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PAPER

A well-behaved dynamic library of cyclophane formaldehyde acetals incorporating diphenylmethane units†

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A new well-behaved dynamic library (DL) based on acetal cyclophanes incorporating diphenylmethane units is described. The effective molarities of the first two members of this library of cyclic oligomers $\mathbf{C_2}$ and $\mathbf{C_3}$ have been obtained from concentration profiles. Amplification of the dimer in the presence of a silver template, and cross-equilibration experiments are also reported.

Introduction

Dynamic Combinatorial Chemistry (DCC)[1] is based on the reliability of chemical reactions under full thermodynamic control in the absence of any incursion of irreversible side processes. Many successful examples of Dynamic Libraries (DLs) composed of interconverting compounds matching these strict prerequisites have been reported during the last decade.[2,3] We found that transacetalation involving cyclophane acetals of formaldehyde with *para* and *meta* isomers of benzenedimethanol (Fig. 1) is fully reversible when carried out in chloroform or dichloromethane at 25 °C in the presence of catalytic amounts of trifluoromethanesulfonic acid (TfOH).[3] With the aim of widening the scope of this metathesis reaction to more structured cyclophane systems, we first extended these investigations to the acid catalyzed transacetalation of **1**, featuring a calix[4]arene unit blocked in the *cone* conformation by the four propyl substituents at the lower rim.[4] Only short-lived DLs were obtained in that case, the durability of the dynamic system being extensively spoiled by the incursion of irreversible side-reactions associated to the easy formation of benzyl-type carbocations, strongly stabilized by the presence of alkoxy substituents at the lower rim of the calix[4]arene unit.

Looking for long-living DLs of more structured cyclophane formaldehyde acetals with possibly improved binding abilities, we turned our attention to the diphenylmethane unit that has been widely and successfully employed in the design of cyclophane systems for recognition and catalysis.[5] The development of a new well-behaved dynamic library of cyclophane formaldehyde acetals $\mathbf{C}_i$ incorporating the diphenylmethane spacer is here reported.

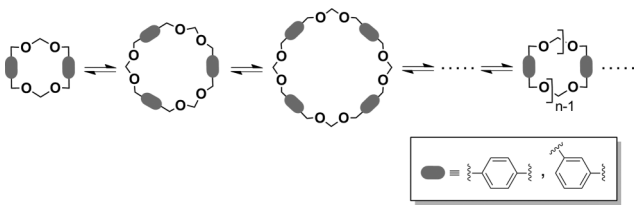
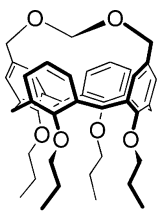


Fig. 1 Dynamic libraries of cyclophane formaldehyde acetals (chloroform, 25 °C, TfOH catalyst).



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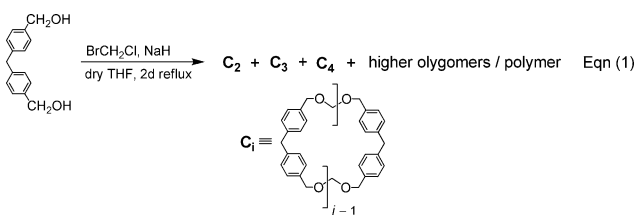
Results and discussion

Samples of cyclophanes $\mathbf{C}_i$ (i = 2, 3 and 4) were prepared by the irreversible process given in Eqn (1). Bis[4-(hydroxymethyl)phenyl]methane was reacted with bromochloromethane in the presence of NaH in boiling THF under high dilution conditions. Careful chromatographic separation of the crude reaction mixture afforded pure samples of $\mathbf{C_2}$, $\mathbf{C_3}$, and $\mathbf{C_4}$ in 7, 3.5, and 4% yields, respectively.



As previously observed in the series of cyclophane formaldehyde acetals incorporating *p*-[3a] and *m*-phenylene[3c] spacers, formation of the monomeric ring $\mathbf{C_1}$ did not occur because the C–O–C–O–C

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† Electronic supplementary information (ESI) available: ^{1}H NMR spectra of cross-equilibration experiments in the presence and absence of template, ^{1}H NMR and ^{13}C NMR spectra of isolated new compounds, details of evaluation of *EM*s and strain energies. See DOI: 10.1039/c1ob06323e

chain is definitely too short to span the *para* positions of the diphenylmethane unit.

Equilibration experiments were carried out in order to ascertain the reversibility of the transacetalation reaction involving formals $\mathbf{C}_i$ under the usual conditions[3] ($CDCl_3$, 25 °C, 2.5% mol TfOH catalyst). In each experiment $\mathbf{C}_2$ was used as the starting material and equilibrium with the generation of the entire family of cyclooligomers $\mathbf{C}_i$ was achieved within 40 h from the addition of the catalyst. Results obtained in a set of experiments carried out at total monomer concentration c_{mon} varying in the range 5–200 mM are shown in Fig. 2 and 3. In all cases, evidence in favor of the reversible nature of the reaction was not only the time invariance of the product composition after the achievement of equilibrium, but also the lack of any trace of free formaldehyde[4] in the ^{1}H NMR spectrum of the equilibrates.

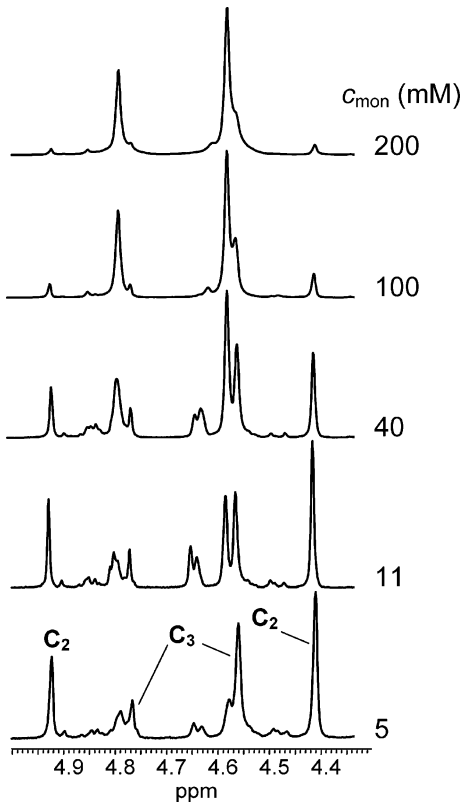


Fig. 2 ^{1}H NMR spectra ($CDCl_3$, 25 °C, aliphatic region) of equilibrium solutions of TfOH catalysed transacetalation of cyclophane formals $\mathbf{C}_i$ at varying total monomer concentration (from 5–200 mM).

As predicted by theory,[6] the monomer concentration has a marked influence on the equilibrium composition. High dilution favors the lower cycles at the expense of high molecular weight materials, while the opposite holds at high concentration. In Fig. 3 it is shown that equilibrium concentrations of $\mathbf{C}_2$ and $\mathbf{C}_3$ increase with total monomer concentration, and according to theory[6] reach plateau values that coincide with the thermodynamic effective molarity EM_i of the given macrocycle, namely 4.4 ± 0.2 mM for $\mathbf{C}_2$ and 1.45 ± 0.07 mM for $\mathbf{C}_3$ (Fig. 3).[7] Experimental *EM* values of $\mathbf{C}_2$ and $\mathbf{C}_3$ turn out to be definitely lower than the effective molarity values *EM** estimated[8,9] for strainless analogs of the oligomeric rings, namely *EM** = 33 mM for $\mathbf{C}_2$ and *EM** = 9.4 mM for $\mathbf{C}_3$.

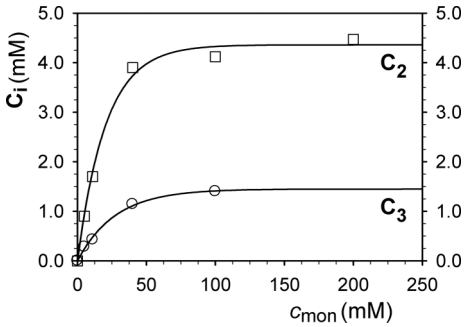


Fig. 3 Equilibrium concentration of $\mathbf{C}_2$ and $\mathbf{C}_3$ as a function of total monomer concentration. Data points are experimental and the curves are calculated on the basis of empirical equations given in ref. 7.

These values translate into strain energies of 1.2 kcal mol^{-1} for $\mathbf{C}_2$ and 1.1 kcal mol^{-1} for $\mathbf{C}_3$, calculated as RT ln (EM_i*/EM_i). The origin of such a strain for these large 28- and 42-membered rings, is ascribed to deviations from the most stable *gg* (*gauche–gauche*) conformation imposed by the cyclic arrangement to the highly conformationally demanding[10] C–O–C–O–C chain.

^{1}H-NMR signals of $\mathbf{C}_i$ with $i \geq 4$ turned out to be superimposed to the signals of higher cyclooligomers. As a consequence, the *EM* values of these cyclic oligomers could not be determined.

Amplification and cross-equilibration experiments

Previous studies[3a,c] showed that the equilibrium composition obtained by acid catalyzed transacetalation of cyclophanes with *p*-phenylene spacer ***p*-$\mathbf{C}_i$** in chloroform solutions is strongly biased towards ***p*-$\mathbf{C}_2$** by the presence of silver bis(trifluoromethanesulfonyl)imide ($AgNTf_2$), that tightly binds to this macrocycle.

Here we report on the effect of the same silver salt on the equilibrium composition of formals $\mathbf{C}_i$ (Fig. 4). ^{1}H NMR spectra of the equilibrium reaction mixtures obtained from 20 mM $\mathbf{C}_2$ in the absence and presence of excess solid $AgNTf_2$ are shown in traces *a* and *b*, respectively. The ^{1}H NMR spectrum of uncomplexed species obtained after removal of the silver template by extraction with aqueous ammonia is given in trace *c*.

It turns out that the equilibrium total concentration of $\mathbf{C}_2$ is nearly doubled, from 3.9 mM to 6.9 mM, in the presence of silver ions. The latter acts as a template for the production of $\mathbf{C}_2$, although definitely much less efficient than in the case of ***p*-$\mathbf{C}_2$**, for which amplification factors higher than 100 were measured.[3c]

Cross-equilibration experiments were carried out by mixing the homodimers $\mathbf{C}_2$ and ***p*-$\mathbf{C}_2$** in chloroform, in the presence of TfOH catalyst. A more complex DL of cyclophanes is generated that, in principle, contains all the possible homo- and hetero-cyclooligomers. Trace *c* in Fig. 5 is the ^{1}H NMR spectrum of the equilibrium reaction mixture obtained in a cross-equilibration experiment of acid catalyzed transacetalation carried out on an equimolar solution of $\mathbf{C}_2$ and ***p*-$\mathbf{C}_2$** (12.5 mM each, 50 mM total monomer concentration). Traces *a* and *b* refer to independently equilibrated solutions of $\mathbf{C}_2$ and of ***p*-$\mathbf{C}_2$**, respectively (50 mM monomer concentration in both experiments). Comparison of trace *c* with traces *a* and *b*, shows that in the cross-experiment the concentrations of homodimers ***p*-$\mathbf{C}_2$** and $\mathbf{C}_2$ decrease for obvious statistical reasons. The equilibrium concentration of the

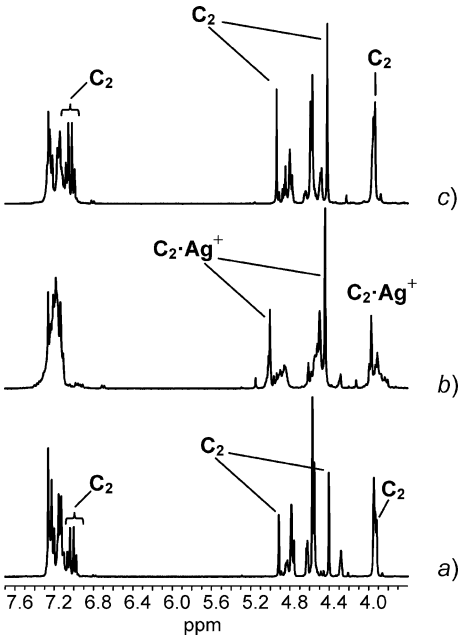
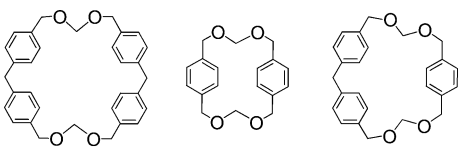


Fig. 4 ^{1}H NMR spectra ($CDCl_3$, 25 °C) of equilibrated solutions obtained from: *a*) 20 mM $\mathbf{C_2}$; *b*) 20 mM $\mathbf{C_2}$ in the presence of excess solid $AgNTf_2$; *c*) equilibrated reaction mixture of trace *b* after removal of silver ion by quenching and extraction with aqueous ammonia.

homodimer ***p*-C$_2$** is notably low, due to the high strain energy (3.3 kcal mol^{-1})[3a] of this cyclic oligomer. Interestingly, a new signal belonging to the heterodimer **2** (*vide infra*) appears in trace *c* at 6.23 ppm.



The template effect of silver ion on the mixed DL was investigated. The solution of trace *c* of Fig. 5 was re-equilibrated in the presence of excess solid $AgNTf_2$ and the spectrum shown in trace *d* was obtained. Not only is the homodimer ***p*-C$_2$**largely amplified upon equilibration in the presence of the silver template, but so is the heterodimer **2**. The ^{1}H NMR spectrum (Fig. ESI1†) of the equilibrated mixture taken after quenching and removal of the silver salt shows that comparable quantities of ***p*-C$_2$** and **2** are formed in the re-digestion. It also appears that, as expected, the homodimer $\mathbf{C_2}$ is amplified in the re-equilibration process in the presence of solid $AgNTf_2$. Both compounds are amplified by the presence of silver, but amplification is much larger for ***p*-C$_2$** than for **2**,[11] the concentration of the former being lower in the absence of the template than the concentration of the latter, because statistically and strain-energetically disfavored. It should be noted that ***p*-C$_2$**, **2**, and any other species able to bind the silver salt are not competing for the template, since excess solid silver salt in all runs acts as an inexhaustible source of material and allows each member of the DCL to bind to as much silver as it can, independent of the presence of other competitors. DCL members only compete among each other for monomeric units. Since the experiments were run at monomer concentrations

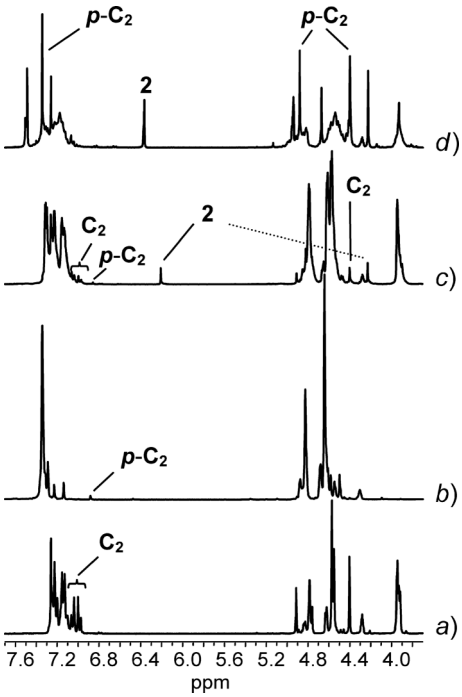


Fig. 5 ^{1}H NMR spectra ($CDCl_3$, 25 °C) of equilibrated solutions obtained from: *a*) 25 mM $\mathbf{C_2}$; *b*) 25 mM ***p*-C$_2$**; *c*) 12.5 mM $\mathbf{C_2}$ + 12.5 mM ***p*-C$_2$**; *d*) same as *c* in the presence of excess solid $AgNTf_2$.

lower than the critical concentration CC[6c], the most favored macrocycles are those having high binding constants for the template and among them those with low polymerization degrees (heterocyclooligomers being favored over homocyclooligomers).[12]

After quenching with aqueous ammonia, the mixed library was subjected to chromatographic separation and the heterodimer **2** was isolated by preparative TLC as the major component of the family of heterocyclooligomers, and fully characterized by HR-MS and NMR.

Conclusions

Well-behaved dynamic libraries have been generated by acid catalyzed transacetalation of cyclophanes $\mathbf{C}_i$ incorporating diphenylmethane units. Thermodynamic characterization of the first two members of the new family of acetal cyclophanes $\mathbf{C}_i$ by evaluation of their effective molarity from concentration profiles obtained in equilibration experiments has been also reported. In a cross-equilibration experiment silver ion proved to act as an effective template not only for the amplification of the homodimer $\mathbf{C_2}$, but also of the heterodimer **2**.

The durability of the transacetalation-based DL of cyclophane $\mathbf{C}_i$ allows the involvement of the diphenylmethane moiety as a useful structural motif for the generation of DLs with high degree of diversity, thus opening nice perspectives in the target-driven amplification of effective ligands.

Experimental section

Instruments and general methods

NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts of the ^{1}H NMR spectra are reported as δ values in ppm

from tetramethylsilane added as internal standard, while in the ^{13}C NMR spectra the $CDCl_3$ signal was set at 77.0 ppm. Equilibration reactions were carried out in the NMR tube in the thermostatted probe of the spectrometer. High-resolution mass spectra (HR-MS) were performed by an Electrospray Ionization Time-Of-Flight spectrometer. Flash chromatography was performed on Merck silica gel (230–400 mesh).

Materials

CD_3NO_2 and $AgNTf_2$ were commercial samples and used without further purification. THF was dried by distillation from sodium benzophenone ketyl. $CDCl_3$ was dried over activated molecular sieves (Aldrich, 4 Å).

Acid catalyzed transacetalations

The calculated amount of $\mathbf{C_2}$ was weighted in the NMR tube and $CDCl_3$ was added to obtain solutions at the desired total monomer concentration. The calculated volume of a 2.2 mM mother solution of TfOH in CD_3NO_2 was added to obtain a 2.5% mol catalyst concentration. Equilibrations were monitored by ^1H NMR.

Acid catalyzed transacetalations in the presence of template

To solutions prepared as described above, enough solid $AgNTf_2$ was added to obtain saturated solutions all the experiment long.

Cyclic oligomers C_2–C_4

Bis[4-(hydroxymethyl)phenyl]methane[13] (1.36 g, 6 mmol) was added to a suspension of NaH (60% w/w, 1.5 g, 37 mmol) in dry THF (90 mL). The suspension was heated to reflux and bromochloromethane (2.4 mL, 37 mmol) in dry THF (50 mL) was added dropwise by a syringe during 6 h under an argon atmosphere. The resulting mixture was refluxed for 2 days and then cooled to room temperature. Sodium hydroxide (1 M) was added to quench the excess of NaH. After addition of water, the mixture was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and evaporated to give 2.0 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 6 : 4, elution with CH_2Cl_2/heptane/acetone 10 : 4 : 0.2 gave the pure title compounds in the given order.

5,7,13,15-Tetraoxa-1,3,9,11(1,4)-tetrabenzenacyclohexadecaphane (C_2)

(100 mg, 7% yield). Mp 184.5–185.0 °C. ^1H NMR (300 MHz; $CDCl_3$) δ 7.03 (AA′BB′, 16H), 4.94 (s, 4H), 4.42 (s, 8H), 3.93 (s, 4H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 150.1, 135.9, 127.9, 126.8, 97.4, 71.3, 42.7; UV-vis $\lambda_{max}(CH_3CN)$/nm 264, 273 (ε/dm^3 mol^{-1} cm^{-1} 1330, 970); HR-MS (ESI-TOF) calculated for $C_{32}H_{32}O_4$+Na^+: 503.2198; found: 503.1924.

5,7,13,15,21,23-Hexaoxa-1,3,9,11,17,19(1,4)-hexabenzenacyclotetracosaphane (C_3)

(50 mg, 3.5% yield). Mp 189–189.6 °C. ^1H NMR (300 MHz; $CDCl_3$) δ 7.17 (AA′BB′, 24H), 4.77 (s, 6H), 4.57 (s, 12H), 3.95 (s, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 140.6, 135.5, 128.9, 128.2, 93.4, 69.0, 41.3; UV-vis $\lambda_{max}(CH_3CN)$/nm 263, 272 (ε/dm^3 mol^{-1} cm^{-1} 2530, 1770); HR-MS (ESI-TOF) calculated for $C_{48}H_{48}O_6$+Na^+: 743.3349; found: 743.3290.

5,7,13,15,21,23,29,31-Octaoxa-1,3,9,11,17,19,25,27(1,4)-octabenzenacyclodotriacontaphane (C_4)

(60 mg, 4% yield). Mp 195.6–196.1 °C. ^1H NMR (300 MHz; $CDCl_3$) δ 7.18 (AA′BB′, 32H), 4.80 (s, 8H), 4.59 (s, 16H), 3.96 (s, 8H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 140.6, 135.6, 128.9, 128.3, 93.9, 69.3, 41.3; UV-vis $\lambda_{max}(CH_3CN)$/nm 263, 272 (ε/dm^3 mol^{-1} cm^{-1} 3380, 2360); HR-MS (ESI-TOF) calculated for $C_{64}H_{64}O_8$+Na^+: 983.4499; found: 983.4224.

5,7,11,13-Tetraoxa-1,3,9(1,4)-tribenzenacyclotetradecaphane (2)

Cyclic oligomers ***p*-$\mathbf{C_2}$** (2.25 mg) and $\mathbf{C_2}$ (3.6 mg) were dissolved in 560 µL of $CDCl_3$. To the latter solution excess $AgNTf_2$ was added to obtain a saturated solution for the length of the experiment. The mixture was sonicated for ten minutes and after addition of 37 µL of a 20 mM CD_3NO_2 mother solution of TfOH, the suspension was stirred for three days at room temperature in the dark. The reaction was quenched with aqueous ammonia, and the organic phase was washed with water, dried over Na_2SO_4, and evaporated. Preparative TLC (CH_2Cl_2/heptane/acetone 10 : 4 : 0.2) of the crude product gave **2** (2 mg, 17% yield). Mp 148.0–150.2 °C. ^1H NMR (300 MHz; $CDCl_3$) δ 7.31 (s, 8H), 6.23 (s, 4H), 4.84 (s, 4H), 4.64 (s, 4H), 4.25 (s, 4H), 3.91 (s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 141.1, 137.7, 136.4, 128.7, 128.6, 128.1, 96.9, 73.1, 69.4, 42.2; UV-vis $\lambda_{max}(CH_3CN)$/nm 260, 273 (ε/dm^3 mol^{-1} cm^{-1} 773, 442); HR-MS (ESI-TOF) calculated for $C_{25}H_{26}O_4$+Na^+: 413.1729; found: 413.1727.

Acknowledgements

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7 The simple exponential equation $[\mathbf{C}_i] = EM_i\,[1 - \exp(-c_{mon})]$, where EM_i and a are adjustable parameters, fits remarkably well the experimental data in the plot of $[\mathbf{C}_i]$ *vs.* c_{mon}. Optimized values of EM_i (mM) and a (mM^{-1}), and the rms deviation (mM) are reported below in the given order for the two cyclic oligomers. $\mathbf{C}_2$: 4.36; 0.0485; 0.12. $\mathbf{C}_3$: 1.45; 0.0364; 0.033 (see ESI†).

8 The *EM** values given in the text coincide with the entropic component of the effective molarity for the cyclization of a bifunctional chain with r rotatable bonds (from ref. 9) divided by the symmetry number σ of the oligomeric ring. For the investigated $\mathbf{C}_i$ system, $r_i = 8i - 1$ and $\sigma_i = 2i$ (see ESI†).

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