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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3029–3032

Synthesis and disproportionation of ABAC-type oxacalix[4]arenes

Hisatoshi Konishi,* Takayuki Mita, Osamu Morikawa and Kazuhiro Kobayashi

Department of Materials Science, Faculty of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan

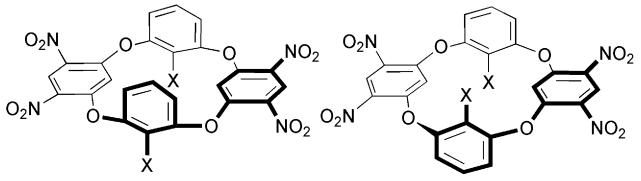
Received 28 December 2006; revised 19 February 2007; accepted 26 February 2007
Available online 1 March 2007

Abstract—An efficient method to prepare ABAC-type oxacalix[4]arenes by a '3+1' fragment synthesis and their CsF-catalyzed disproportionation producing an equilibrium mixture of three oxacalix[4]arenes are described.

Replacement of the methylene bridges between the aromatic units of calixarenes by heteroatoms such as sulfur,[1] nitrogen,[2] and oxygen[3] forms heteroatom-bridged calixarenes.[4] Since this replacement modifies the size, conformational mobility and molecular recognition properties of the macrocycles, these modified calixarenes have attracted considerable research interest as molecular building blocks for constructing supramolecular architectures.

Generally, heteroatom-bridged calixarenes have been obtained by a single-step reaction. For example, oxacalixarenes have been prepared by the reaction of activated 1,3-dihalobenzenes and 1,3-dihydroxybenzenes. This process produces ABAB-type macrocycles in which two different aromatic units are incorporated in an alternating order. As far as we are aware, three different aromatic units have not previously been incorporated into these macrocycles.

Recently, we demonstrated the kinetically and thermodynamically controlled synthesis of oxacalix[4]arenes **1**.[5] Thus, the triethylamine-catalyzed nucleophilic aromatic substitution of 1,5-difluoro-2,4-dinitrobenzene **2** with 2-propylresorcinol **3b** in a 1:1 molar ratio in acetonitrile produced a mixture of two oxacalix[4]arenes (*syn*- and *anti*-isomers, Fig. 1) and oxacalix[6]arene. In this reaction, the reaction time had little effect on the product distribution. Furthermore, these cyclic compounds did not interconvert in the presence of triethylamine. Hence, it is concluded that this nucleophilic aromatic substitution mostly results in kinetically controlled product distribution. On the other hand, although the reaction catalyzed by CsF in DMF produced a mixture of cyclic compounds, the product distribution depended upon the reaction time, that is, the C–O bond formation is a reversible process. Analogous ether bond cleavage of aromatic polyethers bearing electron-withdrawing groups catalyzed by the fluoride ion in aprotic solvents was reported.[6] Thus, CsF-catalyzed the conversion of the *anti*-isomer and the hexamer to the *syn*-isomer in this solvent, which is selectively prepared in good yields in the CsF/DMF system. These data established that the *syn*-isomer of oxacalix[4]arene is the thermodynamically favored product.



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a. X=H; b. X=*n*-Pr; c. X=NO_2; d. X=Br

Figure 1. Schematic representation of the *syn*- and *anti*-isomers of ABAB-type oxacalix[4]arenes.

We have now applied the kinetically controlled conditions to obtain a linear trimer with an ABA-sequence, and have prepared ABAC-type oxacalixarenes by a '3+1' fragment synthesis.[7,8] Furthermore, we have developed the disproportionation of the ABAC-type macrocycles into ABAB- and ACAC-type ones under thermodynamically controlled conditions.

The triethylamine-catalyzed reaction of **2** with resorcinol **3a** (3:1 molar ratio) in MeCN produced linear

Keywords: Oxacalixarene; Metacyclophane; Disproportionation.
* Corresponding author. Fax: +81 857315331; e-mail: konis@chem.tottori-u.ac.jp

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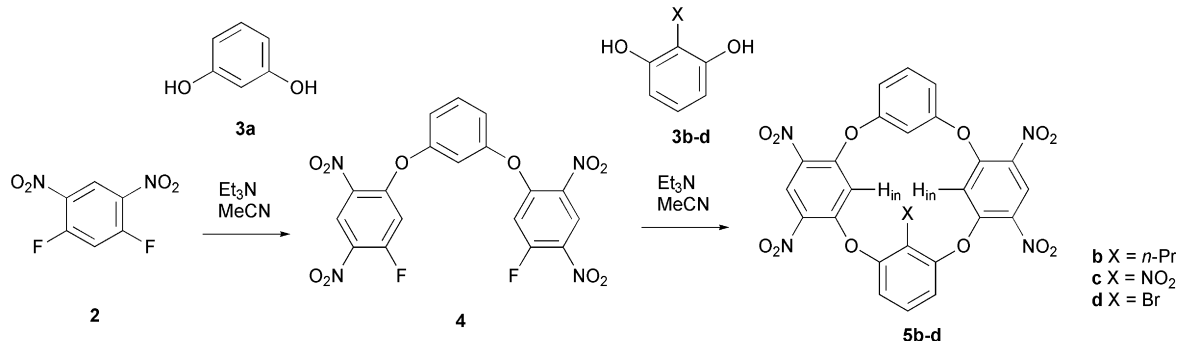
doi:10.1016/j.tetlet.2007.02.118



Scheme 1. Synthesis of ABAC-type oxacalix[4]arenes.

trimer **4** in 71% yield (Scheme 1).[†] This indicates that the remaining fluorine atom of **4** is much less reactive than that of **2**. The macrocyclization of linear trimer **4** with resorcinols **3b–d** (1:1 molar ratio) sufficiently took place in Et_3N/MeCN, and the ABAC-type oxacalix[4]arenes **5b–d** were obtained in 69–78% yields.[‡] In DMSO-d_6 at 50 °C, the ABAC-type oxacalix[4]arenes **5b**, **5c** and **5d** display the signals of their intra-annular aromatic protons of the dinitrobenzene units (H_{in}) at 5.53, 5.79 and 5.58 ppm, respectively. The up-field shifts of these signals, by 0.8–1.1 ppm compared to those of the corresponding signals of **1a** that have no substituents at the intra-annular position, can be accounted for by the ring current effect of the neighboring resorcinol rings. Since the H_{in} protons of ***syn*-1b** and ***anti*-1b** appear at 5.34 and 5.63 ppm, respectively, it is suggested that the preferred conformations of these oxacalix[4]arenes bearing one or two substituents at the intra-annular positions are similar. In the solid state, the conformation of ***syn*-1b** and ***anti*-1b** is schematically represented as 'boat (or 1,3-alternate)' and 'chair', respectively (Fig. 1).[5] For both isomers, the two resorcinol rings are almost perpendicular to the plane formed by the four bridging oxygen atoms and the H_{in} protons are located in the shielding region of the neighboring resorcinol rings. Since the *syn*-isomer is thermodynamically more stable than the *anti*-isomer, we estimate that the preferred conformations of these ABAC-type oxacalix[4]arenes are boat (or 1,3-alternate) in solution.

It is noteworthy that the CsF-catalyzed reaction of **2** with resorcinol **3a** (3:1 molar ratio) in DMF produces oxacalix[4]arene **1a** as the major product and trimer **4** only in trace amounts. Under these conditions, the C–O bond formation is a reversible process, therefore, the thermodynamically most stable product **1a** selectively forms. From these results, it could be expected that the ABAC-type macrocycles should convert to the ABAB- and ACAC-type ones in the presence of CsF. To determine whether it is possible for the product distribution to reach its thermodynamic equilibrium, the disproportionation experiment of **5b** was done in an NMR tube in DMSO-d_6 in the presence of CsF at 80 °C.[§] The ^{1}H NMR spectral spectra were recorded at regular time intervals. The spectral changes in the region of H_a signals are shown in Figure 2. The signal for **5b** gradually decreased and new signals assigned to **1a**

[†] *Preparation of linear trimer* **4**: To a solution of 1,5-difluoro-2,4-dinitrobenzene **2** (612 mg, 3 mmol) and resorcinol **3a** (110 mg, 1 mmol) in MeCN (5 ml) was added Et_3N (122 mg, 1.1 mmol) under an argon atmosphere. The solution was stirred at 60 °C for 6 h. After most of the solvent was removed under reduced pressure, the residue was dissolved in $CHCl_3$, and then washed with dil hydrochloric acid, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was recrystallized from $CHCl_3$–hexane to yield **4** (340 mg, 71%). Mp 162 °C. Calcd. for $C_{18}H_8N_4O_{10}$: C, 54.92; H, 3.05; N, 9.49. Found: C, 54.52; H, 3.23; N, 9.44. 400 MHz. ^{1}H NMR (DMSO-d_6, 50 °C) δ 7.27 (dd, 2H, $J = 2.2$ Hz, 8.1 Hz), 7.32 (t, 1H, $J = 2.2$ Hz), 7.54 (d, 2H, $J = 12.8$ Hz), 7.66 (t, 1H, $J = 8.1$ Hz), 8.93 (d, 2H, $J = 8.1$ Hz). ($CDCl_3$) δ 6.86 (d, 2H, $J = 10.6$ Hz), 7.00 (t, 1H, $J = 2.2$ Hz), 7.15 (dd, 2H, $J = 2.6$ Hz, 8.2 Hz), 7.65 (t, 1H, $J = 8.2$ Hz), 8.88 (d, 2H, $J = 7.3$ Hz).

[‡] *Synthesis of ABAC-type oxacalixarene: General reaction conditions.* Under an argon atmosphere, linear trimer **4** (0.5 mmol) and resorcinol **3** (0.5 mmol) were dissolved in MeCN (2.5 ml). To this was added Et_3N (0.5 mmol), and the mixture was stirred at 70 °C for 8 h. After cooling, the reaction mixture was poured into a mixture of water (5 ml) and MeOH (5 ml). The precipitated crude product was collected by filtration, washed with MeOH, dried in vacuo, and recrystallized from appropriate solvents. Compound **5b**: 69%. Mp 256 °C (from $CHCl_3$–hexane). Anal. Calcd for $C_{27}H_{18}N_4O_{12}$: C, 45.19; H, 1.67; N, 11.72. Found: C, 45.12; H, 1.82; N, 11.65. ^{1}H NMR (400 MHz, DMSO-d_6, 50 °C) δ 0.75 (t, 2H, $J = 7.2$ Hz, $CH_2CH_2CH_3$), 1.48 (sext, 2H, $J = 7.2$ Hz, $CH_2CH_2CH_3$), 2.04 (t, 3H, $J = 7.2$ Hz, $CH_2CH_2CH_3$), 5.53 (s, 2H, H_{in}), 7.25 (d, 2H, $J = 8.0$ Hz), 7.26 (d, 2H, $J = 8.0$ Hz), 7.40 (t, 1H, $J = 2.0$ Hz), 7.47 (t, 1H, $J = 8.0$ Hz), 7.64 (t, 1H, $J = 8.0$ Hz), 8.96 (s, 2H, H_{out}). MS (FAB) 591.1 ($[M+1]^+$). Compound **5c:** 78%. Mp 310 °C (dec) (from DMF–MeOH). Anal. Calcd for $C_{24}H_{11}N_5O_{14}$: C, 48.57; H, 1.85; N, 11.80. Found: C, 48.43; H, 1.90; N, 11.72. ^{1}H NMR (400 MHz, DMSO-d_6, 50 °C) δ 5.79 (s, 2H, H_{in}), 7.30 (m, 3H), 7.67 (t, 1H, $J = 8.8$ Hz), 7.72 (d, 2H, $J = 8.8$ Hz), 7.96 (t, 1H, $J = 8.8$ Hz), 8.95 (s, 2H, H_{out}). Compound **5d:** 71%. Mp 320 °C (dec) (from DMF). Anal. Calcd for $C_{24}H_{11}N_4O_{14}Br{\cdot}H_2O$: C, 44.72; H, 2.02; N, 8.67. Found: C, 44.95; H, 1.90; N, 8.51. ^{1}H NMR (400 MHz, DMSO-d_6, 50 °C) δ 5.58 (s, 2H, H_{in}), 7.28 (m, 3H), 7.51 (d, 2H, $J = 8.0$ Hz), 7.66 (m, 2H), 8.99 (s, 2H, H_{out}).

[§] *Determination of the disproportionation of the oxacalix[4]arenes.* Oxacalix[4]arene **5b** (5 mg) and CsF (1 mg) were placed in an NMR tube under an argon atmosphere. To this was added DMSO-d_6 (0.5 ml). The sample was heated to 80 °C and its ^{1}H NMR spectra were determined at 20-min intervals. The isomer ratio was determined from the integrals of the H_a signals. The ^{1}H NMR spectra that are shown in Figure 2 are normalized to the signal height of the residual protons of the solvent.

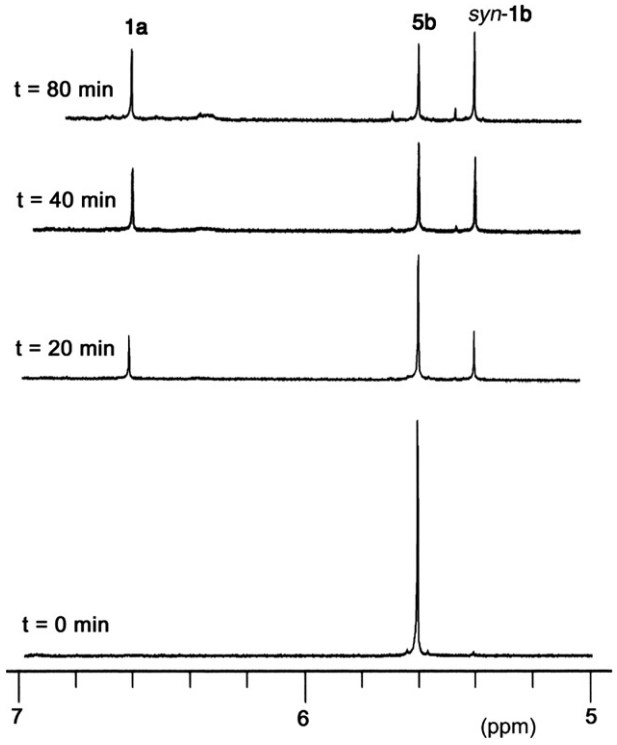


Figure 2. Changes in the ^{1}H NMR spectra with time for the disproportionation of **5b** in the presence of CsF in DMSO-d_6 at 80 °C. The region of H_{in} protons for **5b**, **1a** and ***syn*-1b** is shown.

and ***syn*-1b** appeared. After 1 h, the spectral changes almost ceased and the ratio of **5b**, **1a** and ***syn*-1b** was approximately 1:1:1. Moreover, treatment of a 1:1 mixture of **1a** and ***syn*-1b** under the same conditions resulted in the formation of a 1:1:1 mixture of **5b**, **1a** and ***syn*-1b**. These results clearly indicate that an equilibrium between the three oxacalix[4]arenes is reached in the presence of CsF in DMSO (see Scheme 2). However, it was found that prolonged heating of the DMSO solution gradually resulted in the hydrolysis of the cyclic tetramer. Indeed, the heating of the DMSO solution of ***syn*-1b** in the presence of excess CsF yielded a complex mixture, from which linear tetramer **6** and dimer **7** that have hydroxyl groups at both ends were isolated as major products (see Fig. 3). It can therefore be presumed that the minor signals, which appeared in the ^{1}H NMR spectrum after 80 min, were assigned to analogous oligomers.

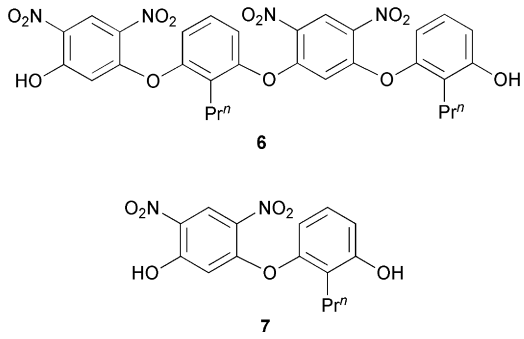
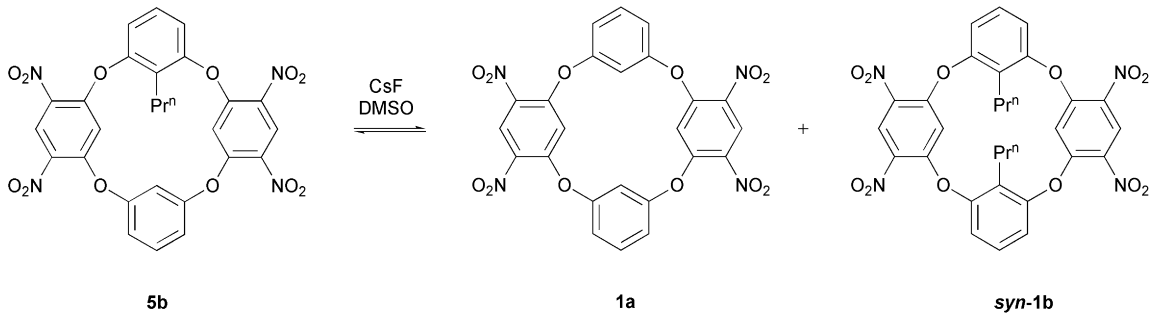


Figure 3. Hydrolysis products of ***syn*-1b**.

On the other hand, the CsF-catalyzed reaction of **5c** did not produce an equilibrium mixture of macrocycles. Under the same conditions, the signal of **5c** decreased. However, the ^{1}H NMR spectrum indicated the formation of a small amount of the ABAB-type oxacalix[4]arenes **1a** and **1c** and a complex mixture of linear oligomers. Similarly, the CsF-catalyzed reaction of **5d** also produced an ambiguous mixture of oligomers. These observations can be explained as follows. For **5b**, the fluoride anion attacks the dinitrobenzene carbon that is attached to the bridging oxygen atom, and cleaves the macrocycles. The phenolate terminal group generated by the bond cleavage acts as a nucleophile, and also attacks the dinitrobenzene core. Thus, the fluoride ion and phenolate cleave the C–O bond, affording linear oligomers with a dinitrofluorobenzene terminal group and/or a phenolate terminal group. Finally, the reaction between these species produces an equilibrium mixture of oxacalix[4]arenes. On the other hand, in the case of **5c** and **5d**, the resorcinol units have an electron-withdrawing group, therefore, the *ipso*-attack of nucleophiles may occur on both the dinitrobenzene ring and the resorcinol ring. That is, the ether bonds are nonselectively cleaved to afford various types of oligomers. Therefore, a further reaction between the oligomers resulted in the formation of only a small amount of the calix[4]arenes and a large amount of a complex mixture of oligomers.

In conclusion, we have developed an efficient method to prepare ABAC-type oxacalix[4]arenes by a '3+1' fragment synthesis. The CsF-catalyzed disproportionation of the ABAC-type oxacalix[4]arenes bearing an alkyl group on the resorcinol unit produced an equilibrium



Scheme 2. The CsF-catalyzed disproportionation of **5b** to form **1a** and ***syn*-1b.**

mixture of three oxacalix[4]arenes. On the other hand, when the resorcinol unit is substituted with an electron-withdrawing group, the ether bonds are randomly broken to afford a complex mixture of oligomers.

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