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On the 'livingness' of a dynamic library of cyclophane formaldehyde acetals incorporating calix[4]arene subunits

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The acid catalyzed transacetalation of cyclophane formaldehyde acetals incorporating calix[4]arene subunits generates a short-lived dynamic library of macrocycles. The side reaction responsible for the loss of 'livingness' is the unexpected decomposition of monomeric units into a bridged ether and formaldehyde. A plausible mechanism is suggested, in which the crucial step is the formation of benzyl carbocations strongly stabilized by the alkoxy substituents at the lower rim of the calix[4]arene moieties. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: dynamic covalent chemistry; dynamic combinatorial chemistry; transacetalation; reaction mechanism; cyclodepolymerization; metathesis; ring–ring equilibrium

INTRODUCTION

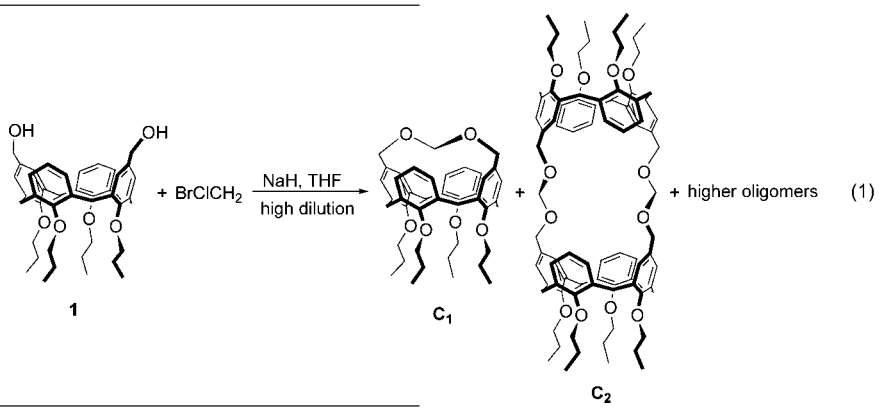
Investigations of reactions involving the formation of covalent bonds under fully reversible conditions has received a renewed interest in recent years in the light of the increasing attention devoted to Dynamic Combinatorial Chemistry.[1–15] We have lately reported[16–18] that the acid-catalyzed metathesis reaction (transacetalation) of formaldehyde acetals, carried out in chloroform or methylene chloride under mild conditions, nicely serves to the purpose of generating dynamic families of cyclic oligomers. The formaldehyde acetals of 1,4- and 1,3-benzenedimethanol were found to produce long-lived dynamic libraries of oligomeric cyclophanes (Scheme 1), virtually free from undesired side reactions.

In the aim at extending the scope of the metathesis reaction to more structured cyclophanes, we have investigated the acid catalyzed transacetalation of cyclophane formaldehyde acetals of diol **1**, featuring a calix[4]arene unit blocked in the *cone* conformation by the four propyl substituents at the lower rim.[19–21] Here we report on the synthesis of the cyclic monomer $\mathbf{C_1}$ and dimer $\mathbf{C_2}$, and suggest a plausible mechanism for the unexpected side-reaction that is responsible for the substantial loss of 'livingness' of the dynamic system under acid catalysis.

RESULTS AND DISCUSSION

Synthesis of C_1 and C_2

Pure samples of the lowest oligomers $\mathbf{C_1}$ and $\mathbf{C_2}$ were obtained from the irreversible reaction of dialcohol **1** with bromochloromethane in the presence of NaH in boiling THF under Ziegler's high dilution conditions [Eqn (1)]. Chromatographic treatment of the crude reaction product gave in the given order a 10% yield of pure dimer $\mathbf{C_2}$ and a 30% yield of pure monomer $\mathbf{C_1}$. A third fraction, amounting to about 1/3 of the crude product, was shown by ESI–MS spectrometry to be a mixture of $\mathbf{C_1}$, cyclic trimer $\mathbf{C_3}$, and higher oligomers.



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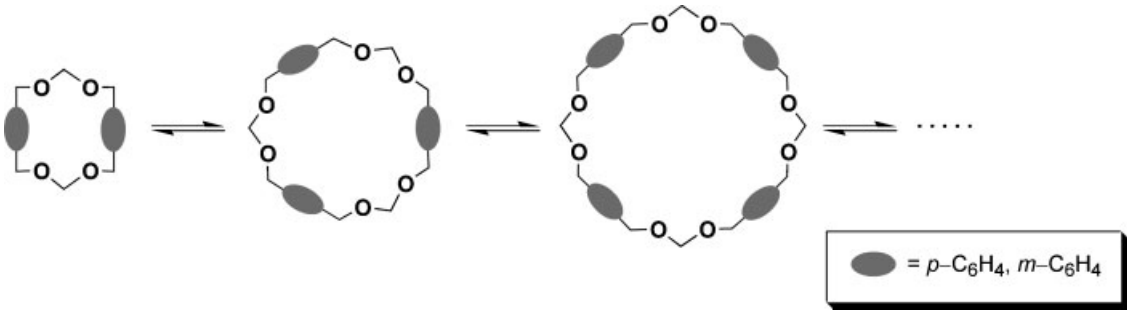


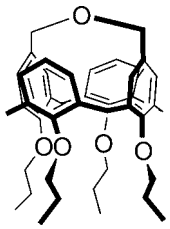
Scheme 1. Ring–ring equilibria of cyclophane formaldehyde acetals

Interestingly, whereas the five atom COCOC chain is too short to span a *p*-phenylene or a *m*-phenylene moiety,[16,18] it is long enough to bridge the gap between distal aromatic carbons of the flexible calix[4]arene moiety, as shown by the molecular model in Fig. 1. The ^{1}H NMR spectra of compounds $\mathbf{C_1}$ and $\mathbf{C_2}$ (Fig. 2) are substantially similar, with the sole significant difference that the singlet of the OCH_2O protons of $\mathbf{C_1}$ are strongly upfield shifted, as a result of the diamagnetic shielding of the aromatic nuclei facing those protons (Fig. 2).

Equilibration experiments

As actually found in our previous works on the formaldehyde acetals of the *para* and *meta* isomers of benzenedimethanol,[16–18] the composition at equilibrium of a truly reversible system should be independent of which oligomer or mixture of oligomers is used as feedstock, but solely dependent on total concentration expressed in terms of monomer units. This implies that any change in the concentration of one or more components, even once the system has reached the equilibrium composition dictated by the initial conditions, causes a readjustment of the product distribution to the new total concentration. In a sense, therefore, dynamic systems behave as living polymers.

Following a well-established protocol,[16–18] chloroform solutions of pure monomer $\mathbf{C_1}$, pure dimer $\mathbf{C_2}$, or the mixture of oligomers obtained as the third fraction of the chromatographic purification of the crude reaction mixture (see above) were treated with a catalytic amount of triflic acid (TfOH) at 25 °C. Disappointing results were obtained in all cases. The ^{1}H NMR spectra of the reaction mixtures, taken after 3–4 h from start, showed a complete lack of signals attributable to the expected family of cyclic formaldehyde acetals. The situation illustrated by the ^{1}H NMR spectra in Fig. 3 is typical. The very broad band centered at δ 5.8 was attributed to the protons of the bridged aromatic rings of cyclic ether **2** on the basis of the close analogy with the ^{1}H NMR spectrum of a similar calix[4]arene derivative, reported by Arduini *et al.*[22] featuring the same —CH_2OCH_2— bridge between distal aromatic rings. The highly distorted flattened *cone* conformation is responsible for the high field resonance shown by the given protons. Structure **2** is consistent with the base peak at 657 *m/z* (**2**+Na^+) in the ESI−MS spectrum of the crude reaction product. An analytical sample of compound **2** (m.p. 161–162.5 °C) was actually obtained from TLC chromatography of the crude reaction product derived from a scaled-up equilibration experiment.



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Interestingly, Fig. 3 reveals that dramatic changes of the mixture composition have already taken place after 30 min. None of the components of the mixture of oligomers $\mathbf{C_i}$ ($i \geq 3$), responsible for the complex ArH signals in the range of δ 6.2–6.95,

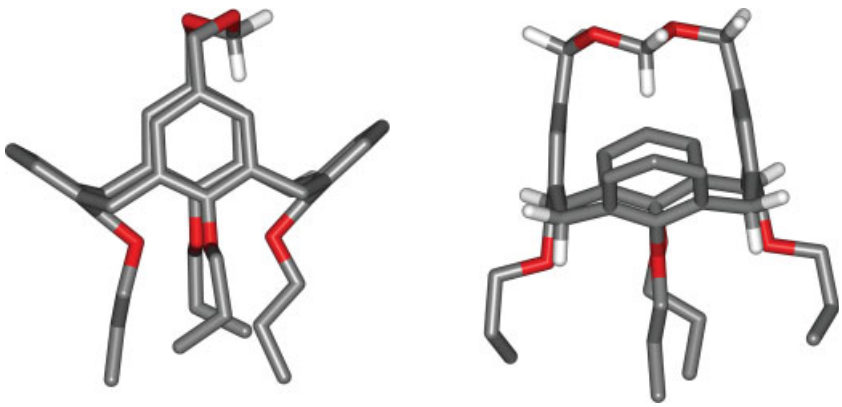

Figure 1. Side and front views of the computer drawn molecular model of the cyclic monomer $\mathbf{C_1}$. Some hydrogen atoms are not shown for clarity

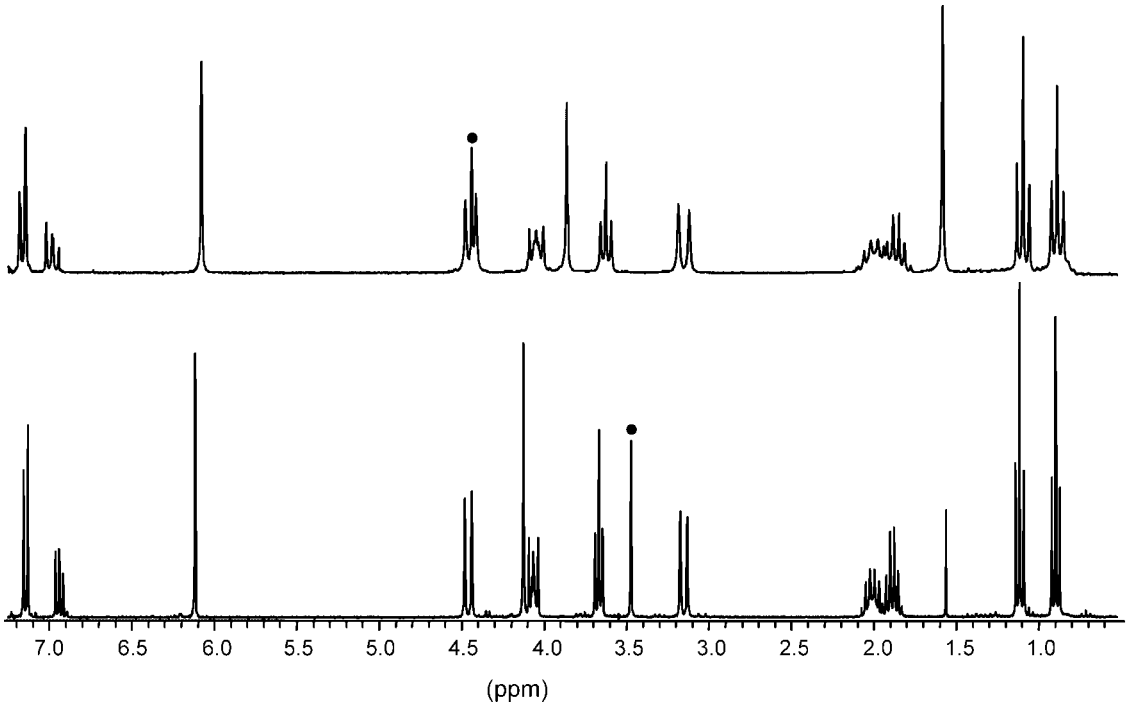

Figure 2. ^{1}H NMR spectra ($CDCl_3$) of $\mathbf{C_1}$ (bottom) and $\mathbf{C_2}$ (top). The singlets of the protons of OCH_2O are marked with a dot. Singlets at δ 6.11 and δ 6.08 correspond to the protons of the bridged aromatic rings in $\mathbf{C_1}$ and $\mathbf{C_2}$, respectively

has survived the 30 min treatment with TfOH, with the possible exception of unidentified species corresponding to the tiny singlets at δ 6.25–6.30. The integrated intensity of the signals shows that the major component of the mixture is the cyclic ether **2**, already amounting to a 62% yield. Highly significant is the presence of a substantial amount of the cyclic monomer $\mathbf{C_1}$ (32%), whose concentration is much higher than that present at time zero (6%). The intensity of the signal corresponding to $\mathbf{C_1}$ decreases afterwards in the time course of the reaction and eventually becomes negligibly small. The picture which emerges from the data is one in which the expected metathesis reaction of formaldehyde acetals actually takes place upon addition of the acid catalyst[23] on a time scale consistent with previous transacetalation experiment of para- and metacyclophanes under very similar conditions.[16–18] However, a dramatic loss of 'livingness' of the dynamic system is caused by the incursion of the unexpected side reaction leading to cyclic ether **2**, as outlined in Scheme 2.

Reaction mechanism

In a thorough investigation of the mechanism of the metathesis reaction of formaldehyde acetals,[17] we demonstrated the operation of ring-fusion/ring-fission processes in which all elementary steps are substitution reactions of the S_N2-type involving oxonium ion intermediates. As shown in Scheme 3, the first reaction step is the nucleophilic attack of an oxygen nucleophile at the methylene of a protonated acetal function. Such a reaction occurs intermolecularly in ring-fusion, and intramolecularly in ring-fission.

A plausible mechanism for the transformation of $\mathbf{C_1}$ into **2** (Scheme 4) again involves a protonated species as key intermediate, but in this case the protonated substrate undergoes a monomolecular ring-opening reaction of the S_N1-type. The driving force for such a reaction, not observed in our previous studies,[16–18] is the formation of a benzyl carbocation strongly stabilized by the *p*-propyloxy substituent. Para-alkoxy substituents are known to bring about rate-enhancements as high as 10^5-fold in solvolysis reactions of $ArCH_2X$ substrates.[24,25]

It is unknown whether the lifetime of carbocation intermediate **I** is long enough for the hemiacetal function to undergo acid-catalyzed cleavage into formaldehyde and benzyl alcohol **II** that would be followed by easy ring closure to **2** (route *a*). Alternatively, **I** might undergo conversion into **III** via nucleophilic attack of the neighboring oxygen atom, followed by decomposition into **2** and formaldehyde (route *b*). A low intensity singlet at δ 9.73, corresponding to the protons of formaldehyde was actually observed in the spectra taken at 30, 60, and 90 min (Fig. 3), but not in those taken at longer times, showing that the liberated formaldehyde does not accumulate beyond a certain level, most likely on account of acid-catalyzed polymerisation and/or copolymerization processes.

Additional pathways for the production of **2** plus CH_2O can be envisaged. It is conceivable that cyclic oligomers other than $\mathbf{C_1}$, once protonated, undergo S_N1-type ring-opening reaction, as shown in Scheme 5 for the case of the cyclic dimer $\mathbf{C_2}$. A back-biting process involving nucleophilic attack of the nearest oxygen atom at the benzyl carbocation, as well as acid-catalyzed decomposition of the hemiacetal function, transforms intermediate **IV** into oxonium ion **V**. Subsequent intramolecular alkylation of the benzyl alcohol completes the transformation of $\mathbf{C_2}$ into a mixture of $\mathbf{C_1}$, **2**, and CH_2O. Analogous pathways (not shown) can be envisaged for the cyclodepolymerization of $\mathbf{C_3}$ and higher homologues, involving sequences of back-biting processes analogous to that in Scheme 5.

Although the proposed mechanisms are admittedly speculative, we stress the point that the dissociative pathway leading to benzyl carbocations strongly stabilized by the *p*-alkoxy

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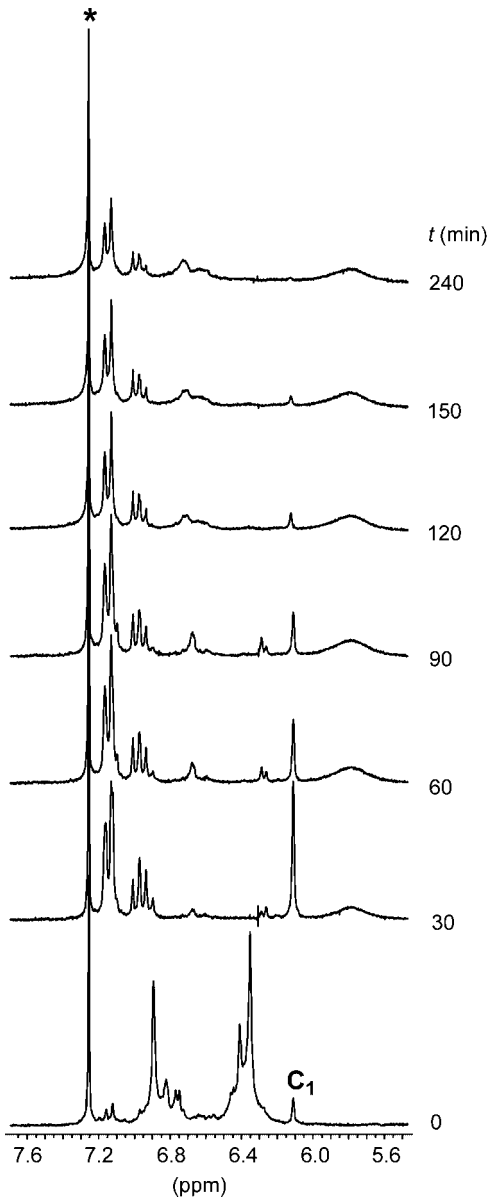
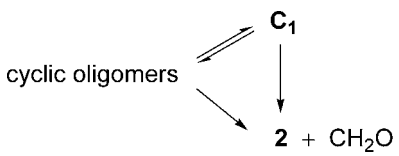


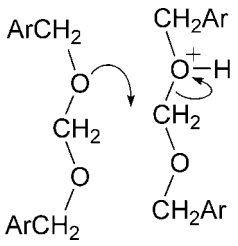
Figure 3. Time evolution of the ArH region of the ^{1}H NMR spectrum ($CDCl_3$, 25°C) of an oligomeric mixture (see text) of $\mathbf{C_1}$, $\mathbf{C_3}$ and higher oligomers (0.10 M in terms of monomer units) in the presence of 0.50 mM TfOH ($CHCl_3$ marked with an asterisk)



Scheme 2. Competing acid-catalyzed cyclodepolymerisation processes

substituents appears to be the only key to understand why the dynamic behavior of the calix[4]arene-based cyclooligomers $\mathbf{C}_i$ is spoiled by decomposition into **2** and formaldehyde, whereas the analogous cyclophanes derived from 1,4- and 1,3-benzenedimethanol undergo reversible transacetalation processes over many days, with no trace of side-reactions.

In conclusion, the results of the present work clearly indicate that a crucial prerequisite for a dynamic library of cyclophane formaldehyde acetals to be long-lived is the absence of structural features, such a *p*-alkoxy substituent, that strongly stabilize a benzyl carbocation, thus making way for the loss of monomeric units in the form of side products.



Scheme 3. Initial step in the acid-catalyzed metathesis of formaldehyde acetals

EXPERIMENTAL

Instruments and general methods

NMR spectra were recorded on a Bruker AC 200 spectrometer. Chemical shifts are reported as δ values in ppm 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 Electrospray Ionisation Time of Flight Micromass spectrometer.

Materials

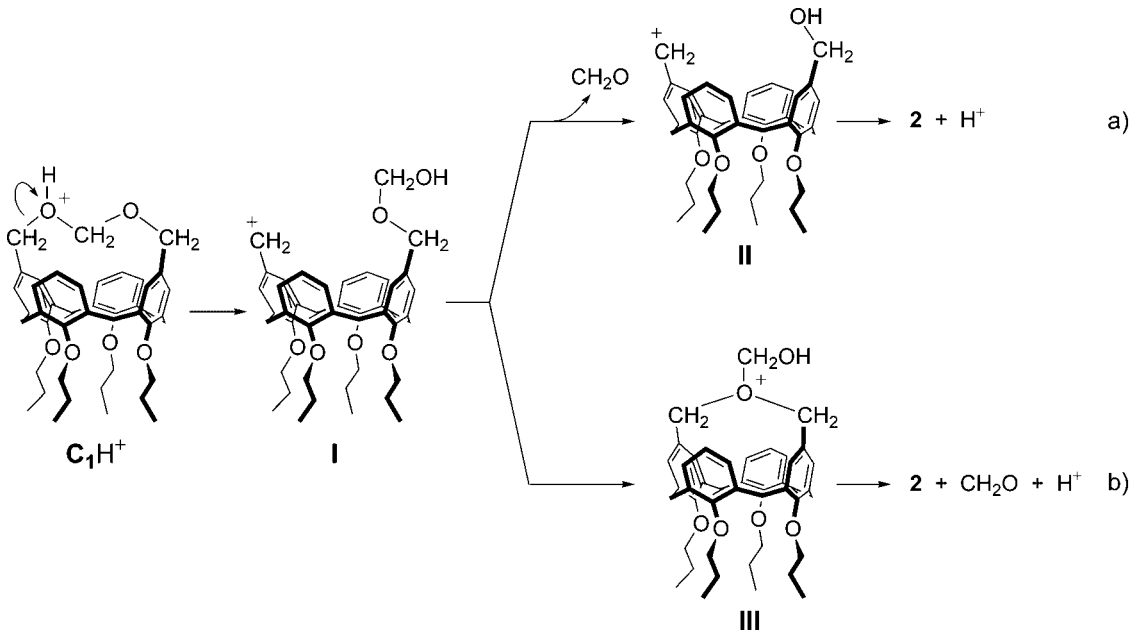
Dialcohol **1** was prepared as previously described in the literature.[26] THF was dried by distillation from sodium benzophenone ketyl. Triflic acid (CF_3SO_3H) was a commercial sample and was used without further purification. $CDCl_3$ was dried over activated molecular sieves (4 Å).

Cyclic oligomers C_1 and C_2

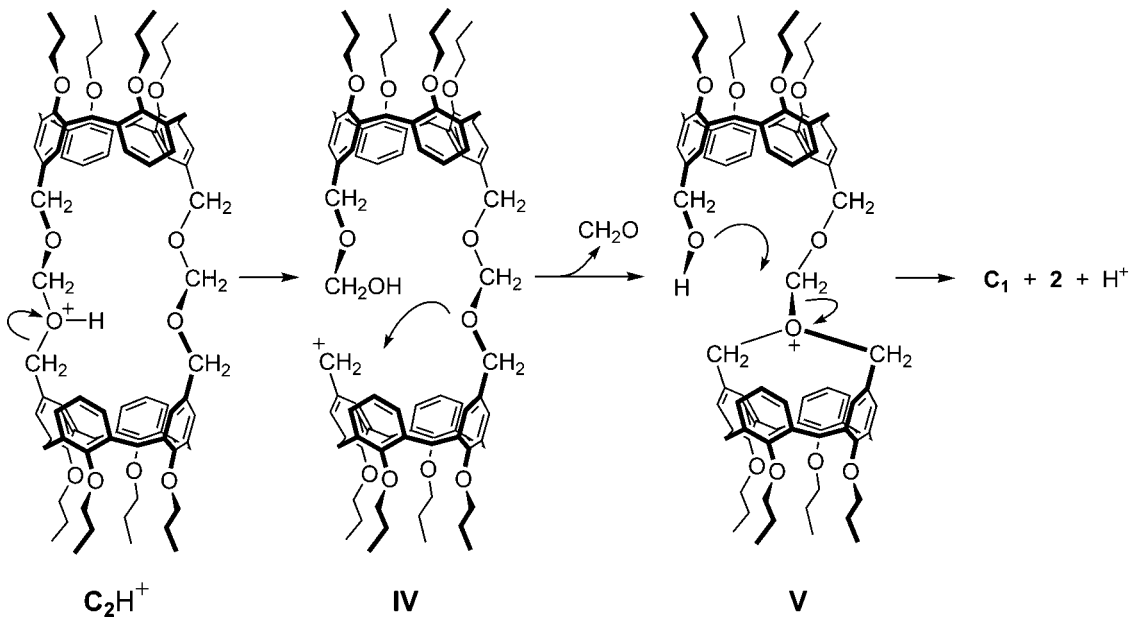
Bromochloromethane (0.115 ml, 1.87 mmol) was added to a suspension of NaH (60% w/w, 0.075 g, 1.78 mmol) in dry THF (10 ml). The mixture was heated to reflux and a solution of **1** (200 mg, 0.31 mmol) in THF (1 ml) was added dropwise by a syringe during 8 h under an argon atmosphere. The mixture was subsequently refluxed for 2 days, then cooled to room temperature, and *ca.* 0.2 ml of 1 M sodium hydroxide were added to quench the excess of NaH. After addition of water (25 ml) the mixture was extracted with CH_2Cl_2 (2 × 25 ml). The combined organic phases were dried over Na_2SO_4 and evaporated to give 150 mg of crude product. Pure samples of $\mathbf{C_1}$ and $\mathbf{C_2}$ were obtained by preparative TLC on silica gel 60 F254 plates (0.25 mm thickness), with $CHCl_3$ as eluent. The dimer $\mathbf{C_2}$, the monomer $\mathbf{C_1}$, and a mixture containing $\mathbf{C_1}$, $\mathbf{C_3}$ and higher oligomers were eluted in the given order.

C_1

(60 mg; yield 30%), m.p. 166–167.5 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.12 (d, J = 5.1 Hz, 4H), 6.94 (t, J = 5.1 Hz, 2H), 6.12 (s, 4H), 4.45 (d, J = 8.8 Hz, 4H), 4.12 (s, 4H), 4.06 (t, J = 5.5 Hz, 4H), 3.66 (t, J = 4.3 Hz, 4H), 3.47 (s, 2H), 3.14 (d, J = 8.8 Hz, 4H), 2.06–1.55 (m,



Scheme 4. Alternative mechanisms for the acid-catalyzed reaction $\mathbf{C_1} \rightarrow \mathbf{2} + CH_2O$



Scheme 5. Proposed mechanism for the acid-catalyzed reaction $\mathbf{C_2} \rightarrow \mathbf{C_1} + \mathbf{2} + CH_2O$

8H), 1.10 (t, $J = 4.9$ Hz, 6H), 0.87 (t, $J = 5.1$ Hz, 6H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ 157.4, 154.7, 136.6, 133.0, 128.9, 127.9, 121.9, 87.4, 76.38, 76.33, 68.1, 30.7, 23.2, 22.7, 10.6, 9.5. HR-MS: calcd for $C_{43}H_{52}O_6$+Na^+: 687.3662; found: 687.3664.

C_2

(20 mg; yield 10%), m.p. > 200 °C (decomp.). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.16 (d, $J = 7.2$ Hz, 8H), 6.97 (t, $J = 6.6$ Hz, 4H), 6.08 (s, 8H), 4.44 (d, $J = 13$ Hz, 8H), 4.43 (s, 4H), 4.04 (t, $J = 8.4$ Hz, 8H), 3.85 (s, 8H), 3.62 (t, $J = 6.6$ Hz, 8H), 3.15 (d, $J = 13$ Hz, 8H), 2.09–1.77 (m, 16H), 1.08 (t, $J = 7.2$ Hz, 12H), 0.88 (t, $J = 7.4$ Hz, 12H). ^{13}C-NMR (50 MHz, $CDCl_3$) $\delta = 157.8$, 154.7, 136.9, 133.0, 131.3, 128.9, 126.5, 121.9, 94.7, 77.2, 69.4, 30.9, 23.5, 22.9, 10.8, 9.7. HR-MS: calcd for $C_{86}H_{104}O_{12}$+Na^+: 1351.7426; found: 1351.7451.

Cyclic Ether *2*

An analytical sample of cyclic ether **2** was obtained from the crude product derived from a scaled-up equilibration experiment by preparative TLC on silica gel 60 F254 plates (0.25 mm thickness), with $CHCl_3$ as eluent. M.p. 161–162.5 °C. ^{1}H NMR

(200 MHz, $CDCl_3$): δ 7.15 (d, $J = 7.4$ Hz, 4H), 6.97 (t, $J = 7.4$ Hz, 2H), 5.78 (very broad singlet, 4H), 4.54 (bs, 2H), 4.42 (d, $J = 13.5$ Hz, 4H), 3.91 (t, 8.6Hz, 4H), 3.64 (t, $J = 6.7$Hz, 4H), 3.53 (bs, 2H), 3.11 (t, $J = 13.5$ Hz, 4H), 1.91-1.74 (m, 8H), 1.10 (t, $J = 7.4$ Hz, 6H), 0.83 (t, $J = 8.0$ Hz, 6H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ 154.6, 137.6, 133.2, 129.1, 129.0, 127.3, 127.2, 121.6, 77.1, 76.2, 75.9, 34.7, 31.0, 23.5, 23.0, 10.8, 9.8. HR-MS: calcd for $C_{42}H_{50}O_5+Na^+$: 657.3556; found: 657.3572.

Acknowledgements

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[23] The equilibrium or quasi-equilibrium composition of the dynamic system is strongly biased toward the cyclic monomer **C_1**, which appears to be thermodynamically favoured over its higher homologues. That the Effective Molarity (*EM*) of the cyclic monomer is significantly higher than that of its larger oligomers is not really surprising, taking into account the limited number of rotatable bonds involved in the formation of the former ring. For a discussion of the influence of the number of rotatable bonds on the *EM* see reference [18], and references cited therein.
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