CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200600983

A Ring-Fusion/Ring-Fission Mechanism for the Metathesis Reaction of Macrocyclic Formaldehyde Acetals

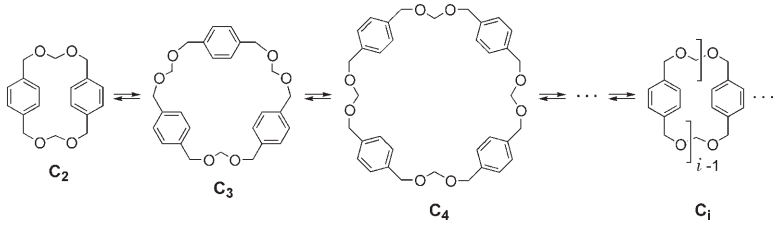
Roberta Cacciapaglia,* Stefano Di Stefano, and Luigi Mandolini*[a]

Abstract: Important insight has been obtained into the mechanism of the reversible acid-catalysed transacetalation of cyclophane formaldehyde acetals (formals) $\mathbf{C}_i$ in $CDCl_3$, at 25 °C. The order of appearance of the lowest oligomers in the early stages of the equilibration reaction is fully consistent with ring-fusion/ring-fission processes in which oxonium ion intermediates undergo S_N2 reactions, according to an acid-catalysed bimolecular (A2) mechanism. The alternative acid-catalysed monomolecular (A1) reaction path, based on "back-biting" processes of carbenium ions generated by S_N1-type cleavage of oxonium ion intermediates, predicts sequences that are in marked contrast with experimental findings.

Keywords: cyclophanes · dynamic covalent chemistry · molecular mitosis · ring-opening polymerization · transacetalation

Introduction

The current interest in dynamic covalent chemistry has spurred a renewed search for reaction systems involving the formation of covalent bonds under thermodynamic control.[1] We have lately reported[2] that the metathesis reaction of formaldehyde acetals (formals), carried out in chloroform or methylene chloride in the presence of catalytic amounts of trifluoromethanesulfonic acid (TfOH) nicely serves to the purpose of generating a dynamic family of oligomeric cyclophanes $\mathbf{C}_i$ (Scheme 1), that are fully interchangeable under mild conditions. In a strict sense, the process in Scheme 1 is a pure ring-opening oligomerisation/polymerisation only when the starting material is $\mathbf{C}_2$.[3] When the feedstock is a mixture of high molecular weight materials the process is better described as a cyclodepolymerisation. However, the problem is merely semantic. In fact, as expected for a truly reversible system, the composition at equilibrium should be, as actually found in our system,[2] independent of which oligomer or oligomeric mixture is used as feedstock, and solely dependent on total concentration expressed in terms of monomer units.



Scheme 1. Ring-ring equilibria of cyclophane formaldehyde acetals $\mathbf{C}_i$.

The cationic ring-opening polymerisation of 1,3-dioxacycloalkanes, such as 1,3-dioxolane, was intensively investigated by polymer chemists in the sixties and seventies.[4] A number of reaction mechanisms were proposed,[5] but none found a definite confirmation.[6] Herein, we report on a number of observations related to early stages of the equilibration process in Scheme 1, which supply clues to the mechanism of the metathesis reaction of macrocyclic formals and, more in general, provide useful insights into the mechanism of the cationic ring-opening polymerisation of 1,3-dioxacycloalkanes.

Results and Discussion

Several kinds of initiators have been used to promote the cationic ring-opening polymerisation of cyclic formals, in-

[a] Dr. R. Cacciapaglia, Dr. S. Di Stefano, Prof. Dr. L. Mandolini
Dipartimento di Chimica e
IMC-CNR Sezione Meccanismi di Reazione
Università di Roma La Sapienza, Box 34—Roma 62
00185 Roma (Italy)
Fax: (+39) 06-490-421
E-mail: roberta.cacciapaglia@uniroma1.it
luigi.mandolini@uniroma1.it

cluding strong Brønsted acids, trialkyloxonium salts, either alone or in combination with acetic anhydride or organoaluminium compounds, Lewis acids and combination of Lewis acids with CH_3COCl.[5] In this work, like in the previous one,[2] we have used submillimolar quantities of TfOH, which was found to be much more active than CF_3CO_2H.

A portion of the ^{1}H NMR spectrum of a typical equilibrated mixture of cyclophane formals (Figure 1) shows that the Ar-H protons of cyclic oligomers from $\mathbf{C_2}$ to $\mathbf{C_4}$ appear

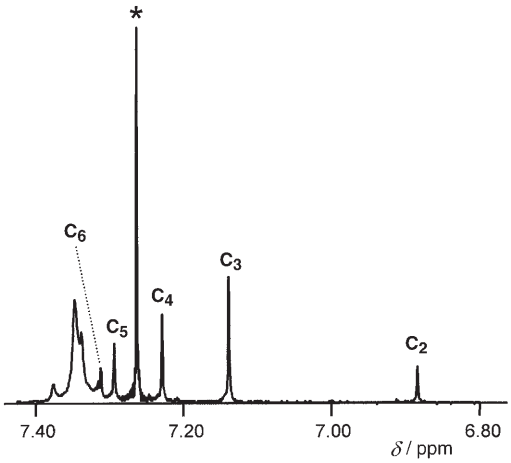


Figure 1. Portion of the ^{1}H NMR spectrum ($CDCl_3$, 25 °C, Ar-H region) of an equilibrated mixture of cyclophane formals derived from 5.0 mM $\mathbf{C_2}$ in the presence of 0.5 mM TfOH. Spectrum taken after 6 h from start ($CHCl_3$ marked with an asterisk). Equilibrium concentrations (mM) are: $\mathbf{C_2}$, 0.21; $\mathbf{C_3}$, 0.45, $\mathbf{C_4}$, 0.25, $\mathbf{C_5}$, 0.15.

as well-resolved singlets; this resolution allows their analytical concentration to be precisely determined by integration. The situation is somewhat complicated for $\mathbf{C_5}$, and much more so for $\mathbf{C_6}$, because of overlap with the complex signal of higher molecular weight materials.

In an experiment in which cyclooligomerisation of 25 mM $\mathbf{C_2}$ ($CDCl_3$, 25 °C) was started by addition of 0.5 mM TfOH, the composition of the reaction mixture was monitored by ^{1}H NMR spectroscopy as a function of time (Figure 2). The corresponding time-concentration curves for oligomers $\mathbf{C_2}$–$\mathbf{C_5}$ are reported in Figure 3. The first-observed oligomer is $\mathbf{C_4}$, clearly generated by dimerisation of $\mathbf{C_2}$, whereas $\mathbf{C_3}$ and $\mathbf{C_5}$ appear at later stages. Oligomers $\mathbf{C_3}$ and $\mathbf{C_5}$ do not belong to the same generation, because the $[\mathbf{C_5}]/[\mathbf{C_3}]$ ratio becomes negligibly small when the reaction time approaches zero. The spectrum recorded after 12 min (Figure 2) shows that the signal of $\mathbf{C_6}$ is small, but clearly detectable, whereas that of $\mathbf{C_5}$ is hardly noticeable. More difficult is to ascertain whether $\mathbf{C_3}$ and $\mathbf{C_6}$ belong to the same generation or whether $\mathbf{C_6}$ precedes $\mathbf{C_3}$, because the signal of $\mathbf{C_6}$ cannot be integrated with acceptable precision.

In spite of the uncertainty concerning the hierarchy of generation of $\mathbf{C_3}$ and $\mathbf{C_6}$, the observed sequences strongly suggest that the host of chemical transformations occurring in the equilibrating system (Scheme 1) can be simply described in terms of inter- and intramolecular processes of the kind shown in Equation (1), with both m and $n \neq 1$ because of the nonexistence of $\mathbf{C_1}$.[3] In the reaction from left to right two rings meet each other and fuse into one ring, whereas in the reverse process a ring splits into two smaller rings.[7] The ring-fission route is not accessible to $\mathbf{C_2}$ and $\mathbf{C_3}$, because the smallest oligomer that can split into rings is clearly $\mathbf{C_4}$.[3,8]

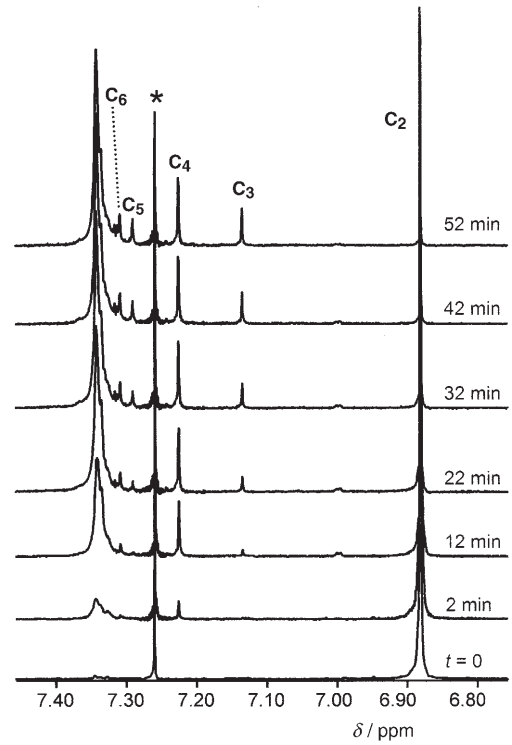


Figure 2. Time evolution of the Ar-H region of the ^{1}H NMR spectrum ($CDCl_3$, 25 °C) of ring-opening cyclooligomerisation of 25 mM $\mathbf{C_2}$ in the presence of 0.5 mM TfOH ($CHCl_3$ marked with an asterisk).

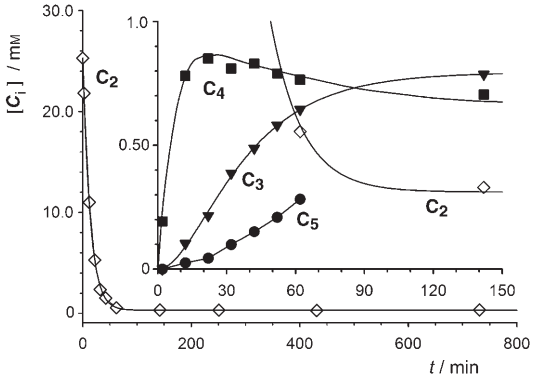
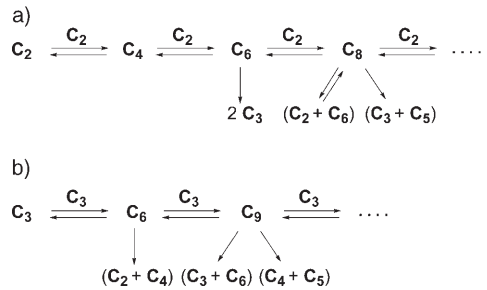


Figure 3. Time-dependent concentration of 25 mM $\mathbf{C_2}$ after addition of 0.5 mM TfOH, $CDCl_3$, 25 °C (data from Figure 2). The inset shows the concentration–time plots for the smallest oligomers. Integration of the $\mathbf{C_5}$ signal became unreliable at $t > 60$ min.

$$\mathbf{C}_m + \mathbf{C}_n \underset{\text{ring fission}}{\overset{\text{ring fusion}}{\rightleftharpoons}} \mathbf{C}_{m+n} \qquad (1)$$



Scheme 2. Succession of the lowest oligomers according to the ring-fusion/ring-fission scheme of Equation (1): a) starting from pure $\mathbf{C_2}$; b) starting from pure $\mathbf{C_3}$.

Application of the above hypothesis to the first few percent of the ring-opening cyclooligomerisation of $\mathbf{C_2}$ leads to Scheme 2a. Since in the very early stages of the reaction the starting oligomer is the most abundant species in solution, only intermolecular fusion processes in which the starting material dimerises or reacts with the lowest fusion products are considered.[9] This implies that only even numbered oligomers are produced from $\mathbf{C_2}$ after a short time from the start and that odd numbered species must derive from intramolecular ring-fission processes. Accordingly, $\mathbf{C_3}$ derives from $\mathbf{C_6}$, and $\mathbf{C_5}$ from $\mathbf{C_8}$.[10] Unfortunately, no information on $\mathbf{C_8}$ and $\mathbf{C_7}$ is provided by ^{1}H NMR spectra, because their signals are most likely buried in the complex signal centred at $\delta = 7.34$ ppm, and the evidence for the growth of $\mathbf{C_6}$ is not corroborated by reliable quantitative data. Nevertheless, the order of appearance of the various oligomers in the scene of the reaction as inferred from ^{1}H NMR spectra (Figures 2 and 3) is substantially consistent with Scheme 2a.

Extension of Scheme 2a to the case in which $\mathbf{C_3}$ is the starting material is straightforward (Scheme 2b). Here the first-observed oligomer is predicted to be $\mathbf{C_6}$, from which $\mathbf{C_2}$ and $\mathbf{C_4}$ are produced simultaneously, whereas $\mathbf{C_5}$ is produced from $\mathbf{C_9}$ at a later stage.[10] Concentration–time curves for oligomers $\mathbf{C_2}$ and $\mathbf{C_4}$–$\mathbf{C_6}$ in a run in which $\mathbf{C_3}$ was the starting material is shown in Figure 4. Compared with the analogous experiment in which $\mathbf{C_2}$ was the starting material (Figures 2 and 3), the lower concentration of monomer units (28 vs. 50 mM) as well as of acid catalyst (0.1 vs. 0.5 mM), caused a much lower overall reaction rate, which allowed a large number of data points to be collected in the early stages of the reaction and, more importantly, to obtain signals of $\mathbf{C_6}$ uncontaminated by signals of higher oligomers over a reasonably long time range. The concentration–time curves plotted in Figure 4 are fully consistent with predictions based on Scheme 2b. Whereas the primogeniture of $\mathbf{C_6}$ is out of question, oligomers $\mathbf{C_2}$ and $\mathbf{C_4}$ are clearly produced at identical rates in parallel reactions, as shown by the fact that their profiles coincide over a time period of more than 2 h from the start, after which time each ring follows its own thermodynamic fate. Finally, there is a strong indication that production of $\mathbf{C_5}$ is not simultaneous to that of $\mathbf{C_2}$ and $\mathbf{C_4}$, but occurs at a later stage, because the $[\mathbf{C_5}]/[\mathbf{C_2}]$ (or $[\mathbf{C_5}]/[\mathbf{C_4}]$) ratio becomes increasingly smaller as the reaction time approaches zero.

Now the problem is to devise a reaction mechanism for the ring-fusion/ring-fission pathway. Schemes 3 and 4 show two reasonable possibilities, illustrated for the simple case of the reversible oligomerisation of $\mathbf{C_2}$; they involve the secondary and tertiary oxonium ions **I** and **II**, respectively, as common reactive intermediates. The two mechanisms are labelled A1 and A2 by analogy with A1 (acid-catalysed, monomolecular) and A2 (acid-catalysed, bimolecular)

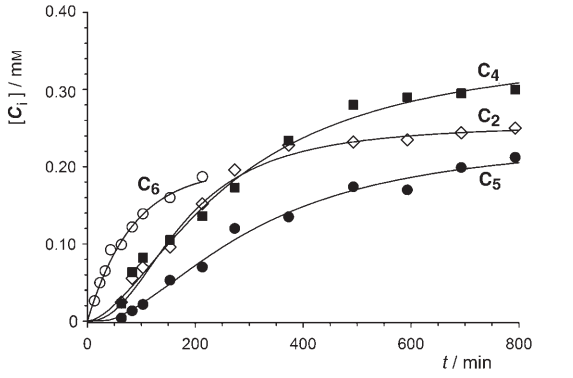
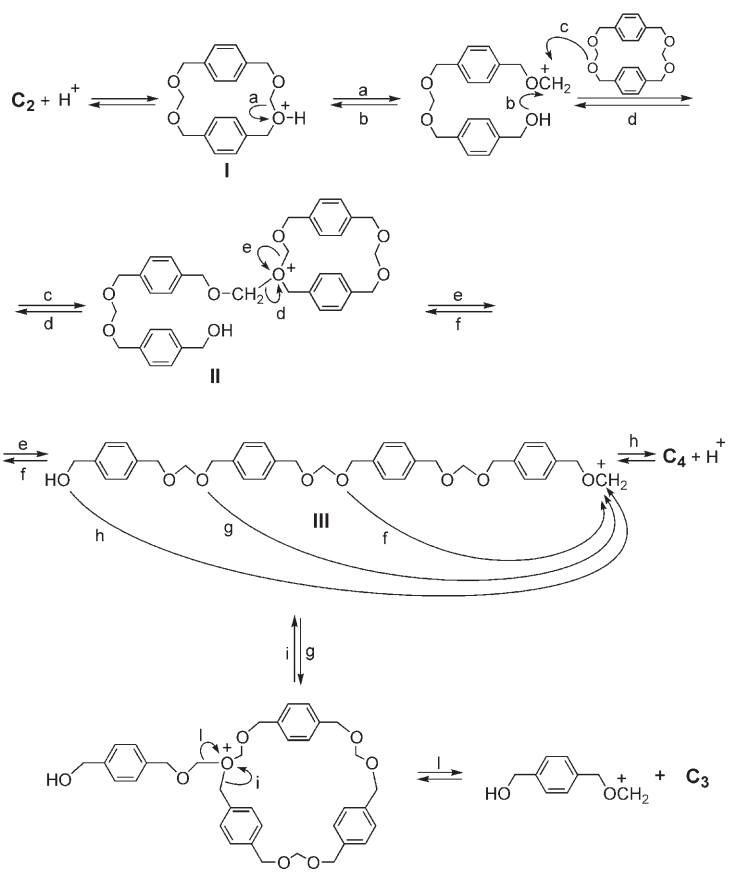
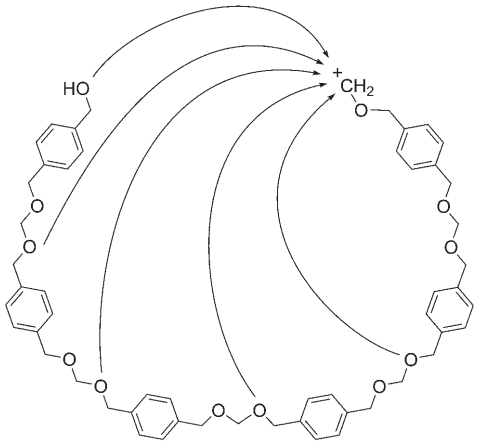


Figure 4. Concentration–time plots for the smallest oligomers in an equilibration run in which 9.3 mM $\mathbf{C_3}$ was the starting material ($CDCl_3$, 25 °C, 0.1 mM TfOH). Data from ^{1}H NMR spectra. Integration of the $\mathbf{C_6}$ signal became unreliable at $t > 200$ min.



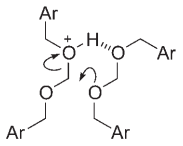
Scheme 3. Mechanism A1.

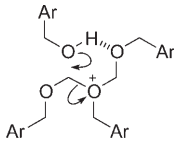
mechanisms of acetal hydrolysis.[11] Secondary and tertiary oxonium ion intermediates involved in mechanism A1 (Scheme 3) undergo S_N1-type bond cleavage (steps a, d, e, i, l, ···), yielding oxygen stabilised carbenium ions that lead to oxygen–carbon bond formation through electrophilic attack at either acetal (steps c, f, g, ···) or hydroxyl (steps b, h, ···) oxygen. The key intermediate is the tetrameric open-chain carbenium ion **III**. Formation of $\mathbf{C_4}$ by the reaction between the chain termini (step h) is accompanied by "back-biting" processes (steps f and g), through which **III** reverts back to $\mathbf{C_2}$ or proceeds to $\mathbf{C_3}$, respectively. This mechanism is clearly inconsistent with the experimental observation that $\mathbf{C_3}$ and $\mathbf{C_4}$ are not produced by concurrent reactions. The discrepancy between facts and predictions based on mechanism A1 is even more striking when the dimerisation of $\mathbf{C_3}$ is considered. Here the hexameric open-chain intermediate **IV**, in addition to $\mathbf{C_6}$ formation by means of reaction between the chain termini, would undergo "back-biting" processes leading to $\mathbf{C_2}$–$\mathbf{C_5}$ oligomers through parallel reactions, in marked contrast to the order in which the various oligomers accumulate in the reaction mix.

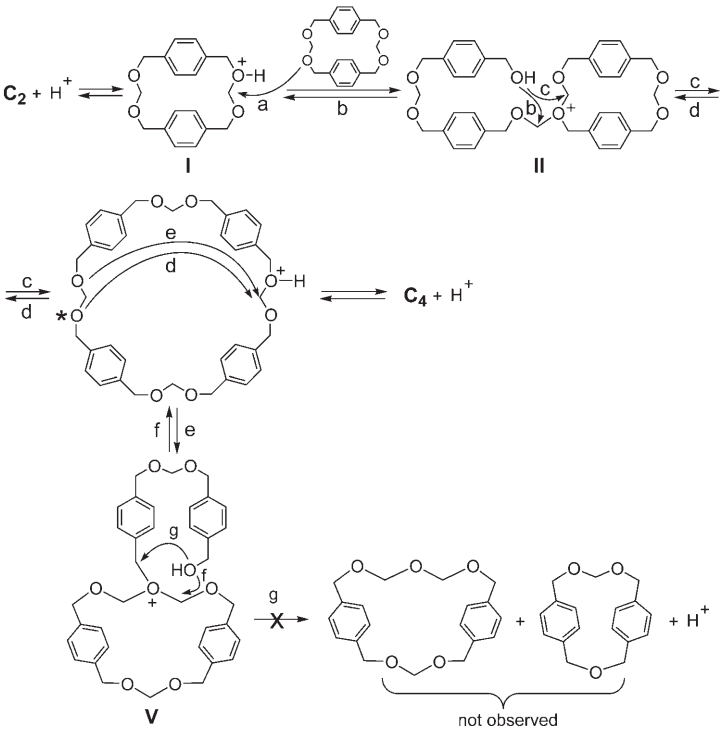


IV

At variance with mechanism A1, all elementary steps in mechanism A2 (Scheme 4) are substitution reactions of the S_N2-type. Displacement of a benzyl alcohol moiety by an acetal oxygen (step a) is followed by an intramolecular[12] S_N2 attack of the benzyl alcohol at an acetal carbon of the tertiary oxonium ion **II**. Whereas step c yields a protonated $\mathbf{C_4}$, through step b **II** reverts to starting material. It seems likely that the transition states of both kinds of S_N2 processes are stabilised by hydrogen bonding, as shown in the six-membered pseudocyclic structures **VI** and **VII**.


VI


VII



Scheme 4. Mechanism A2.

Given the reversibility of the overall reaction, each step is fully reversible. Hence the crucial step in ring-fission involves an intramolecular (intraannular) nucleophilic attack of the oxygen marked with an asterisk at the secondary oxonium function in $\mathbf{C_4H^+}$ (step d). Nucleophilic attack of the twin acetal oxygen (step e) leads to a dead-end, because the benzylic carbon in **V** (step g) cannot rival with the acetal carbon (step f) in a competition with the hydroxyl nucleophile.[13] The oxygen atoms, belonging to monomeric units adjacent to the protonation site are prevented from intramolecular nucleophilic attack for evident steric reasons. Extension of the above mechanism to higher oligomers is straightforward. There are $(i-3)$ oxygen atoms, belonging to different monomeric units, which can act as neighbouring groups to start ring-fission of a protonated $\mathbf{C}_i$ oligomer, whereas participation of the other twin oxygen atoms in the same monomeric units yields nonproductive tertiary oxonium ions. It is evident that mechanism A2 is fully consistent with the order of appearance of the various oligomers during the first stages of the reaction.

Interestingly, in reference [11b] the A2 mechanism is qualified as a "pathway seldom if ever seen". The low polarity of the chloroform solvent used in the metathesis of macrocyclic formaldehyde acetals and the absence of cation stabilising substituents on the acetal carbon strongly discourage the dissociative mechanism. On the other hand, the S_N2 mechanism is strongly favoured by the lack of bulky substituents on the acetal carbon atom. It appears therefore that all of the factors at play in our system concur in favouring the emergence of an unusual mechanism, involving S_N2

reactions of acetal and hydroxyl oxygens at either secondary or tertiary oxonium ions.

Conclusion

In conclusion, the order of appearance of the lowest oligomers in the early stages of the equilibration of macrocyclic formaldehyde acetals is fully consistent with ring-fusion/ring-fission processes in which all elementary steps are S_N2 reactions of both secondary and tertiary oxonium ion intermediates. An alternative mechanism, based on "back-biting" processes of carbenium ions, predicts sequences in marked contrast with experimental findings. Although some caution is required in an extension of the above conclusion to the more concentrated solutions usually employed in ring-opening polymerisation experiments, in which the balance between intra- and intermolecular processes is strongly biased towards the latter, the results of the present study are well in keeping with earlier suggestions[5b] that in the cationic polymerisation of 1,3-dioxolane carbenium ions are not involved as intermediates, and that chain propagation occurs by S_N2 reactions of oxonium ions with monomer.

Experimental Section

Materials, instruments, and general procedures were as previously reported.[2]

[1] a) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem.* **2002**, *114*, 938–993; *Angew. Chem. Int. Ed.* **2002**, *41*, 898–952; b) R. T. S. Lam, A. Belenguer, S. L. Roberts, C. Naumann, T. Jarrosson, S. Otto, J. K. M. Sanders, *Science* **2005**, *308*, 667–669; c) K. C.-F. Leung, F. Aricó, S. J. Cantrill, J. F. Stoddart, *J. Am. Chem. Soc.* **2005**, *127*, 5808–5810; d) P. T. Corbett, L. H. Tong, J. K. M. Sanders, S. Otto, *J. Am. Chem. Soc.* **2005**, *127*, 8902–8903; e) B. de Bruin, P. Hauwert, J. N. H. Reek, *Angew. Chem.* **2006**, *118*, 2726–2729; *Angew. Chem. Int. Ed.* **2006**, *45*, 2660–2663.

[2] R. Cacciapaglia, S. Di Stefano, L. Mandolini, *J. Am. Chem. Soc.* **2005**, *127*, 13666–13671.

[3] The cyclic monomer $\mathbf{C_1}$ is too strained to exist, because a five-atom chain is evidently too short to span a *p*-phenylene unit.

[4] R. C. Schulz, K. Albrecht, W. Hellermann, A. Kane, Q. Van Tran Thi, *Pure Appl. Chem.* **1981**, *53*, 1763–1776, and references therein.

[5] a) M. Okada, Y. Yamashita, Y. Ishii, *Makromol. Chem.* **1964**, *80*, 196–207; b) V. Jaaks, K. Boehlke, E. Eberius, *Makromol. Chem.* **1968**, *118*, 354–360; c) Y. Firat, F. R. Jones, P. H. Plesch, P. H. Westermann, *Makromol. Chem. Suppl.* **1975**, *1*, 203–216.

[6] Y. Kawakami, Y. Yamashita, *Macromolecules* **1977**, *10*, 837–839.

[7] A ring-fission process, denoted "molecular mitosis" by Gutsche, was suggested as a possible mechanism of the reaction calix[8]arene → 2calix[4]arene, but it was subsequently found that the reaction is not a "molecular mitosis" but occurs according to a fragmentation-recombination mechanism. See: C. D. Gutsche, "Calixarenes Revisited", The Royal Society of Chemistry, Cambridge, **1998**, pp. 28–31.

[8] $\mathbf{C_4}$ and $\mathbf{C_5}$ can split only in one way, yielding $2\,\mathbf{C_2}$ and $\mathbf{C_3}+\mathbf{C_2}$, respectively. $\mathbf{C_6}$ and $\mathbf{C_7}$ can split into two different ways, namely, $\mathbf{C_6}$ gives $2\,\mathbf{C_3}$ and $\mathbf{C_2}+\mathbf{C_4}$, and $\mathbf{C_7}$ gives $\mathbf{C_5}+\mathbf{C_2}$ and $\mathbf{C_3}+\mathbf{C_4}$. In general, a cyclic oligomer $\mathbf{C}_i$ can undergo ring-fission in $(i/2)-1$ ways if i is even and $[(i-1)/2]-1$ ways if i is odd.

[9] Figure 2 shows that production of high molecular weight species is already significant after 2 min, which indicates the occurrence of fast intermolecular processes under the reaction conditions.

[10] Adoption of more extended reaction schemes including reactions of the starting oligomer with firstly generated fission products does not alter the order of appearance of the lowest oligomers.

[11] a) T. H. Lowry, K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed, Harper & Row, New York, **1987**, pp. 694–701; b) E. V. Anslyn, D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Book, Sansalito, CA, **2006**, p. 578; the most common mechanism of acetal hydrolysis, designated A-S_E2, was not considered because in the present work it is immaterial whether the carbenium ions are produced stepwise through S_N1 dissociation of a protonated acetal, or in a concerted step from the acetal and a general acid.

[12] The possibility that the benzylic hydroxyl reacts intermolecularly with an activated acetal carbon should be considered. However, since the submillimolar analytical concentration of the TfOH acid catalyst sets an upper limit to the total concentration of activated cationic species, it seems likely that the intramolecular pathway is highly favoured over intermolecular competing processes.

[13] It is known that α-alkoxy substituents strongly enhance rates of S_N2 reactions. For example, in the reaction with potassium iodide in acetone CH_3OCH_2Cl reacts about 10^5 times as fast as CH_3Cl (P. Ballinger, P. D. B. de la Mare, G. Kohnstam, B. M. Prestt, *J. Chem. Soc.* **1955**, 3641–3647).

Received: July 10, 2006
Published online: September 19, 2006

