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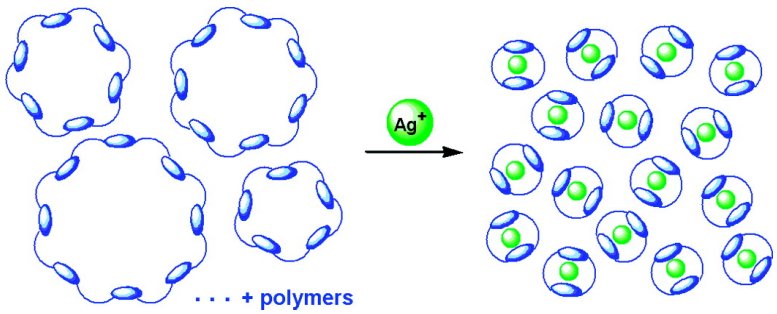

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Metathesis Reaction of Formaldehyde Acetals: An Easy Entry into the Dynamic Covalent Chemistry of Cyclophane Formation

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Abstract: The acid-catalyzed transacetalation of formaldehyde acetals (formal metathesis) is a suitable reaction for the generation of well-behaved Dynamic Libraries of cyclophane formals. The composition of the equilibrated mixtures solely depends on concentration, and is totally independent of whether the feedstock is any of the pure cyclic oligomers, or a mixture of oligomers/polymers. Effective Molarities related to the formation of the lower cyclic oligomers were directly measured as their equilibrium molar concentrations above the critical monomer concentration. The finding that silver cation acts as a selective binder toward the cyclic dimer $\mathbf{C_2}$, coupled with the "proof reading and editing" capability of our quickly equilibrating system, translated into significant amplifications of $\mathbf{C_2}$ when the equilibrated mixtures were exposed to the action of the silver template. These results highlight the potential of Dynamic Combinatorial Chemistry as a powerful tool for the preparation in synthetically useful amounts of an otherwise elusive macrocyclic compound. The possibility of using a mixture of high molecular weight byproducts as feedstock adds considerably to the practical value of the procedure.

Introduction

The number of synthetically useful irreversible reactions involving the formation of covalent bonds largely outweighs that of reversible ones. Yet, the past decade has witnessed a renewal of interest in the investigation of reactions carried out under thermodynamic control (Dynamic Covalent Chemistry).[1] Such an interest has been mainly motivated by the prospects of "proof reading and editing" via repeated bond dissociation−recombination processes, and of amplification of a desired component of the equilibrated mixture via specific interaction with a target entity (template). Various reactions leading to covalent connection between reactants have been employed, such as olefin metathesis,[2] imine,[3] and hydrazone[4] formation, transesterification,[5] thiol-disulfide interchange,[6] and transacetalation.[7]

In a search for reactions useful for the synthesis of cyclophanes[8] under mild dynamic conditions, our attention was attracted by the acid-catalyzed transacetalation of 1,3-dioxacycloalkanes and related compounds.[9] Here, we report that the acid catalyzed transacetalation of formaldehyde acetals (formals) nicely serves to the purpose of generating dynamic families of oligomeric cyclophanes $\mathbf{C_i}$ (Scheme 1), which are fully interchangeable under mild conditions.

Results and Discussion

Pure samples of the lowest cyclophane oligomers were obtained in low yields from the irreversible reaction of 1,4-benzenedimethanol with bromochloromethane in the presence of NaH in boiling THF (eq 1) under Ziegler's high dilution conditions. The complexity of the crude reaction product is shown by the ^{1}H NMR spectrum in Figure 1. ESI−TOF−MS analysis revealed the presence of cyclic oligomers ranging from the dimer $\mathbf{C_2}$ up to at least the cyclic hexamer $\mathbf{C_6}$ (54 ring atoms). The absence of the cyclic monomer $\mathbf{C_1}$ is not surprising, as a five atom chain is obviously too short to span a *p*-phenylene moiety. Column chromatography of the crude product afforded

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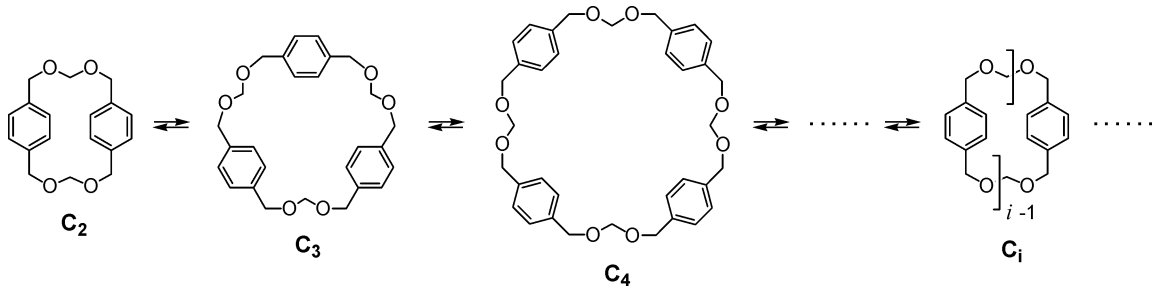
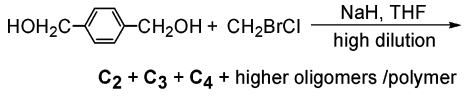
Scheme 1. Ring-Ring Equilibria of Cyclophane Formals



in the given order pure samples of $\mathbf{C_2}$, $\mathbf{C_3}$, and $\mathbf{C_4}$ in 1.2, 3.7, and 2.7% yield, respectively.[10]



(1)

The singlets of the aromatic hydrogens of the lowest oligomers are well separated signals (Figure 1), whereas the intense signal in the range of δ 7.30−7.36 is assigned to higher oligomers, whose nature should be largely cyclic, because no sign of end groups is visible in the ^{1}H NMR spectrum.

A simple version of the acid-catalyzed transacetalation reaction involving open chain reactants served to the purpose of demonstrating the full reversibility under mild conditions. An equimolar 10 mM mixture of the formals of benzyl alcohol and of *p*-methylbenzyl alcohol (**1** and **2**, respectively) was exposed to the action of 0.5 mM triflic acid (TfOH) in anhydrous $CHCl_3$ at 25 °C (eq 2). After 4 h, an equilibrium was reached, characterized by a gaschromatographically determined composition **1**:**2**:**3** = 1:1:2, which amounts to a *K* value of 4 and is exactly what predicted for a purely entropy driven equilibrium. The reaction is conveniently described as a reversible formal metathesis, in that interchange of alkoxy partners bound to the formal methylene takes place.

The ring opening oligomerization[11] of dilute solutions of $\mathbf{C_2}$ in $CDCl_3$ at 25 °C was initiated by the addition of catalytic amounts of TfOH. The ^{1}H NMR spectra of typical reaction mixtures are shown in Figure 2, traces a and c. These spectra were taken after about 4−5 h from start, after which time no

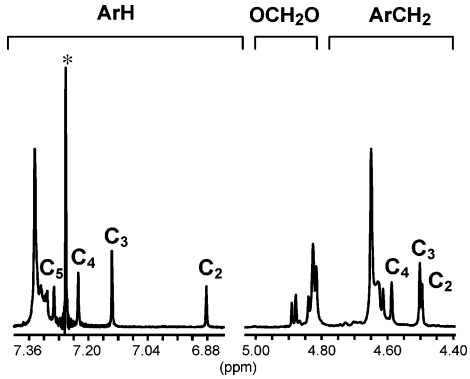


Figure 1. ^{1}H NMR spectrum ($CDCl_3$, 25 °C) of the crude product from reaction 1. ($CHCl_3$ marked with an asterisk.)

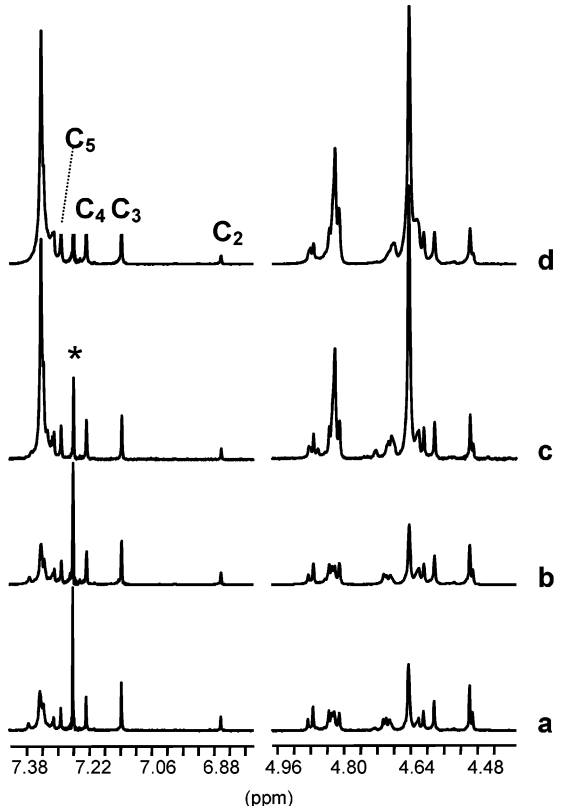
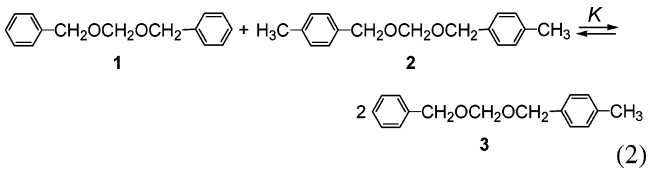


Figure 2. ^{1}H NMR spectra ($CDCl_3$, 25 °C) of equilibrated solutions of cyclophane formals: (a) from 5 mM $\mathbf{C_2}$, (b) from 3.33 mM $\mathbf{C_3}$, (c) from 25 mM $\mathbf{C_2}$, (d) from 16.7 mM $\mathbf{C_3}$. ($CHCl_3$ marked with an asterisk.)

further changes took place.[12] It appears that the composition of the reaction mixtures closely resembles that of the irreversible reaction of eq 1 (Figure 1). The reversible nature of the acid catalyzed formal metathesis is not only demonstrated by the time invariance of the product composition, but even more so



(2)

by the finding that the ^{1}H NMR spectra of the reaction mixtures

(10) Although the cyclic pentamer $\mathbf{C_5}$ was not obtained in a pure form, unequivocal assignment of the peak at δ 7.29 (Figure 1) as associated to its aromatic hydrogens was based on a chromatographic fraction in which $\mathbf{C_5}$ was shown by ESI−TOF−MS to be the major component. Unfortunately, precise integration of this signal was prevented by overlap with other signals.

(11) Ring opening oligomerization is here preferred to the more widely used ring opening polymerization because of the low concentrations used in our experiments.

Table 1. Metathesis of Cyclophane Formals, Equilibrium Yields and Concentrations[a]

entry	source	$[\mathbf{M}]_{tot}$, mM[b]	yield, %[c]			$[\mathbf{C}_i]$, (mM)		
			$\mathbf{C_2}$	$\mathbf{C_3}$	$\mathbf{C_4}$	$\mathbf{C_2}$	$\mathbf{C_3}$	$\mathbf{C_4}$
1	$\mathbf{C_2}$	4.35	6.4	14.4	8[d]	0.14	0.21	0.09[d]
2	$\mathbf{C_2}$	10.0	4.1	13.5	9.7	0.21	0.45	0.25
3	$\mathbf{C_3}$	10.0	3.8	13.2	10.8	0.19	0.44	0.27
4	$\mathbf{C_2}$	25.0	2.1	9.1	7.9	0.27	0.77	0.50
5	$\mathbf{C_3}$	25.0	2.3	8.2	7.5	0.29	0.69	0.47
6	$\mathbf{C_2}$	50.0	1.3	4.9	4.5	0.33	0.81	0.56
7	$\mathbf{C_3}$	50.0	1.3	5.3	4.4	0.32	0.88	0.55
8	$\mathbf{C_3}$	50.0	1.2	5.2	4.8	0.31	0.87	0.60
9	$\mathbf{C_4}$	50.0	1.2	5.8	5.0	0.30	0.96	0.62
10	$\mathbf{C_3}$	82.2	0.71	3.2	2.8	0.29	0.89	0.57

[a] Equilibration reactions carried out in $CDCl_3$ at 25 °C in the presence of 0.5 mM TfOH. Analytical data from integration of the ^{1}H NMR signals in the ArH region. [b] $[\mathbf{M}]_{tot}$ is the equivalent concentration in monomer units. [c] Calculated as $(i[\mathbf{C}_i]/[\mathbf{M}]_{tot}) \times 100$. [d] Affected by severe uncertainty because of interference from chloroform signal.

obtained from 5 mM $\mathbf{C_2}$ (Figure 2a, entry 2 in Table 1) and 3.33 mM $\mathbf{C_3}$ (Figure 2b, entry 3 in Table 1) are practically indistinguishable, so are the spectra of the reaction mixtures obtained from 25 mM $\mathbf{C_2}$ (Figure 2c, entry 6 in Table 1) and 16.7 mM $\mathbf{C_3}$ (Figure 2d, entry 8 in Table 1). Thus, as expected for a truly reversible system, the composition at equilibrium is the same, no matter what oligomer is used as feedstock, on condition that the equivalent concentration expressed in monomer units ($[\mathbf{M}]_{tot}$) is the same. On the other hand, concentration has a marked influence on the equilibrium composition. High dilution favors the lower cycles at the expense of high molecular weight materials, as shown by a comparison of traces a and b with c and d in Figure 2, and on a more quantitative basis by the equilibrium concentrations and yields of oligomers $\mathbf{C_2}-\mathbf{C_4}$ listed in Table 1.

An important characteristic of dynamic systems is the ability to readjust the product distribution by changing the factors that rule the equilibrium, even once the system has reached the equilibrium composition dictated by the initial conditions. Trace a in Figure 3 refers to an equilibrated reaction mixture in which 8.33 mM $\mathbf{C_3}$ ($[\mathbf{M}]_{tot} = 25$ mM, entry 5 in Table 1) was the starting material. The equilibrium was perturbed by adding an amount of solid $\mathbf{C_3}$ such as to double the equivalent monomer concentration ($[\mathbf{M}]_{tot} = 50$ mM). Comparison of the ^{1}H NMR spectrum taken immediately after complete dissolution of $\mathbf{C_3}$ (trace b) with that taken after reequilibration (trace c, entry 8 in Table 1) shows that excess $\mathbf{C_3}$ was digested and mostly transformed into high molecular weight materials, as the equivalent concentration in the original solution was not far from the critical monomer concentration (see below). That the spectrum in trace c belongs to a fully equilibrated mixture is demonstrated by the fact that it is indistinguishable from that (trace d, entry 6 in Table 1) taken on an equilibrated reaction mixture derived from 25 mM $\mathbf{C_2}$ ($[\mathbf{M}]_{tot} = 50$ mM).

Similar results were obtained from an experiment in which the equilibrium was perturbed by dilution (^{1}H NMR spectra not shown). Briefly, a 33 mM solution of $\mathbf{C_3}$ ($[\mathbf{M}]_{tot} = 100$ mM) was equilibrated in the usual way. After the equilibrium was reached, the reaction mixture was diluted 1 to 10 by adding $CDCl_3$ containing 0.5 mM TfOH, so as to leave unchanged the catalyst concentration. A new state of equilibrium was reached (entry 3 in Table 1), whose composition was again indistinguishable from that obtained from 5 mM $\mathbf{C_2}$ as the starting material (entry 2 in Table 1).

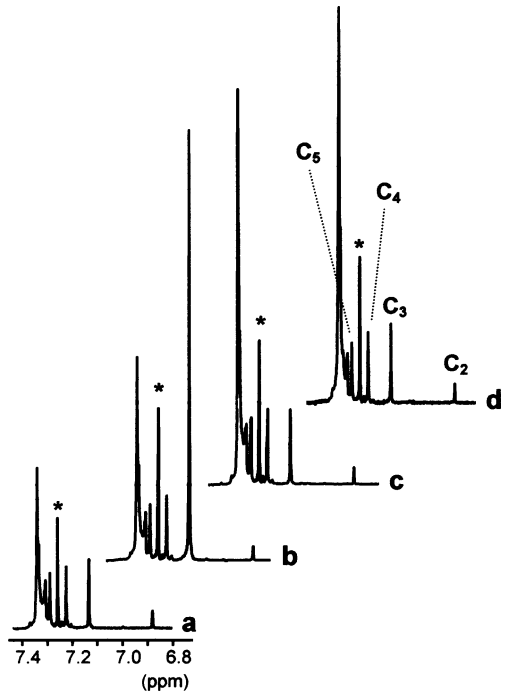


Figure 3. ^{1}H NMR spectra ($CDCl_3$, 25 °C) of: (a) equilibrated solution from 8.33 mM $\mathbf{C_3}$, (b) solution of trace a immediately after addition of solid $\mathbf{C_3}$ so as to double the concentration, (c) solution of trace b after equilibration, (d) equilibrated solution from 25 mM $\mathbf{C_2}$. The axis refers to spectrum a. Other spectra are offset with respect to the next one by 0.4 ppm ($CHCl_3$ marked with an asterisk).

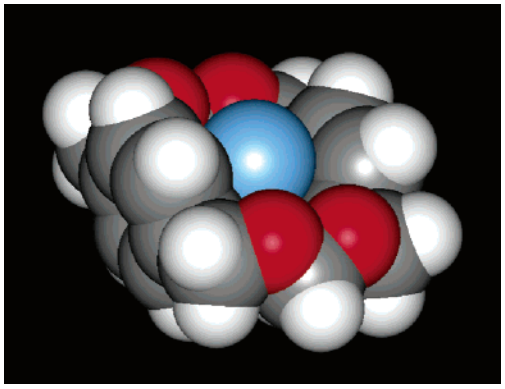


Figure 4. Computer generated molecular model of the $\mathbf{C_2}\cdot Ag^+$ complex.

Amplification Experiments. Even more significant is the equilibrium perturbation caused by the addition of a selective template, which can lead to amplification of a desired component of the dynamic library. The affinity of the silver cation toward π-base receptors such as cyclophanes and calix[4]arenes is well-known.[13] Molecular models indicate that silver ion has the right size to be hosted between the aromatic rings of $\mathbf{C_2}$ in a highly distorted sandwich structure (Figure 4). Strong ^{1}H NMR evidence was obtained that $\mathbf{C_2}$, unlike its higher homologues, forms a complex of definite stability with Ag^+,[14] but the very

(12) Occasional checks showed that the ^{1}H NMR spectra of equilibrated solutions remained unchanged even after more than one week. This indicates the virtual absence of irreversible side reactions.

(13) Lhoták, P.; Shinkai, S. *J. Phys. Org. Chem.* **1997**, *10*, 273−285.

(14) $\Delta\delta$ values of +0.42, +0.051, −0.046 for the ArH, $-OCH_2O-$, and $ArCH_2O-$ signals, respectively, were observed in the presence of excess solid TfOAg.

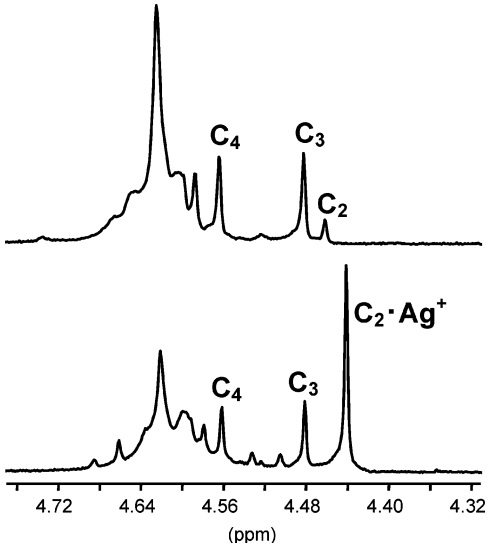


Figure 5. ^{1}H NMR spectrum of the $ArCH_2$ region (CD_2Cl_2, 25 °C) of an equilibrated solution from 6.25 mM **C4**, in the absence (top) and presence (bottom) of solid TfOAg (aromatic region not shown because overlap of the ArH signals of $\mathbf{C_2}\cdot Ag^+$ with other signals).

low solubility of the parent salt TfOAg in chloroform prevented a quantitative estimate of the binding affinity.

The outcome of the formal metathesis reaction changed significantly in the presence of the silver template. When an equilibrated mixture derived from **C4** ($[\mathbf{M}]_{tot}$ = 25 mM, TfOH = 0.5 mM, $CDCl_3$, 25 °C) was treated with TfOAg (1 mol per monomer equivalent) and left to stand at 25 °C for 4 h, the yield of **C2** raised from 2.2 to 11%. Clearly, the silver cation selectively bound to **C2** and shifted the ring−ring equilibrium position in its favor. Changing the solvent to CD_2Cl_2 caused a further increase to 20% of the yield of **C2** (Figure 5), presumably due to a higher solubility of the salt in this solvent.

Given the superiority of methylene chloride over chloroform, a preparative scale experiment was carried out in the latter solvent. As feedstock we used the mixture of oligomeric/polymeric material with $i \geq 5$, recovered from the reaction of 1,4-benzenedimethanol with CH_2BrCl (eq 1) as waste material after the chromatographic isolation of oligomers **C2**−**C4**. A solution of 500 mg of the above material (3.3 monomer mequiv) in 140 mL of dry CH_2Cl_2 was treated at room temperature with 1 g of TfOAg (3.9 mol) and TfOH (0.06 mmol) for 4 h. Workup with aqueous ammonia, followed by column chromatography afforded pure **C2** (170 mg) in 34% yield.[15] All the remaining material was recovered by elution with acetone and reequilibrated under the same conditions to give additional 75 mg of pure **C2**, thus leading to a 49% isolated overall yield of **C2** after two templated equilibration steps. The latter experiment illustrates well the high synthetic potential of the "proof reading" and "error checking" capability of the dynamic formal metathesis, when carried out in the presence of such selective template as a silver cation. Clearly, the templating efficiency is greatly influenced by the heterogeneous nature of the reaction mixture caused by the sparing solubility of the salt used as a source of silver ions. In fact, in the late part of this work we discovered that even better results could be obtained using the noncommercially available $(CF_3SO_2)_2NAg$ as a template. When an amplification experiment was carried out in the NMR tube in the presence of 1 mmol equiv of $(CF_3SO_2)_2NAg$ under heterogeneous conditions in $CDCl_3$, the yield of **C2** raised to 60%, to be compared with the 11% yield obtained in the analogous experiment with TfOAg, most likely due to a higher solubility of the former salt.

(15) The higher yield of **C2** in the preparative experiment, carried out under efficient stirring, might indicate incomplete equilibration in the NMR tube where the experiment of Figure 5 was carried out.

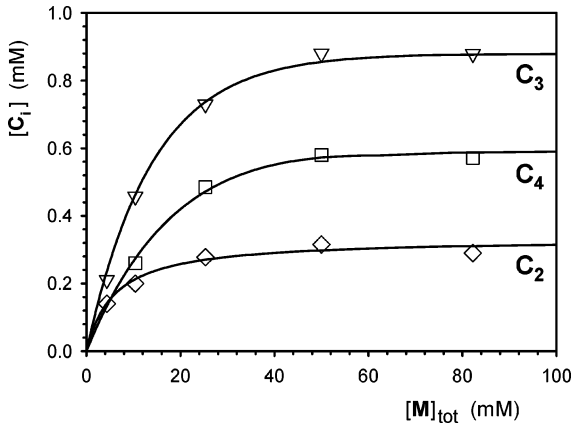


Figure 6. Equilibrium concentration of **C2**−**C4** as a function of total monomer concentration (data from Table 1).

Effective Molarities. Plots of the molar concentrations of macrocycles **C2**−**C4** against equivalent monomer concentration (Figure 6) display negative curvatures, with an unmistakable tendency toward saturation in the high concentration region. This behavior is well in keeping with what predicted by theory,[16] and fully confirmed by experiment.[17] According to the theory of macrocyclization equilibria,[16] as the monomer concentration is raised, the concentration of each individual cyclic species increases until a critical monomer concentration is reached. Above such critical value, the concentration of each cyclic species remains constant, and coincides with the effective molarity EM_i[18] of the given cyclic oligomer. Although our data do not allow the critical monomer concentration to be precisely determined, inspection of the data plotted in Figure 6 strongly indicates that the critical monomer concentration should lie somewhere in the range from 50 to 100 mM. We note that the EM_i values related to the formation of cyclic oligomers **C2**−**C5** (Table 2) are surprisingly low. In fact, they are much lower than the EMs usually recorded for the formation of a large number of macrocycles of comparable sizes,[19] which provides a strong indication that oligomers **C2**−**C5** are affected by considerable strain. An admittedly crude estimate of the strain energies involved can be obtained by a comparison of the experimental EM_i values with the EM_i* values (Table 2) estimated for strainless rings in which the ease of formation is

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(18) Polymer chemists usually refer to the macrocyclization equilibrium constant K_i (see Flory, P. J. "Statistical Mechanics of Chain Molecules" Wiley Interscience, New York, 1969). It was shown that $K_i = EM_i$ within the usual approximation of reactivity of end groups independent of chain length (see ref 19). It should be noted that, by definition, the critical monomer concentration is equal to the quantity $\Sigma_i\, iEM_i$.

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Table 2. Experimental EM_i Values and Calculated Strain Energies of Cyclic Oligomers $\mathbf{C_2}$-$\mathbf{C_5}$

i	ring atoms	EM_i (M)[a]	EM_i* (M)[b]	strain energy (kcal/mol)[c]
2	18	3.0×10^{-4}	8.5×10^{-2}	3.3
3	27	9.0×10^{-4}	1.6×10^{-2}	1.7
4	36	5.9×10^{-4}	7.0×10^{-3}	1.5
5	45	4.2×10^{-4} [d]	4.0×10^{-3}	1.3

[a] Error limits in the range of ±10% unless otherwise stated. [b] Taken from the compilation of entropic components of EM as a function of the number *r* of rotatable bonds reported in Table 1 of ref 19b. For the present system $r = 6i - 1$. The listed EM_i* data have been corrected for the symmetry number of $\mathbf{C_i}$, namely, $\sigma_i = 2i$. [c] Calculated as $RTln(EM_i^*/EM_i)$. [d] Approximate value, due to the poor precision of the integrated intensity of the ^1H NMR signal at $\delta = 7.29$ (see ref 10). A conservative estimate of the uncertainty is in the range of ±25%.

solely determined by the conformational entropy loss upon cyclization of open-chain precursors composed of *r* rotatable bonds.[19]

As shown by the data in Table 2, the strain energy, which is quite high for cyclic dimer $\mathbf{C_2}$, shows the tendency to decrease on increasing the ring size, but is still appreciable for the cyclic pentamer $\mathbf{C_5}$ (45 ring atoms). Although too much emphasis cannot be placed on exact figures, in view of the approximate nature of the treatment involved, the observed trend is believed to be real. As to the origin of strain in our cyclophane formals, electron diffraction studies and ab initio calculations[20] show that the gauche (g) conformation of the C···O—C···O bond of dimethoxymethane is more stable than the trans (t) conformation (anomeric effect). A number of different sources[20] indicate that the most stable conformation, gg (denoting two gauche bonds of the same sign), corresponds to a deep and narrow energy well. Examination of CPK molecular models of the cyclic oligomers shows that geometrical constraints imposed by the cyclic structures force the C—O—C—O—C chains to adopt conformations somewhat different from the most stable gg conformation, and that such geometrical constraints become less severe when the ring size gets larger. In conclusion, the torsional strain arising from deviations of the C—O—C—O—C chains from the ideal *gg* conformation is believed to be responsible for the low EM_i values of oligomers $\mathbf{C_2} - \mathbf{C_5}$.

Concluding Remarks

In summary, the acid-catalyzed formal metathesis is a suitable reaction for the generation of rapidly equilibrating and long-lived libraries of cyclophane formals. Depending on whether the feedstock is pure $\mathbf{C_2}$ or a mixture of high molecular weight materials, the process can be formally described either as a ring-opening cyclooligomerization/polymerization or as a cyclodepolimerization, but it is clear that the composition of the equilibrated mixtures solely depends on the total concentration of monomer units, and is independent of the source of such units. The thermodynamic sink featured by the selective complexation of the cyclic dimer $\mathbf{C_2}$ with silver salts results in high degree of amplifications of $\mathbf{C_2}$ under silver(I) template action. These results establish Dynamic Combinatorial Chemistry as a convenient method for the synthesis of an otherwise elusive macrocycle, and emphasize the crucial importance of the availability of a selective template for the exploitation of dynamic libraries in synthetic work. The finding that oligomeric/polymeric materials obtained as undesirable and otherwise useless byproducts can be recycled and converted into synthetically useful amounts of $\mathbf{C_2}$ adds considerably to the practical value of the method.

As an important "byproduct" of the work, the equilibration experiments carried out above the critical concentration provided direct access to the Effective Molarities of the lower cyclic oligomers, which are the fundamental thermodynamic quantities in any physicochemical discussion of ring−chain and ring−ring equilibria.

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 in ppm from tetramethylsilane added as an internal standard. Equilibration reactions were carried out in the NMR tube in the thermostated probe of the spectrometer. High-resolution mass spectra (HR−MS) were performed by an Electrospray Ionization Time-of-Flight spectrometer.

Materials. CF_3SO_3H and CF_3SO_3Ag were commercial samples and used without further purification. $(CF_3SO_2)_2NAg$ was prepared as described in the literature.[21] THF was dried by distillation from sodium benzophenone ketyl. $CDCl_3$ was dried over activated molecular sieves (4 Å).

1,5-Diphenyl-2,4-dioxapentane (1). Bromochloromethane (0.480 mL, 7.4 mmol) and benzyl alcohol (0.380 mL, 3.7 mmol) were added to a suspension of NaH (60% w/w, 0.450 g, 11.2 mmol) in dry THF (70 mL). The mixture was refluxed for 14 h, cooled to room temperature, and sodium hydroxide (1 M) was added to quench the excess of NaH. Water (70 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to give the pure product as a colorless oil. Yield: 0.340 g, 81%. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.34$ (m, 10H), 4.84 (s, 2H), 4.65 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 137.79, 128.41, 127.91, 127.70, 93.90, 69.48; HR-MS calcd for $C_{15}H_{16}O_2+Na^+$: 251.1048; found: 251.1054.

1,5-Di-*p*-tolyl-2,4-dioxapentane (2). Bromochloromethane (0.480 mL, 7.4 mmol) and 4-methylbenzyl alcohol (0.450 g, 3.7 mmol) were reacted as above to give the pure product as a colorless oil. Yield: 0.408 g, 86%. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.24$ (ABq, $J = 8.02$ Hz, 8H), 4.85 (s, 2H), 4.64 (s, 4H), 2.38 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 137.37, 134.77, 129.06, 128.05, 93.60, 69.25, 21.13; HR-MS calcd for $C_{17}H_{20}O_2+Na^+$: 279.1361; found: 279.1362.

Cyclic Oligomers $\mathbf{C_2}$−$\mathbf{C_4}$. 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 (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, then cooled to room temperature, and sodium hydroxide (1 M) was added to quench the excess of NaH. After 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 $\mathbf{C_2}$, $\mathbf{C_3}$, and $\mathbf{C_4}$ 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 ($\mathbf{C_2}$). Yield: 40 mg, 1.2%. Mp 161.5−163 °C; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 6.88$ (s, 8H), 4.89 (s, 4H), 4.49 (s, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 137.33$,

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126.75, 96.54, 70.70. HR-MS calcd for $C_{18}H_{20}O_4+H^+$: 301.1440; found: 301.1428; calcd for $C_{18}H_{20}O_4+Na^+$: 323.1255; found 323.1259.

2,4,13,15,24,26-Hexaoxa[5,5,5]paracyclophane (C_3). Yield: 120 mg, 3.7%. Mp 104.5−105.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.14 (s, 12H), 4.88 (s, 6H), 4.50 (s, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 137.69, 128.31, 96.01, 70.71; HR-MS calcd for $C_{27}H_{30}O_6+Na^+$: 473.1940; found: 473.1929; 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 (C_4). Yield: 90 mg, 2.7%. Mp 102−104 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.23 (s, 16H), 4.84 (s, 8H), 4.58 (s, 16H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 137.46, 128.11, 94.63, 69.77; HR-MS calcd for $C_{36}H_{40}O_8+Na^+$: 623.2621; found: 623.2635; calcd for $C_{36}H_{40}O_8+K^+$: 639.2360; found: 639.2386.

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