Dynamic Covalent Chemistry

Amplification of Dynamic Chiral Crown Ether Complexes During Cyclic Acetal Formation**

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Dynamic covalent chemistry[1] relates to the study of chemical reactions carried out under thermodynamic control. Labile coordinative bonds associated with certain metal–ligand interactions,[2] ring-opening/ring-closing metathesis reactions,[3] and protocols for the formation of imines[4] and disulfides[5] have all been exploited in the strict self-assembly of catenanes and rotaxanes.[6] A wide range of other functionalities[7–11] have also been explored in the creation of dynamic combinatorial libraries (DCLs). We describe here the efficient and selective acid-catalyzed formation of a chiral macropolycyclic polyether constituted of multiple [24]crown-8 frameworks, which incorporate either two D- or two L-threitol residues as bicyclic diacetals, by using dynamic template-directed approaches[12] to amplify the production of the most thermodynamically preferred complex(es).

Carbohydrates command a unique status[13] in the realm of dynamic covalent chemistry.[1] Acid-catalyzed formation[13,14] of cyclic acetals from alditols and aldehydes or ketones provides a well-known reaction[15] in which covalent (C–O) bonds are made and broken with varying degrees of ease under thermodynamic control. The constitutions of the configurationally isomeric *erythro*- and *threo*-1,2,3,4-butanetetraols result[16] in their undergoing three different kinds of acetal ring closures with aldehydes and ketones: 1) 1,3:2,4-diacetal formation yields "6/6" bicycles, 2) 1,2:3,4-diacetal formation affords "5/5" bicycles, and 3) 1,4:2,3-diacetal formation yields "5/7" bicycles. With aldehydes, "6/6" or 1,3,5,7-tetraoxadecalin (TOD) formation usually predominates at equilibrium, whereas with ketones, "5/5" bicycles are invariably the major products. The TOD-forming reactions involving aldehydes (RCHO) are completely diastereospecific, that is, erythritol gives *trans*-TOD and threitol affords *cis*-TOD. The latter has long attracted the interest of stereochemists because of its highly distinctive stereoelectronic properties.[17]

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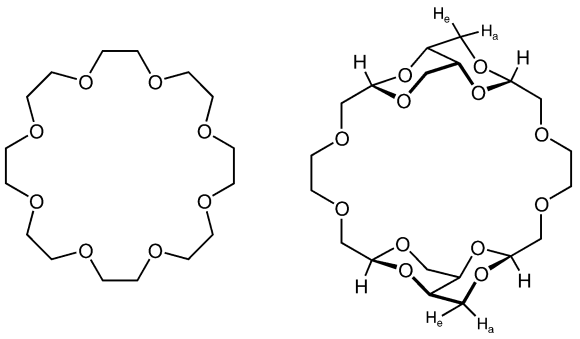
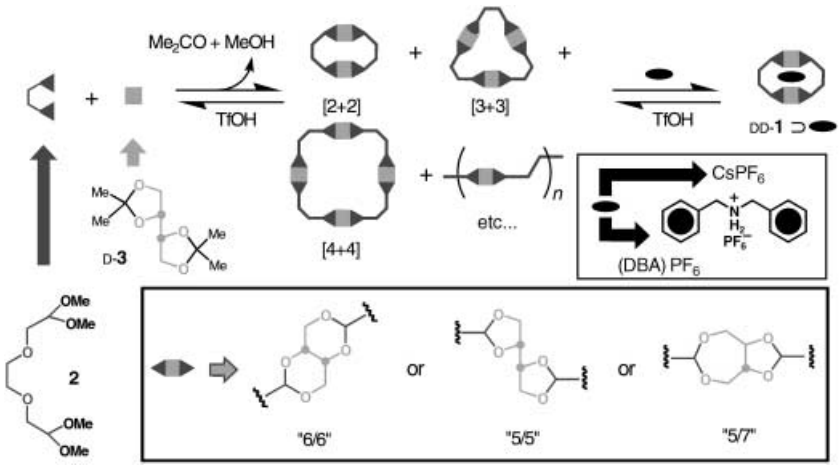
It is beyond any doubt that the O-inside conformations of *cis*-TOD with equatorial substituents (R) prevail at equilibrium.

In a recent quest for chiral [24]crown-8 derivatives that will form either complexes (pseudorotaxanes) or interlocked molecular compounds (catenanes or rotaxanes) with secondary dialkylammonium ($R'_2NH_2^+$) ions,[18] we have identified (Scheme 1) the macropolycyclic polyether DD-**1** containing two 2,6-disubstituted *cis*-TOD residues with O-inside conformations which is derived from D-threitol and linked in a macrocyclical manner by linkers containing bismethylenedioxy units. Numerous [24]crown-8 constitutions can be identified within DD-**1**. Inspection of molecular models reveals that all 12 of the oxygen atoms in DD-**1** can orient themselves toward the center of the relatively rigid host, thus creating an electron-rich environment for the complexation of electron-deficient guests, for example, $R'_2NH_2^+$ ions.

An initial attempt to react D-threitol[19] with the diacetal **2**[20] failed because of the insolubility of the former in organic solvents. We therefore decided to use a soluble derivative of D-threitol—namely the diacetonide D-**3**, which was prepared[21] by stirring the tetraol in Me_2CO in the presence of H_2SO_4. In the absence of a template, transacetalations (Scheme 2) between **2** and D-**3** proceed rapidly at room temperature in both CD_3CN and $CDCl_3$, after addition of an acid catalyst (triflic acid, TfOH) to give a complex mixture of products, including [2+2] TOD-containing [24]crown-8 derivatives, as indicated (Supporting Information) by mass spectrometry and ^{1}H NMR spectroscopy. The transacetalations are expected to occur with both enthalpic and entropic gains. For example, when DD-**1** is a product, the thermodynamically more stable "6/6" bicycles (TODs) should be formed in preference to "5/5" bicycles, such as is present in D-**3**. Entropy should increase during the reaction of two molecules of **2** with two molecules of D-**3** to give DD-**1** with the expulsion of four molecules of Me_2CO and eight molecules of MeOH.



Scheme 1. Structural formulas of [24]crown-8 and the [2+2] TOD-containing macropolycyclic polyether DD-**1**.



Scheme 2. The dynamic combinatorial virtual library (DCVL) generated in $CDCl_3$ solution from the diacetal **2** and the diacetonide D-**3**, prior to the addition of $CsPF_6$, after which [DD-**1**⊃Cs]$^+$ becomes amplified from a mixture which could, in principle, contain bicycles with "6/6", "5/5", and "5/7" constitutions in all possible permutations. Although the use of (DBA)PF_6 as a template did amplify the formation of [2+2] macropolycycles in CD_3CN, it did not produce [DD-**1**⊃DBA]$^+$ as a pure [2]pseudorotaxane.

The outcome of the reaction changed completely when dibenzylammonium hexafluorophosphate ((DBA)PF_6) was employed as the template. When this salt (1 equiv) was added to a solution of dry $CDCl_3$ containing equimolar amounts (40 mM) of **2** and D-**3**, a dynamic process could be initiated by addition of TfOH. Equilibrium was established after 3 days at 45 °C, and, while mass spectrometry revealed that the major products are [2+2] macropolycycles, ^{1}H NMR spectroscopy indicated that they are also a complex mixture of isomers that contain different bicyclic diacetals. The region in the ^{1}H NMR spectrum where signals for the acetal methine protons appear ($\delta = 4.4$–5.5 ppm) shows that, among the several products present, no more than 64% of the diacetal units[22] are "6/6" bicycles. Nonetheless, while a mixture of bicyclic diacetals was present in the reaction products, the MALDI-TOF mass spectrum revealed a relatively intense peak at m/z 662.32 which corresponds to the [2]pseudorotaxane composed of a DBA^+ ion template encircled by a [2+2] macropolycycle. Although it is possible that the various complexes are kinetically stable under the conditions of the reaction, and so do not equilibrate, it is more likely that [2+2] macropolycycles containing "6/6" and other bicycles form close to isoenergetic [2]pseudorotaxanes.

Changing the template[23] to $CsPF_6$ had a significantly beneficial effect upon the outcome (Scheme 2) of the dynamic transacetalations. The reaction between equimolar proportions (40 mM) of the diacetal **2** with the diacetonide D-**3** in dry $CDCl_3$ at 45 °C, using Cs^+ ions as the template, was initiated by addition of TfOH as a catalyst. The equilibration process was monitored (Figure 1) by ^{1}H NMR spectroscopy, primarily by focusing on the region ($\delta = 4.4$–5.5 ppm) where the acetal methine protons resonate in the spectrum. As the initially observed methine proton triplet at $\delta = 4.52$ ppm arising from the starting diacetal **2** decreases over several days, numerous new acetal methine signals begin to appear further downfield beyond $\delta = 4.8$ ppm. Presumably, a com-

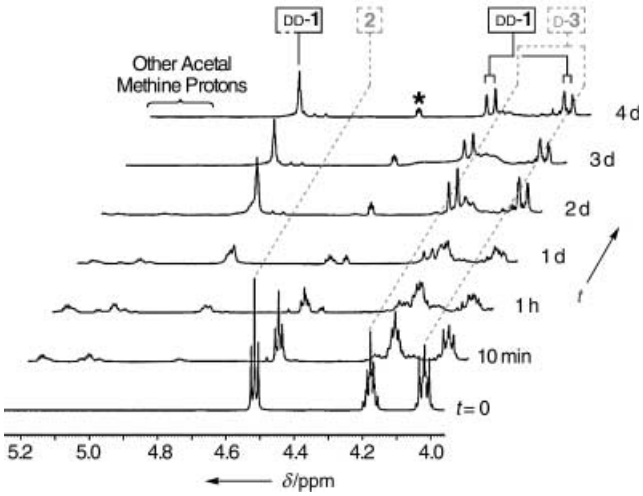


Figure 1. Stack of partial ^{1}H NMR spectra (500 MHz, $CDCl_3$, 298 K) recorded with time of an equilibrating equimolar (40 mM) mixture of the diacetal **2** and the diacetonide D-**3** in which Cs^+ ions are employed as the template. The slanting scale entries display the times after addition of the catalyst (TfOH) to initiate the equilibration process, which is complete after four days. The product is identified by solid lines and the reactant by dashed ones. The signal centered around $\delta = 4.5$ ppm and indicated by the asterisk results from a by-product formed during the reaction. It is removed during purification.

plex mixture containing isomeric bicyclic diacetals with "5/5", "6/6", and "5/7" constitutions is formed (Figure 2) under kinetic control. Subsequently and concomitantly, the resonances for these initially formed kinetic products decrease and a single predominantly broad singlet at $\delta = 4.86$ ppm, associated with the acetal methine protons in the "6/6" bicycle, begins to experience an increase in its relative intensity. Signals for the H_a and H_e protons (Scheme 1) in DD-**1** were also characteristically present in the spectrum as a broadened pair of doublets, centered on $\delta = 4.01$ ppm and 4.22 ppm, respectively. Thus, it is clear (Figure 2) that, as the resonances for the kinetic products undergo a decrease in their relative intensities, those associated with the macropolycyclic polyether containing two "6/6" bicycles increase in

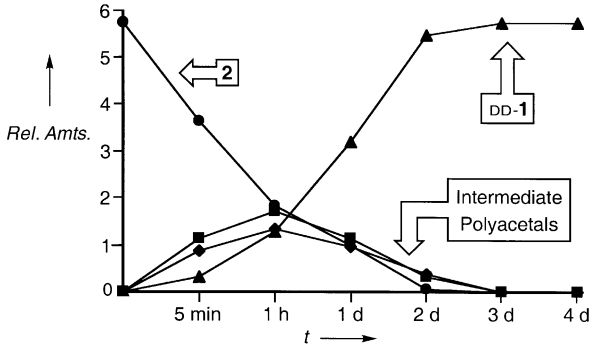


Figure 2. A graphical representation of the relative integrals (Rel. Amts.) for the acetal proton signals with time illustrating the consumption of the diacetal **2** (●), the production of two other intermediate polyacetals (■ and ◆) formed under kinetic control, and the formation of the macropolycyclic polyether DD-**1** from **2** and D-**3**, both 40 mM in $CDCl_3$ at 318 K.

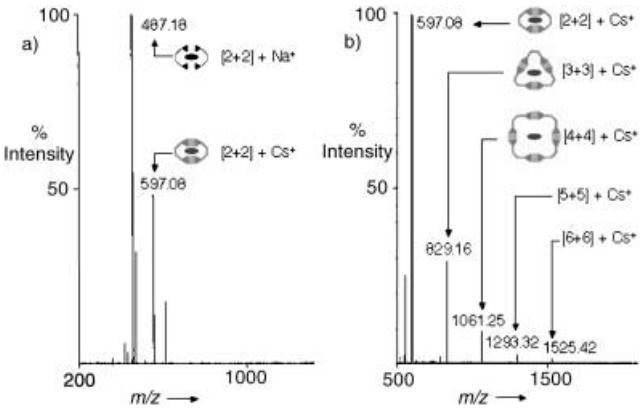
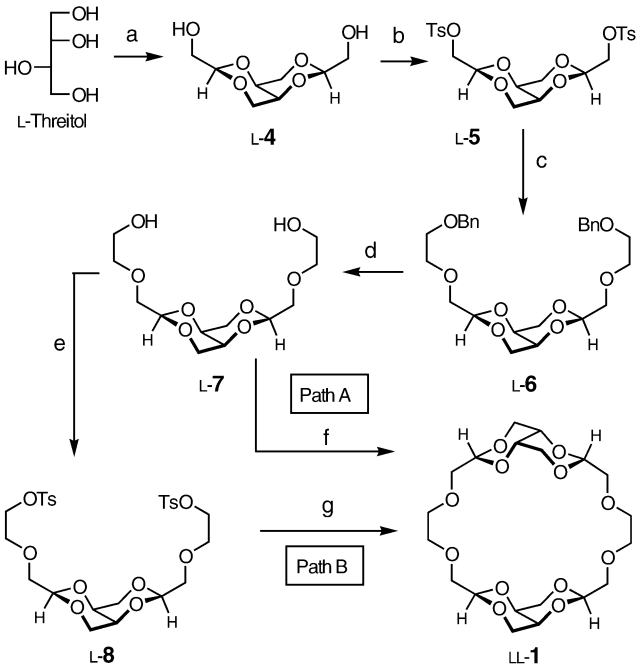


Figure 3. MALDI-TOF mass spectra of the equilibrium mixtures, obtained when the diacetal **2** and the diacetonide D-**3** were equilibrated for nine days in a) $CDCl_3$ and b) CD_3CN in the presence of $CsPF_6$ as template and TfOH as catalyst.

their relative intensities, which indicates that DD-**1** is being amplified in the presence of the Cs^+ ion template. ^{1}H NMR spectroscopy indicates that the conversion[24] of **2** and D-**3** into DD-**1** is all but quantitative after 3 days, that is, $> 95\%$ in dry $CDCl_3$ at 45 °C. The MALDI-TOF mass spectrum (Figure 3 a) of the equilibrated reaction mixture showed molecular ion peaks for both $[M+Na]^+$ (Na^+ ions are present in the matrix) and $[M+Cs]^+$ arising from the [2+2] macropolycycle. Peaks for higher polycyclic oligomers were absent to all intents and purposes. When this dynamic reaction was scaled up (see Experimental Section), DD-**1** was isolated in a 58% (unoptimized) yield and fully characterized as the [2+2] TOD-containing [24]crown-8 derivative by mass spectrometry and 2D NMR spectroscopy.[25] Interestingly, when CD_3CN is used as the reaction solvent, the Cs^+ ion template is not nearly as effective in amplifying DD-**1** from the dynamic mixture. In addition to this [2+2] macropolycyclic polyether, there is evidence for the presence of higher polycyclic oligomers.

To establish beyond any shadow of a doubt that the structure of the [2+2] macropolycyclic polyether corresponds to DD-**1**, and to be in a position to compare the efficiency of the dynamic approach with kinetic ones, we have synthesized LL-**1** in a conventional manner (Scheme 3). L-Threitol was treated with the glycoaldehyde dimer[26] to give L-**4** in 70% yield. The ditosylate L-**5** was obtained from L-**4** in high yield and was used to alkylate, rather inefficiently, 2-(benzyloxy)-ethanol[27] to afford the dibenzyl ether L-**6** in modest yield. Following near quantitative catalytic hydrogenolysis to give the diol L-**7**, it was tosylated to give the ditosylate L-**8** in a good yield. Macropolycyclization to form LL-**1** was achieved by means of two alternative pathways (Paths A and B) in the presence of base, under high dilution conditions using Cs^+ ions as templates to facilitate[28] the formation of LL-**1**. Reaction (Path A) of the diol L-**7** with the ditosylate L-**5** gave LL-**1** in 6.7% yield, whereas reaction (Path B) of the diol L-**4** with the ditosylate L-**8** gave LL-**1** in 5.8% yield.

Clearly, the isolated overall yields of DD/LL-**1** starting from D/L-threitol using the kinetic approach is considerably lower (1.4% over five steps along Path A and 0.8% over six steps along Path B) than for the thermodynamic approach (mini-



Scheme 3. a) Glycoaldehyde dimer, 1 M HCl, 70%; b) TsCl, NaH, THF, 85 °C, 88%; c) 2-(benzyloxy)ethanol, NaH, DMF, 90 °C, 35%; d) H_2, Pd-C, EtOH, H_2O, 92%; e) TsCl, Et_3N, CH_2Cl_2, 68%; f) L-**5**, CsOTs, NaH, DMF, 100 °C, 6.9%; g) L-**4**, CsOTs, NaH, DMF, 100 °C, 5.8%. Ts = toluene-4-sulfonyl, Bn = benzyl.

mally 30% over two steps), thus proving the superiority of dynamic covalent chemistry[1] over the more conventional procedures (Scheme 3). These preliminary results lay the foundations for the creation of much more intricate transacetalations[29] and DCVLs, which will include many different components in the virtual library, as well as a range of templates, both reusable and consumable.

Experimental Section

2: $HOCH_2CH_2OH$ (5 mL, 90 mmol) was added dropwise to a suspension of NaH (95%, 6.80 g, 269 mmol) in $ClCH_2CH(OMe)_2$ (100 mL, 896 mmol) at 0 °C. The reaction mixture was heated (140 °C) under reflux for 24 h and the resulting brown gum was dissolved in H_2O (100 mL). The aqueous solution was concentrated under high vacuum and then diluted again with H_2O (250 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 250 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under vacuum. The resulting oil was subjected to column chromatography (basic Al_2O_3, hexanes then CH_2Cl_2) to give **2** (19 g, 90%) as a pale yellow liquid. ^{1}H NMR (500 MHz, CD_3OD): $\delta = 3.37$ (s, 12H), 3.50 (d, $J = 5.2$ Hz, 4H), 3.63 (s, 4H), 4.49 ppm (t, $J = 5.2$ Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 54.3$, 71.8, 104.1 ppm; FABMS: *m*/*z*: 499.3 $[2M+Na]^+$, 261.3 $[M+Na]^+$, 207.2 $[M-OMe]^+$; HRMS (FAB) *m*/*z* calcd for $C_{10}H_{22}NaO_6$ $[M+Na]^+$: 261.1314, found: 261.1314.

General procedure for NMR experiments. Compounds **2** (9.5 mg, 40 μmol) and D-**3** (8.1 mg, 40 μmol), in addition to either $(DBA)PF_6$ (8.8 mg, 22 μmol) or $CsPF_6$ (6.1 mg, 22 μmol) as the template, were added to an NMR tube and dissolved in either $CDCl_3$ or CD_3CN (1 mL). TfOH (2 μL, 0.02 μmol) was added to the mixture to initiate the dynamic process while the solutions were maintained at 45 °C. The equilibrations and amplifications of the products in the DCVLs were monitored by ^{1}H NMR spectroscopy and mass spectrometry.

DD-**1**: A mixture of **2** (181 mg, 0.80 mmol), DD-**3** (160 mg, 0.80 mmol), and $CsPF_6$ (122 mg, 0.44 mmol) was added to dry $CHCl_3$ (20 mL) and TfOH (40 μL, 0.45 μmol) was introduced into the stirred solution. The reaction mixture was maintained at 45 °C for 3 days and then quenched with iPr_2NEt. The solvents were removed under vacuum and the resulting oil was subjected to column chromatography (SiO_2, CH_2Cl_2/MeOH (9:1)) to afford DD-**1** (108 mg, 58%) as a foamy solid. $[\alpha]_D = -18.0$ ($c = 1$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.60$–3.78 (m, 20H), 3.79 (s, 4H), 3.98 (d, $J =$ 12.8 Hz, 4H), 4.28 (d, $J = 12.8$ Hz, 4H), 4.86 ppm (br s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 69.1$, 69.6, 69.9, 70.6, 98.6 ppm; MALDI-TOF-MS *m*/*z* calcd for $C_{20}H_{32}NaO_{12}$ $[M+Na]^+$: 487.1786, found: 487.1786.

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[12] A number of dioxadiazadecalin–salen tautomeric macrocycles and complexes have been shown to constitute dynamic combinatorial virtual libraries (DCVLs); see A. Star, I. Goldberg, B. Fuchs, *Angew. Chem.* **2000**, *112*, 2797 – 2801; *Angew. Chem. Int. Ed.* **2000**, *39*, 2685 – 2689.

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[24] This estimate of the extent of the conversion is based on the integration of all the acetal methine proton signals in the ^1H NMR spectrum.

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