satisfied because the statistical linear fraction overwhelms the nonstatistical cyclic fraction. When there are reasons to think that eqs 14 and 15 are not satisfied, the best way to obtain the values of p_a and p_b is from the experimental plateau concentration of one of the cyclic homo-oligomers. For example, p_a can be calculated as the *i*th root of the ratio of the plateau concentration $[^{aaa\cdots}C_i]_{lim}$ of a cyclic homooligomer measured in the two-monomer case to the EM_i of the given oligomer, directly read as its limiting concentration in one-monomer equilibration experiments.

Let us consider again the equilibration experiment of equimolar mixtures of $^{mm}C_2$ and $^{pp}C_2$ plotted in Figure 4 and let p_a refer to the meta isomer. As already noted, the limiting concentration

of the homodimer $^{mm}C_2$ is very nearly 1/4 of the corresponding $^{mm}EM_2$ value (Figure 2), which implies that p_a is virtually 1/2 despite the fact that the meta monomeric unit is clearly biased toward a preferential incorporation into the lower oligomers. This is easily understood if one considers the overwhelming concentration of the presumably strainless high-molecular-weight cyclic oligomers (Figure 3, top spectrum) in which the distribution of monomeric units of the two types is most likely purely statistical. Because $p_a = 1/2$, p_b is also 1/2, and hence the effective molarity $^{mp}EM_2$ of the heterodimer is calculated to be $[^{mp}C_2]_{lim}/2 \times (0.5)^2$ or 22.8 mM.

In conclusion, the theoretical treatment presented in this work allows us to translate limiting concentration data of cyclic heterooligomers into EM data, thus providing easy access to otherwise unaccessible information on the thermodynamic stability of the given ring compounds. An extension of the theoretical treatment to the many-monomer case is presented in the Supporting Information.

Experimental Section

Instruments and General Methods. NMR spectra were recorded on either a 200 or 300 MHz spectrometer. Chemical shifts are reported as δ values from tetramethylsilane added as an internal standard. Equilibration reactions were carried out in the NMR tube in the thermostatted probe of the spectrometer. High-resolution mass spectra (HR-MS) were performed on an ESI-TOF micromass spectrometer.

Materials. TfOH, mesitylene, CD_3NO_2, and terephtalic-2,3,5,6-d_4 acid were commercial samples and were used without further purification. THF was dried by distillation from sodium benzophenone ketyl. $CDCl_3$ was dried over activated molecular sieves (4 Å). Cyclophane formals of the series $^{p,p,p,p,\cdots}\mathbf{C}_i$ and $^{m,m,m,m,\cdots}\mathbf{C}_i$ were available from previous investigation. Stock solutions of TfOH were prepared in CD_3NO_2 because of the low solubility of triflic acid in $CDCl_3$.

1,4-Benzenedimethanol-2,3,5,6-d_4. Terephtalic-2,3,5,6-d_4 acid was converted to the corresponding methyl ester by reaction in refluxing methanol in the presence of catalytic amounts of sulfuric acid. The resulting tetradeuterated diester was then reduced to 1,4-benzenedimethanol-2,3,5,6-d_4 by reaction with $LiAlH_4$ in THF following a standard procedure. mp 118−119 °C (lit.[11] 117.4−117.8 °C). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 5.12 (t, 2H, $J = 5.5$ Hz), 4.47 (d, 4H, $J = 5.5$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 140.74, 125.84 (t, $J = 35.7$ Hz), 62.73.

Cyclic Oligomers ($^{pDpD}\mathbf{C}_2$−$^{pDpDpDpD}\mathbf{C}_4$). Bromochloromethane (8.28 mL, 0.135 mol) was added to a suspension of NaH (60% w/w, 5.4 g, 0.135 mol) in dry THF (450 mL). The mixture was heated to reflux, and 1,4-benzenedimethanol-2,3,5,6-d_4 (3 g, 0.022 mol) in THF (50 mL) was added dropwise by a syringe during 24 h under an argon atmosphere. The mixture was subsequently refluxed for 2 days and then cooled to room temperature, and sodium hydroxide (1 M) was added to quench the excess NaH. After the addition of water (150 mL), the mixture was extracted with CH_2Cl_2 (1 × 400 mL and 2 × 200 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to give 3.1 g of crude product. Pure samples of $^{pDpD}\mathbf{C}_2$, $^{pDpDpD}\mathbf{C}_3$, and $^{pDpDpDpD}\mathbf{C}_4$ were obtained by column chromatography on silica gel. After elution of a colored impurity with CH_2Cl_2/heptane 11:8, elution with CH_2Cl_2/heptane/acetone 11:8:0.7 gave the pure title compounds in the given order.

2,4,13,15-Tetraoxa[5,5]paracyclophane-7,8,10,11,18,19,21,22-d_8 ($^{pDpD}\mathbf{C}_2$). Yield: 80 mg, 2.4%. mp 162−164 °C. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 4.89 (s, 4H), 4.49 (s, 8H). ^{13}CNMR (50 MHz, $CDCl_3$, δ): 137.33, 126.29 (*t*, very weak), 96.54, 70.70. HRMS calcd for $C_{18}H_{12}D_8O_4 + Na^+$, 331.1771; found, 331.1761.

2,4,13,15,24,26-Hexaoxa[5,5,5]paracyclophane-7,8,10,11,18,19,-21,22,29,30,32,33-d_{12} ($^{pDpDpD}\mathbf{C}_3$). Yield: 60 mg, 1.9%. mp 106−108 °C. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 4.88 (s, 6H), 4.45 (s, 12H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 137.50, 128.31, 96.01, 70.59. HR-MS calcd for $C_{27}H_{18}D_{12}O_6 + Na^+$, 485.2710; found, 485.2693; calcd for $C_{27}H_{30}O_6 + K^+$. 489.1679; found. 489.1677.

2,4,13,15,24,26,35,37-Octaoxa[5,5,5,5]paracyclophane-7,8,-10,11,18,19,21,22,29,30,32,33,40,41,43,44-d_{16} ($^{pDpDpDpD}\mathbf{C}_4$). Yield: 65 mg, 2.0%. mp 117−119 °C. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 4.84 (s, 8H), 4.59 (s, 16H). ^{13}CNMR (50 MHz, $CDCl_3$, δ): 137.32, 94.66, 69.69. HRMS calcd for $C_{36}H_{24}D_{16}O_8 + Na^+$, 639.3646; found, 639.3625.

Acknowledgment. Financial contribution from MUR PRIN 2006 is acknowledged. We thank Mr. Alessandro Bolognesi for technical assistance in the synthetic work.

Supporting Information Available: Generalization of the theoretical treatment to a mixture of *r* distinct monomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) By analogy to the kinetic effective molarity, the equilibrium effective molarity is defined by the ratio K_{intra}/K_{inter}, where K_{intra} is the equilibrium constant of the cyclization of an α,ω-bifunctional precursor and K_{inter} refers to the intermolecular model reaction between monofunctional reactants.

(8) A major problem with the concentration profiles in Figures 1, 2, and 4 is that they do not allow the critical monomer concentration to be spotted on the abscissa with any precision. In fact, the cutoff point is "critical" with respect to the acyclic fraction, which undergoes an abrupt concentration increase because above the cutoff point, any excess monomer produces only acyclic species. The concentrations of cyclic oligomers instead approach their limiting values asymptotically. In a sense, however, this is a favorable feature in that equilibrium concentrations below the cutoff point but not too far from it provide reasonable estimates of the limiting concentrations.

(9) The heterodimer is statistically favored over homodimers by a factor of two. The corresponding advantage of the two heterotrimers is a factor of three. This is easily understood if one considers that the symmetry number σ of homodimers is four and that of homotrimers is six, but the symmetry number of the heterodimer and of the two heterotrimers is two. Consequently, the standard

entropy of the heterodimer is higher than that of homodimers by R ln 2. The corresponding entropy difference for trimers is R ln 3. For a recent discussion on statistical factors, see : Ercolani, G.; Piguet, C.; Borkovec, M.; Hamacek, J. *J. Phys Chem. B* **2007**, *111*, 12195−12203 and references therein.

(10) By analogy to the primary structure of peptides and proteins, we can assume that the chain begins with the free −X group on the left and terminates with the free −Y group on the right.

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