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Intramolecular S_NAr Reactions in a Large-Ring Ketocalix[6]arene

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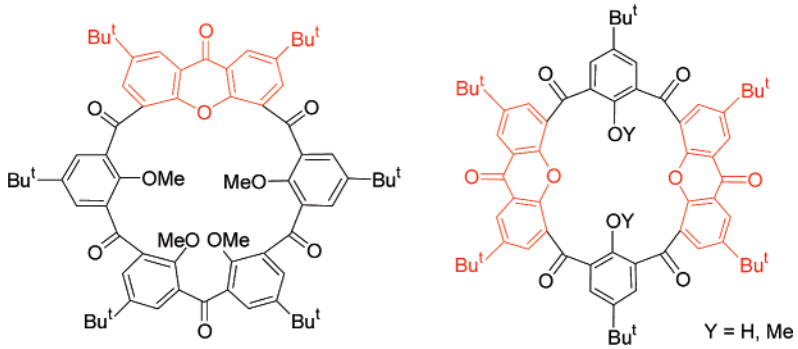
ABSTRACT



Ketocalix[6]arene 2e was prepared by CrO_3 oxidation of the methylene groups of 2a, followed by hydrolysis of the acetate groups. 2e undergoes intramolecular S_NAr reactions under the usual methylation conditions (MeI, base), yielding mono- and dixanthone calixarene derivatives.

The calixarenes are presently one of the most useful building blocks for the construction of molecular hosts.[1] Oxidation of *p-tert*-butylcalix[4]arene (**1b**) and/or its derivatives may afford, depending on the reaction conditions, calixquinones,[2] spirodienone calixarene derivatives,[3] calixcyclitols,[4] or bi-calix[*n*]arenes.[5,6] Oxidation reactions leading to calixarene derivatives possessing carbonyl groups connecting the aryl moieties (dubbed by Gutsche as "ketocalixarenes")[1a] were first described in 1985 by Ninagawa.[7] In 1990, Görmar and co-workers reported that the four methylene groups of *p-tert*-butylcalix[4]arene tetraacetate **1a** can be selectively oxidized to carbonyl functionalities to yield **1d**.[8,9] Basic hydrolysis of the ester groups of **1d** afforded the corresponding tetrahydroxy derivative **1e**.[10]

In contrast to the "classic" calixarenes, the bridges in the ketocalixarenes (carbonyl groups) may be conjugated to the aryl rings. The system should in principle be capable of undergoing aromatic nucleophilic substitution (S_NAr) reac-

(1) For reviews on calixarenes, see: (a) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (b) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001. (c) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, 2003; Chapter 19.

(2) For the preparation and reactions of calixquinones, see, for example: (a) Morita, Y.; Agawa, T.; Kai, Y.; Kanehisa, N.; Kasai, N.; Nomura, E.; Taniguchi, H. *Chem. Lett.* **1989**, 1349. (b) Morita, Y.; Agawa, T.; Kai, Y.; Nomura, E.; Taniguchi, H. *J. Org. Chem.* **1992**, *57*, 3658. (c) Reddy, P. A.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *Isr. J. Chem.* **1992**, *32*, 89. (d) Casnati, A.; Comelli, E.; Fabbi, M.; Bocchi, V.; Mori, G.; Ugozzoli, F.; Lanfredi, A. M. M.; Pochini, A.; Ungaro, R. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 384. (e) Reddy, P. A.; Gutsche, C. D. *J. Org. Chem.* **1993**, *58*, 3245.

(3) For a review on spirodienone calixarene derivatives, see: Biali, S. E. *Synlett* **2003**, 1.

(4) Troisi, F.; Mogavero, L.; Gaeta, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2007**, *9*, 915.

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(6) For a review on the oxidation and reduction of calixarenes, see: Biali, S. E. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001; p 266.

(7) Ninagawa, A.; Cho, K.; Matsuda, H. *Makromol. Chem.* **1985**, *186*, 1379.

(8) Görmar, G.; Seiffarth, K.; Schultz, M.; Zimmerman, J.; Flämig, G. *Macromol. Chem.* **1990**, *191*, 81.

(9) Seri, N.; Simaan, S.; Botoshansky, M.; Kaftory, M.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 7140.

(10) Ketocalixarenes possessing a single carbonyl bridge were synthesized by Sone and co-workers by a stepwise route. See: Ito, K.; Izawa, S.; Ohba, T.; Ohba, Y.; Sone, T. *Tetrahedron Lett.* **1996**, *37*, 5959.

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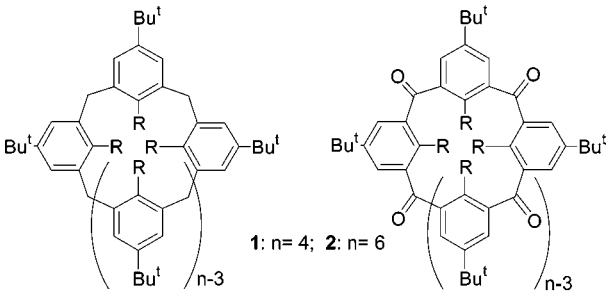
tions, thus enabling replacement reactions of the intraannular groups by a nucleophile.[11] It could be expected that larger ketocalix[*n*]arenes ($n > 4$) should be more reactive in S_NAr reactions because, as inspection of molecular models suggests, the CO−Ar conjugation should be larger. There is only a single example reported in the literature of a large-ring ketocalixarene with all bridges consisting of carbonyl groups. Iwamura and co-workers prepared a OH-depleted ketocalix[6]arene by oxidation ($Na_2Cr_2O_7$/AcOH) of a dehydroxylated calix[6]arene,[12] but its parent hexahydroxy analogue is unknown.



a R = OAc
b R = OH
c R = OMe

d R = OAc
e R = OH
f R = OMe

For the synthesis of the ketocalix[6]arene, we applied the reaction sequence used by Görmar for the preparation of the parent **1e**.[9] In the case of **1a**, the rotation of the rings through the annulus is hindered by the bulky acetate groups and several atropisomeric forms exist (resulting from the different "up" or "down" arrangements of the aryl rings) which can be separated by fractional crystallization.[13,14] We have shown previously that methylene groups located between a pair of geminal rings oriented anti are oxidized faster than those located between syn rings.[15] For the acetyl derivative **2a**, we expected full oxidation under the experimental conditions because this system is conformationally flexible under the laboratory time scale.

Calix[6]arene **2a**[16] was prepared by acetylation of **2b** according to the literature procedure.[17] Oxidation (CrO_3/AcOH/Ac_2O) of the methylene groups of **2a** proceeded readily and afforded ketocalix[6]arene **2d** in 43% yield. Ketocalixarene **2d** displayed broad signals in the ^{1}H NMR spectrum (400 MHz, rt, $CDCl_3$), in particular, for the acetyl groups. At 218 K, the NMR spectrum displayed at least 12 signals for the *tert*-butyl groups, indicating that no single conformer is stabilized relative to the other forms. A single crystal of **2d** was grown from acetonitrile and submitted to X-ray diffraction. The molecule crystallized in an "up−up−down−up−up−down" conformation of approximately C_2 symmetry in which two rings (located in a relative 1,4 position) are pointing in the opposite direction to the rest. One *tert*-butyl and one acetate group were disordered between two positions (Figure 1).

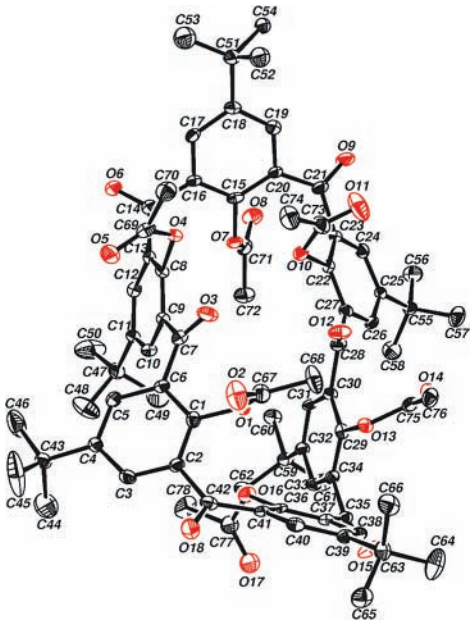


Figure 1. X-ray structure of **2d**.

Basic hydrolysis of **2d** (1M NaOH) afforded the large-ring ketocalix[6]arene **2e**. The ^{1}H NMR spectrum of **2e** (400 MHz, $CDCl_3$, rt) displayed a low-field resonance at 10.05 ppm suggesting the presence of intramolecular OH bonds. At low temperature, the spectrum of ketocalix[6]arene **2e** displayed several signals in the *t*-Bu and aromatic region indicating that no single conformer is significantly populated.

Because the methoxy ether derivatives of the ketocalixarenes may serve as starting materials for the preparation of methylene-functionalized calixarenes (via reaction of organolithium reagents with the carbonyl carbon)[18] as well as, in principle, substrates for S_NAr reactions, we attempted the preparation of the hexamethyl ether **2f**. Because direct oxidation of **2c** ($K_2Cr_2O_7$/AcOH) afforded the ketocalix[6]arene hexamethyl ether **2f** in very low yield (ca. 3%), we examined the base-catalyzed methylation of **2e**.

Surprisingly, under the reaction conditions expected to afford the hexamethylated product (large excess or MeI, K_2CO_3, MeCN, 21 h),[19] ketocalix[6]arene **2e** afforded a mixture of products. ^{1}H NMR analysis of the crude product indicated that a monoxanthone calixarene **3** and the derivatives **4** and **6** possessing two xanthone moieties located at opposite and

(11) Such a synthetic strategy was introduced by Miyano and co-workers who reported the replacement of the methoxy groups of oxidized thiacalixarenes by amino groups. See: Katagiri, H.; Iki, N.; Hattori, T.; Kabuto, C.; Miyano, S. *J. Am. Chem. Soc.* **2001**, *123*, 779.

(12) Matsuda, K.; Nakamura, N.; Takahashi, K.; Inoue, K.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1995**, *117*, 5550.

(13) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, *403*.

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(16) For the preparation of **2b**, see: Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *Org. Synth.* **1989**, *68*, 238.

(17) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.

(18) Kuno, L.; Seri, N.; Biali, S. E. *Org. Lett.* **2007**, *9*, 1577.

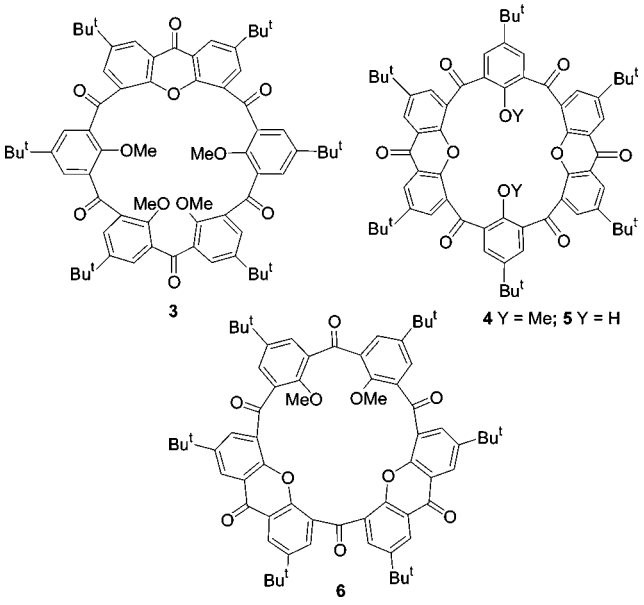
(19) Seri, N.; Biali, S. E. *J. Org. Chem.* **2005**, *70*, 5278.

vicinal positions of the macrocycle, respectively, were obtained (Table 1, entry 1).[20] When the reaction time was shortened to 2 h (entry 2), an additional product (**5**) was detected. Dihydroxydixanthone derivative **5** is probably an intermediate in the formation of **4** because under the reaction conditions of entry 1 it undergoes complete conversion to **4**.

Table 1. Attempted Alkylation of **2e** under Different Reaction Conditions[a]

entry	base	reagent	**3**	**4**	**5**	**2f**	**6**
1	K_2CO_3	MeI (4 × 170 equiv)[b]	40	44	–	–	16
2	K_2CO_3	MeI (102 equiv)	23	15	45	–	17
3	K_2CO_3	MeI (6 equiv)	–	–	>95	–	–
4	K_2CO_3	DMS (18 equiv)	29	17	37	–	17
5[c]	K_2CO_3	DMS (18 equiv)	61	12	18	4	5
6	K_2CO_3	DMS (6 + 18 equiv)[d]	–	25	75	–	–
7[e]	K_2CO_3	BzBr (18 equiv)	–	–	>98	–	–
8[e–g]	Cs_2CO_3	MeI (170 equiv)	<10	–	–	>90	–
9[e,g,h]	Cs_2CO_3	MeI (170 equiv)	<3	–	–	>97	–

[a] 0.5 g of **2e** dissolved in 50 mL of MeCN, 2 h reaction. If not stated otherwise, product ratios were determined by ^{1}H NMR analysis of the crude product. [b]Initially, 170 equiv of MeI was used. After 2, 4, and 9 h, an additional 170 equiv was added and reflux continued for 12 h. [c]In 10 mL of MeCN. [d]Initially, 6 equiv of DMS was used. After 2 h, an additional 18 equiv was added and reflux continued for 3 h. [e]Product ratios determined after precipitation from $CHCl_3$/MeOH. [f]In 80 mL of dry DMA. [g]18 h reaction. [h]In 20 mL of dry DMA.



Monoxanthone **3** and dixanthone **4** were isolated by fractional crystallization from chloroform/methanol. The ^{1}H NMR spectrum of **3** displayed a signal at δ 8.45 ppm assigned to the peri protons of the xanthone moiety and three, two, and six signals for the *tert*-butyl, methoxy, and aromatic protons, respectively, indicating a structure possessing bilateral symmetry in which two types of methoxy groups are present. X-ray diffraction of a single crystal of **3** obtained by slow evaporation of an acetonitrile solution corroborated its structural assignment (Figure 2). Two independent molecules possessing very similar conformations are present in the asymmetric unit. In the crystal, one of the aryl rings nonadjacent to the xanthone moiety is pointing in the opposite direction of the rest of the rings.

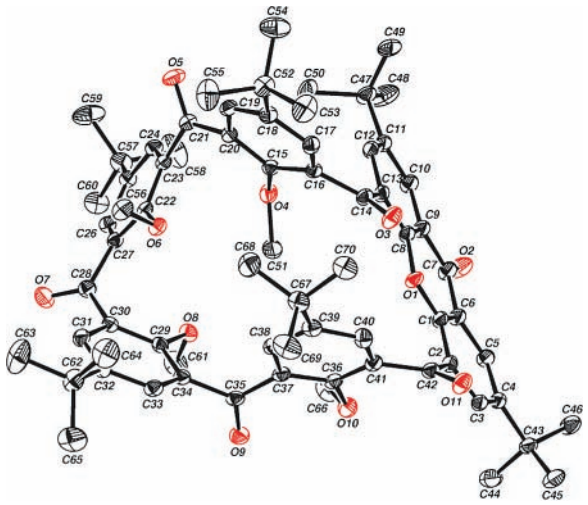


Figure 2. X-ray structure of **3**. Only one of the two independent molecules is shown. Acetonitrile is omitted for clarity.

Large calixarenes incorporating a single xanthene group have been obtained previously via reaction of monospirodienone calixarene derivatives with HCl/MeOH[21] or Et_3SiH/CF_3COOH.[22] The formation of xanthone groups under methylation conditions is most likely facilitated by the activating effects of the carbonyl groups which enable an intramolecular S_NAr reaction between a methylated aromatic ring and a neighboring phenolate serving as the nucleophile (Scheme 1). Only unreacted starting material was obtained when MeI was omitted from the reaction mixture.

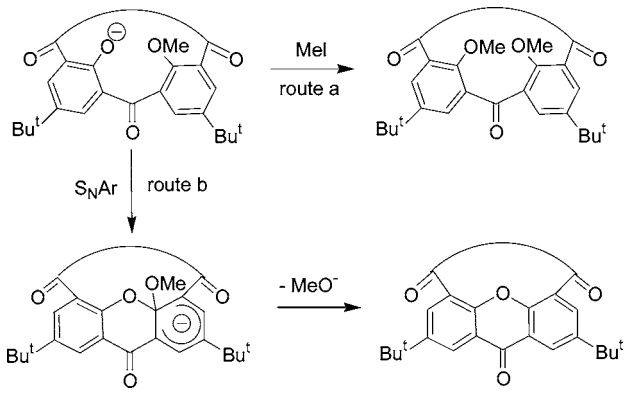
Because the methylation of a phenolate (Scheme 1, route a) is a bimolecular reaction, whereas the xanthone formation (route b) is unimolecular, it could be expected that both the reactivity and concentration of the methylating agent should affect the outcome of the reaction and that in general route b should be favored by a low concentration and/or low reactivity of an alkylating agent. As shown in Table 1, indeed when the concentration of MeI was lowered to 6 equiv the dixanthone derivative **5** was the major product (entry 3). Changing the methylating agent for the more reactive dimethyl sulfate (DMS) and increasing its concentration

(20) Compound **6** was identified on the basis of its NMR spectrum in the crude product mixture and was not isolated in pure form.

(21) (a) Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Am. Chem. Soc.* **1995**, *117*, 9645. (b) Consoli, G. M. L.; Geraci, C.; Cunsolo, F.; Neri, P. *Tetrahedron Lett.* **2003**, *44*, 53.

(22) Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2001**, *66*, 5482.

Scheme 1



(entries 4 and 5) afforded a larger yield of the monoxanthone derivative **3**, in addition to small amounts of the hexamethyl ether **2f**.

Dixanthone **5** was obtained as the exclusive product when DMS was replaced by benzyl bromide (entry 7). Apparently, the rate of alkylation with benzyl bromide is slower than the rate with DMS, and the S_NAr becomes the preferred reaction pathway.

Full alkylation of **2e** was achieved using Cs_2CO_3 as base, dry dimethyl acetamide (DMA) as solvent, and a large excess of MeI at 80 °C (pressure reactor, entries 8 and 9). Hexamethoxyketocalix[6]arene **2f** was characterized by X-ray crystallography (Figure 3). The molecule crystallizes in

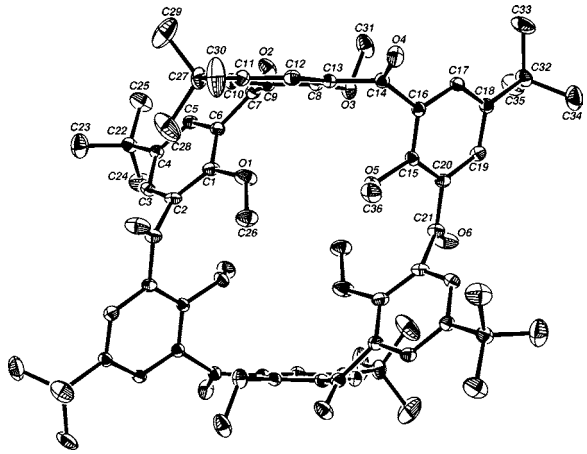


Figure 3. X-ray structure of **2f**.

a conformation of C_i symmetry. For each carbonyl group, one of the CO−Ar torsional angles is significantly smaller than the other. The values of these smaller angles (25.7°, 28.3°, and 32.7°) are reminiscent to those found in the crystal structure of benzophenone (29.4° and 30.9°).[23]

In principle, xanthone derivatives may be obtained in the basic hydrolysis of **2d** if intermediates possessing an acetylated ring and a geminal phenoxy group are present and if an acetoxy group may serve as a leaving group. Examination of the crude product indicated that together with the major product **2e** small amounts of the dihydroxy dixanthone derivative **5** were present. Most likely, under the reaction conditions in a partially hydrolyzed intermediate, the rate of hydrolysis of an acetate group is faster than the rate of intermolecular S_NAr reaction. Because only the rate of the former reaction should be affected by the concentration of base, it could be expected that lowering the concentration of the base should increase the relative yield of xanthone products. Indeed, hydrolysis of **2d** using 0.1 M NaOH (a 10-fold decrease in concentration) afforded after 6 days dixanthone **5** in high yield.

Most likely, the formation of xanthone derivatives is observed in the derivatives of **2e** (and not in **1e**) because the larger calixarene can better accommodate the increase in strain resulting from the introduction of the rigid xanthone group. Moreover, the larger ring enables attainment of conformations where the conjugation between the carbonyl and phenyl groups is larger, thus facilitating the intramolecular S_NAr reactions. The spatial proximity between a phenolate and neighboring methylated or acetylated rings facilitates the reaction.

To conclude, ketocalix[6]arene derivatives undergo intramolecular S_NAr reactions. Both acetate and methoxy groups are readily displaced.

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Supporting Information Available: Experimental procedures for the preparation of **2d**−**f** and **3**−**5** and X-ray data (CIF files) for compounds **2d**, **2f**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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