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Kinetically and thermodynamically controlled synthesis of tetraoxa[1_4]metacyclophanes and hexaoxa[1_6]metacyclophanes

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Abstract—The nucleophilic aromatic substitution of 1,5-difluoro-2,4-dinitrobenzene with 2-propylresorcinol in Et_3N/CH_3CN produces a mixture of *syn* and *anti* conformers of the cyclic tetramer and the cyclic hexamer with a kinetically controlled product distribution. Moreover, the reaction in DMF was catalyzed by CsF to also produce a mixture of these cyclic oligomers. In this case, however, the C–O bond is cleaved by the fluoride ion and the cyclization reaction is reversible; therefore, in the presence of excess CsF, the thermodynamically favored product (*syn*-isomer of cyclic tetramer) is obtained as the major product. The structures of the two conformational isomers of cyclic tetramers were determined by X-ray crystallography.

The synthesis of macrocycles by connecting small building blocks to each other produces a mixture of cyclic and linear oligomers. The product distribution is kinetically determined if the bond formation is an irreversible reaction. The undesired side-reaction is the formation of linear oligomers larger than the appropriate precursor that cyclizes to the target macrocycle. In order to circumvent this reaction, the syntheses of macrocycles are often carried out under high-dilution conditions to favor the intramolecular cyclization over the intermolecular propagation.[1]

Macrocycles that are widely used in supramolecular chemistry, such as calixarenes,[2–4] resorcinarenes,[5–7] and cucurbiturils,[8,9] are readily prepared from simple starting materials with the formation of many bonds under non-high-dilution conditions. Their easy availability makes them useful molecular platforms for constructing a variety of functional molecules. Such a facile and selective formation of a specific product is the subject of dynamic covalent chemistry,[10] where the covalent bond has the ability to be formed and reversibly broken; namely, all products are in equilibrium in a thermodynamically controlled reaction. If by chance the specific macrocycle is the most stable compound, it will be formed in good yield.

A variety of tetraoxa[1_4]metacyclophane **1** (Fig. 1) have been prepared by the nucleophilic aromatic substitution of 1,5-dihalo-2,4-dinitrobenzenes **2** with 1,3-dihydroxybenzenes **3**.[11–14] Very interestingly, a variety of oxygen atom-bridged macrocycles were obtained in remarkably high yields without using high-dilution conditions. Hence, Katz suggested that the formation of the C–O bonds is a reversible process and the cyclic tetramers are the thermodynamically most stable products.[14] Very recently, the first examples of hexaoxa[1_6]metacyclophanes and octaoxa[1_8]metacyclophanes were reported.[15] The yields of these larger macrocycles largely depend upon the reaction conditions. However, the reversible nature of the reaction has not been established.

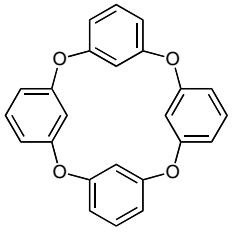

Figure 1. Tetraoxa[1_4]metacyclophane **1**.

Keywords: Oxacalixarene; Tetraoxametacyclophane; Cesium fluoride; Nucleophilic aromatic substitution; Thermodynamically controlled reaction.
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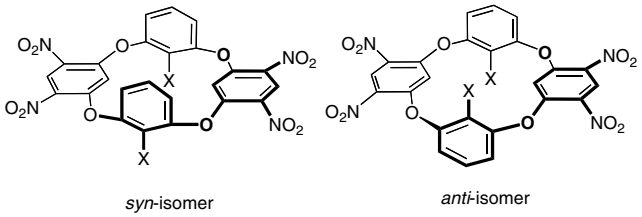


Figure 2. Schematic representation of two conformational isomers of cyclic tetramers.

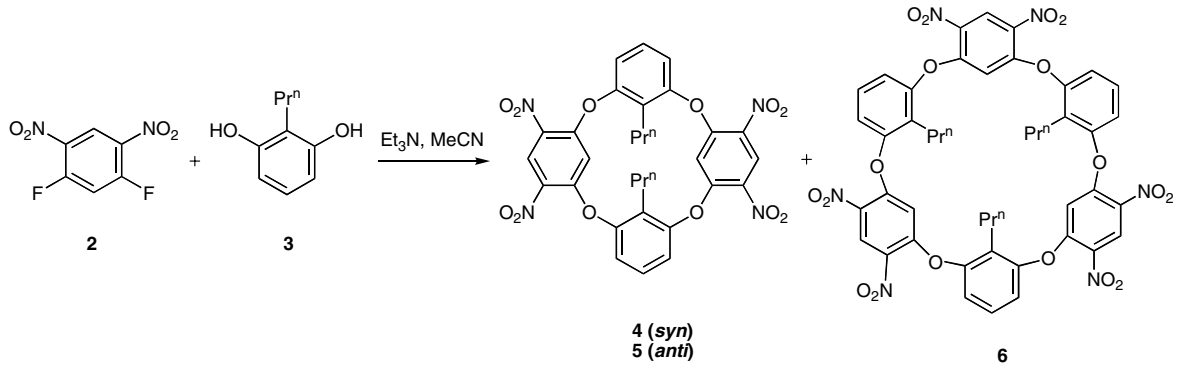
In the [1_4]metacyclophane system, a bulky substituent on the intra-annular position cannot pass through the central annulus.[2] Hence, tetraoxametacyclophanes bearing two sufficiently large groups at the intra-annular positions on the opposite aromatic rings should exist in two non-interconverting *syn* and *anti* conformers as shown in Figure 2. This prediction prompted us to prepare these conformational isomers and to investigate the effect of the reaction conditions on the product distribution. Thus, we have studied the condensation of 1,5-difluoro-2,4-dinitrobenzene **2** with 2-propylresorcinol **3**. Herein, we would like to describe the formation of two cyclic tetramers (*syn* and *anti*) and a cyclic hexamer, and the conversion of the kinetic products into the thermodynamic product.

The reaction of equimolar amounts of **2** and **3** in CH_3CN in the presence of 2.2 equiv of Et_3N was conducted under reflux (Scheme 1).[†] After a 4-h reaction, three cyclic oligomers, that is, two conformational isomers of the cyclic tetramers **4** (*syn* isomer) and **5** (*anti* isomer), and the cyclic hexamer **6**, were isolated in 21%, 20%, and 16% yields, respectively. The stereochemistry of the *syn*- and *anti*-isomers was evaluated by X-ray crystallography, which is shown in Figure 3.[‡] In this reaction, the reaction time has no apparent effect on the product distribution. Furthermore, the interconversion between three cyclic oligomers could not be detected in the presence of Et_3N in CH_3CN. Hence, it is concluded that this nucleophilic aromatic substitution mostly results in the kinetically controlled product distribution.

The reverse reaction requires an aromatic C–O bond scission, which should proceed via an *ipso*-attack of the leaving group, the fluoride anion. The nucleophilicity of the fluoride anion is significantly enhanced in aprotic polar solvents. Indeed, it has been reported that the ether exchange reaction of aromatic polyethers bearing strong electron withdrawing groups was catalyzed by the fluoride ion in aprotic solvents.[16,17] These results prompted us to examine the reaction of the cyclic oligomers with CsF in DMF. The oligomers, **4**, **5**, and **6**, are stable in pure DMF at 100 °C for 4 h, but the addition of a 0.1 equiv of CsF to this DMF solution resulted in the conformational change of **5** to **4** and the reconstruction of hexamer **6** to tetramer **4** within 2 h at 100 °C. These results clearly demonstrate that, in the presence of CsF, the cyclic oligomers **5** and **6** are converted to linear oligomers, which produce the thermodynamically favored cyclic tetramer **4** (Scheme 2). Therefore, we concluded that fluoride ion in aprotic polar solvents has a catalytic activity for the conversion of cyclic oligomers.

[†] Reaction in Et_3N/CH_3CN. A mixture of 1,5-difluoro-2,4-dinitrobenzene (204 mg, 1 mmol) and 2-propylresorcinol (152 mg, 1 mmol) was placed in a 20 ml flask under an argon atmosphere. To this was added a solution of Et_3N (223 mg, 2.2 mmol) in CH_3CN (10 ml), and the mixture was heated under reflux with stirring. After 3 h, the solvent was removed under reduced pressure. The residual material was triturated with ethyl acetate to leave a mixture of **4** and **5** (95 mg). The soluble fraction was washed with water, dried over Na_2SO_4, concentrated to dryness, and subjected to GPC separation. Two fractions, a mixture of **4** and **5** (37 mg) and **6** (51 mg), were obtained. Two conformers **4** and **5** were separated by preparative thin layer chromatography. Yields; **4** (21%), **5** (20%), **6** (16%). *syn*-$1^{4,6},5^{4,6}$-Tetranitro-$3^2,7^2$-dipropyl-2,4,6,8-tetraoxa-1,3,5,7(1,3)-tetrabenzenacyclooctaphane, **4**: Recrystallization from THF/hexane. Mp 231 °C (dec). Anal Calcd for $C_{30}H_{24}N_4O_{12}$: C, 56.96; H, 3.82; N, 8.86. Found: C, 57.06; H, 3.93; N, 8.74. MS (FAB) 633.1 ($[M+1]^+$). ^1H NMR (DMSO-d_6, 50 °C) δ 0.758 (t, 6H, $CH_2CH_2CH_3$), 1.459 (sext, 4H, $CH_2CH_2CH_3$), 1.999 (t, 4H, $CH_2CH_2CH_3$), 5.341 (s, 2H, ArH), 7.238 (d, 4H, ArH), 7.471 (t, 2H, ArH), 8.987 (s, 2H, ArH). *anti*-$1^{4,6},5^{4,6}$-Tetranitro-$3^2,7^2$-dipropyl-2,4,6,8-tetraoxa-1,3,5,7(1,3)-tetrabenzenacyclooctaphane, **5**: Recrystallization from DMSO. Mp 235 °C (dec). Anal Calcd for $C_{30}H_{24}N_4O_{12}$: C, 56.96; H, 3.82; N, 8.86. Found: C, 57.10; H, 3.86; N, 8.73. MS (FAB) 633.1 ($[M+1]^+$). ^1H NMR (DMSO-d_6, 50 °C) δ 0.736 (t, 6H, $CH_2CH_2CH_3$), 1.316 (sext, 4H, $CH_2CH_2CH_3$), 2.177 (t, 4H, $CH_2CH_2CH_3$), 5.634 (s, 2H, ArH), 7.164 (d, 4H, ArH), 7.456 (t, 2H, ArH), 8.950 (s, 2H, ArH). $1^{4,6},5^{4,6},9^{4,6}$-Hexanitro-$3^2,7^2,11^2$-tripropyl-2,4,6,8,10,12-tetraoxa-1,3,5,7,9,11(1,3)-hexabenzenacyclododecaphane, **6**: Recrystallization from chloroform. Mp 228 °C (dec). Anal Calcd for $C_{45}H_{36}N_6O_{18}\cdot CHCl_3$: C, 51.72; H, 3.49; N, 7.87. Found: C, 51.49; H, 3.43; N, 7.78. MS (FAB) 949.3 ($[M+1]^+$). ^1H NMR (DMSO-d_6, 50 °C) δ 0.816 (t, 9H, $CH_2CH_2CH_3$), 1.526 (sext, 6H, $CH_2CH_2CH_3$), 2.579 (t, 6H, $CH_2CH_2CH_3$), 6.776 (s, 3H, ArH), 7.032 (br, 6H, ArH), 7.245 (t, 3H, ArH), 8.969 (s, 3H, ArH).

[‡] X-ray crystal structure analysis: The X-ray data were collected at 173 K using a Rigaku-RAPID imaging plate area detector with graphite monochromated Mo-Kα ($\lambda = 0.7107$ Å) radiation using the ω scan mode. The structure was solved by direct methods (SIR92)[21] and expanded using Fourier techniques (DIRDIF94).[22] The non-hydrogen atoms were anisotropically refined. Hydrogen atoms were included at the calculated positions, but not refined. All calculations were performed using a crystallographic software package, CrystalStructure version 3.6.0. Crystals of **4** were obtained by recrystallization from DMF: $C_{30}H_{24}N_4O_{12}$, $M = 632.54$, tetragonal, space group $I\text{-}42d$ (no. 122), $a = 15.550(9)$, $c = 23.748(8)$ Å, $V = 5742(5)$ Å^3, $Z = 8$, $\rho_c = 1.463$ g cm^{-3}, $2\theta_{max} = 55.0°$. $F(000) = 2624$. A total of 23,585 reflections were measured, 22,948 unique. The final cycle of full-matrix least squares refinement was based on all observed reflections, 210 variable parameters, with factors of $R = 0.134$, $Rw = 0.111$, GOF = 1.062. Crystals of **5** were obtained by vapor diffusion of hexane into chloroform solution: $C_{30}H_{24}N_4O_{12}$, $M = 632.54$, $M = 632.54$, monoclinic, space group $P2_1/n$ (no. 14), $a = 8.814(7)$, $b = 9.514(6)$, $c = 17.61(1)$ Å, $\beta = 99.85(3)°$, $V = 1454(1)$ Å^3, $Z = 2$, $\rho_c = 1.444$ g cm^{-3}, $2\theta_{max} = 55.0°$. $F(000) = 656$. A total of 3192 reflections were measured, 3192 unique. The final cycle of full-matrix least squares refinement was based on all observed reflections, 221 variable parameters, with factors of $R = 0.164$, $Rw = 0.168$, GOF = 1.006. Crystallographic data in cif format (Ref. CCDC 298642 and 298643) can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



Scheme 1.

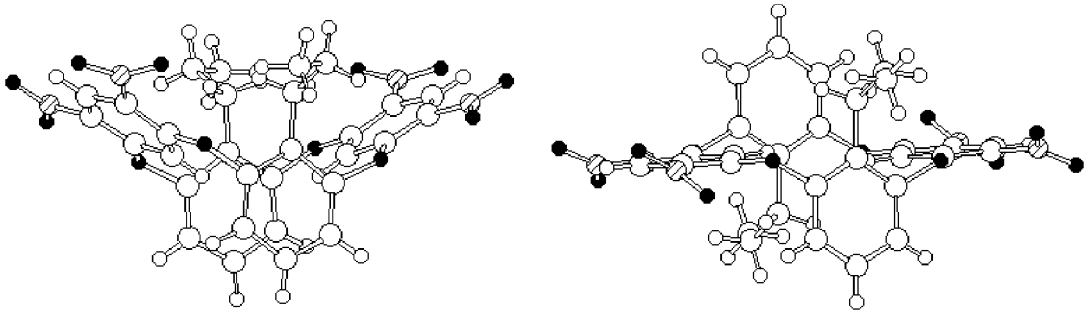
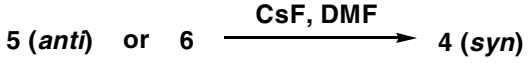


Figure 3. Crystal structures of cyclic tetramers: **4** (left); **5** (right).



Scheme 2.

Next, we describe the CsF-catalyzed cyclocondensation. Cesium fluoride can be used as a base (proton acceptor) for the preparation of aromatic ethers.[18–20] Since the ether formation reaction should be reversible in the presence of CsF, the CsF-catalyzed reaction of **2** and **3** would be expected to afford cyclic oligomers with thermodynamically controlled distribution. Thus, the reaction of an equimolar amount of **2** and **3** was conducted in DMF under argon. The reaction mixture was diluted with aqueous methanol to precipitate the crude products, which were analyzed by ^{1}H NMR spectroscopy.[§] The results of the reactions performed at 100 °C are summarized in Table 1. The yields of the cyclic products depend upon the reaction conditions such as temperature, time, and amount of CsF.

Table 1. The CsF-catalyzed reaction of 1,5-difluoro-2,4-dinitrobenzene **2** with 2-propylresorcinol **3** in DMF at 100 °C[a]

Entry	CsF/mmol	Time/h	Yield/%[b]		
			4	**5**	**6**
1	0	2	0	0	0
2	0.1	2	35	21	14
3	0.1	4	38	18	16
4	0.5	2	62	0	20
5	0.5	4	34	0	7
6	1.0	0.5	52	7	13
7	1.0	1	79	0	9
8	1.0	2	75	0	0
9	2.0	0.5	51	0	25
10	2.0	1	89	0	0
11	2.0	2	9	0	0

[a] Conditions: **2** (0.5 mmol), **3** (0.5 mmol), DMF (2.5 ml).
[b] The yields were determined by analysis of the crude products using ^{1}H NMR spectroscopy.

Since hydrogen fluoride that was generated during the reaction reacts with fluoride ion to form less reactive hydrogen bifluoride, it was anticipated that a minimum of 2 mol of CsF for 1 mol of the resorcinol, which has two hydroxyl groups, must be required for condensation.[17] In the present experiments, we used **2** and **3**, each 0.5 mmol, then the required amount of CsF was 1 mmol. In fact, in the absence of CsF, no cyclic oligomers were obtained (entry 1). However, it is very interesting to note that the reaction with 0.1 or 0.5 mmol of CsF afforded the cyclic oligomers in good yields

[§] Reaction in CsF/DMF: A mixture of 1,5-difluoro-2,4-dinitrobenzene (102 mg, 0.5 mmol), 2-propylresorcinol (77 mg, 0.5 mmol), and CsF (152 mg, 1.0 mmol) in dry DMF (2.5 ml) was stirred at 100 °C for 1 h under an argon atmosphere. After cooling, water (5 ml) and methanol (5 ml) were added to this mixture. The resulting insoluble material was collected by suction, thoroughly washed with methanol, and dried under vacuum to afford **4** in 79% yield.

(entries 2–5). These results clearly indicate that a catalytic amount of CsF is effective for cyclization. The shorter reaction time or the lower reaction temperature resulted in the formation of complex mixture of linear oligomers containing a small amount of cyclic oligomers (data not shown in table). The conversion of **5** to **4** took place much faster than the conversion of **6** to **4**. An excess amount of CsF was needed to complete conversion of **6** to **4**. Thus, the reaction at 100 °C for 1 h in the presence of a 2-fold excess of CsF yielded the thermodynamically favored product in good yield. However, it should be noted that the longer reaction times rapidly reduced the yield of the product (entries 5, 8, and 11). This is probably due to the ether cleavage by water present as a contaminant in the solvent.

Next, we discuss the conformational properties of the two cyclic tetramers, **4** and **5**. In the ^{1}H NMR spectra in DMSO-d_6 at 50 °C, **4** and **5** display the intra-annular aromatic protons as a singlet at 5.34 and 5.63 ppm, respectively. The up-field shifts of these signals, by 1.1–1.4 ppm compared to that of the corresponding signal of **6**, suggested that the intra-annular protons of the cyclic tetramers locate in the shielded region of neighboring aromatic rings. Thus, it is presumed that their preferred conformations in solution resemble those determined by crystallographic analysis, which are shown in Figure 3. In the solid state, the *syn*-isomer adopts a non-symmetrical 1,3-alternate conformation, and the *anti*-isomer adopts a chair conformation. For both molecules, two aromatic rings bearing the propyl group are nearly perpendicular to their mean plane consisting of four bridging oxygen atoms. As described above, the interconversion between **4** and **5** did not occur in DMF at 150 °C. Therefore, it is concluded that the propyl group cannot pass through the central annulus of **1**. Moreover, the variable temperature NMR spectra of **4** and **5** did not reveal significant changes when measured in DMSO-d_6 (303–423 K), indicating rigid molecular frameworks.

In summary, the nucleophilic aromatic substitution of **2** with **3** in Et_3N/CH_3CN produces a mixture of two conformational isomers of the cyclic tetramers (*syn* and *anti* isomer), and the cyclic hexamer with a kinetically controlled product distribution. Moreover, the reaction of **2** and **3** in DMF was catalyzed by CsF to also produce a mixture of cyclic oligomers. Since the C–O bond is cleaved by fluoride ion, the cyclization reaction is reversible. Hence, in the presence of excess CsF, the thermodynamically favored product **4** (*syn* isomer) is selectively obtained.

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