Host–Guest Chemistry

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A Facile and Efficient Preparation of Pillararenes and a Pillarquinone**

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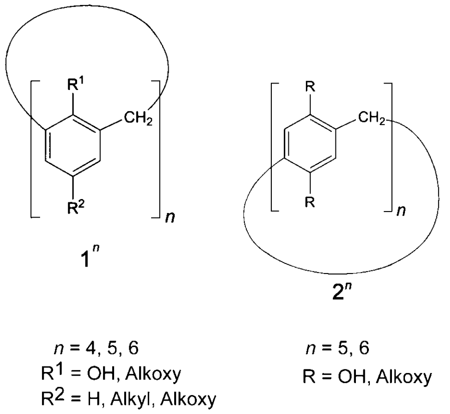
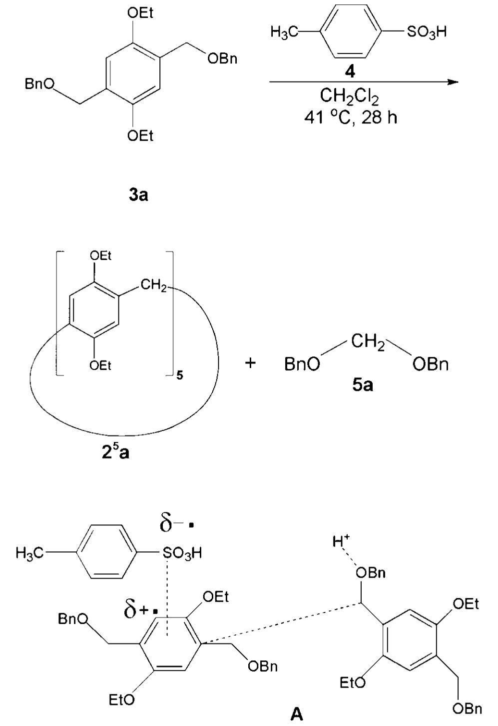
Calixarenes **1** and their derivatives have attracted considerable attention over the past two decades. This attention can be attributed to their applications in areas as diverse as gas adsorption,[1] nanotubes,[2] catalysis,[3] DNA recognition[4] and fullerene chemistry.[5] Recently, many calixarene analogues have been developed in supramolecular chemistry, such as calixpyrroles,[6] thiacalixarenes,[7] and homooxacalixarenes.[8] In contrast to the vast literature about the *meta*-bridged cyclooligomers **1**, very little is known about their *para*-bridged analogues **2**, called pillar[*n*]arenes (Scheme 1). Recently, the first two members **2*ⁿ*** ($n = 5$, $R = OCH_3$, OH) of this series were reported.[9] They exhibit very interesting host–guest properties, but their preparation is rather tedious; the Lewis acid catalyzed condensation of 1,4-dimethoxybenzene and paraformaldehyde furnishes a polymer, which contains some cyclic pentamer $\mathbf{2^5}$ ($R = OCH_3$). Ether cleavage with BBr_3 affords the pillar[5]arene with free hydroxy groups $\mathbf{2^5}$ ($R = OH$). The yields for the respective steps are poor (22.0 and 6.6 %).[9,10]



Scheme 1. Calixarenes **1*ⁿ*** and their *para*-bridged analogues **2*ⁿ***, which are called pillararenes.

We have now found a surprising reaction involving 2,5-bis(benzyloxymethyl)-1,4-diethoxybenzene (**3a**), which was treated in boiling dichloromethane with catalytic amounts of *p*-toluenesulfonic acid (**4**). The reaction mixture turned green and an oligomerization took place, delivering the cyclic pentamer $\mathbf{2^5a}$ and the acetal **5a** in yields of 75 and 73 %, respectively, upon isolation (Scheme 2). Acids such as H_2SO_4 or H_3PO_4 can be used as catalysts as well, but non-oxidative acids, such as HCl or the Lewis acid $BF_3{\cdot}O(C_2H_5)_2$, do not promote the reaction. *ipso*-Substitutions on benzene by a dealkylation/alkylation mechanism are very rare, and they can be observed either in electrochemical processes or in reactions catalyzed by radical cations as one-electron oxidants.[11]



Scheme 2. Generation of ethyl-substituted pillar[5]arene $\mathbf{2^5a}$.

The exact mechanism of the generation of $\mathbf{2^5a}$ and **5a** is not known. We assume a transition-state **A** in which the interaction of **3a** and **4** can lead to a (partial) charge transfer

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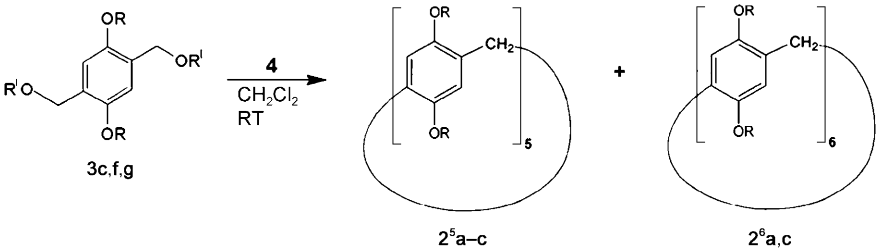
Table 2: Preparation of pillar[5]- and pillar[6]arenes with different alkoxy substituents R; R′ = Et.



3c,f,g **2^5a–c** **2^6a,c**

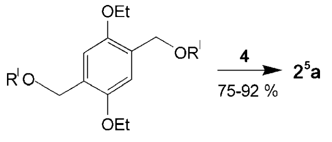
Starting compound	R	*t* [h]	Product	Yield [%]	M.p. [°C]	Product	Yield [%]	M.p. [°C]
3c	Et	3–4	**2^5a**	89	154–156	**2^6a**	8	172–173
3f	Me	1–2	**2^5b**	95	194–195	–[a]	–	–
3g	*n*Bu	15	**2^5c**	86	133–135	**2^6c**	11	87–89

[a] Traces of higher cyclooligomers.

to generate a radical cation of **3a**, having a deep green color in solution, thereby enhancing the reactivity of the positions on the ring to which alkyl groups are appended. Furthermore, the acid facilitates the benzyl ether cleavage, so that a C–C bond can be formed between the benzylic carbon atom and the carbon atom of the ring (dashed line in **A,** Scheme 2). A four-fold cyclocondensation would still involve a geometrically strained transition state, so that the cyclopentamerization is preferred. Cyclizations of higher linear oligomers can be less favorable, because of higher activation entropies.

These first results encouraged us to optimize the preparation of pillararenes. *p*-Toluenesulfonic acid (**4**) in CH_2Cl_2 proved to be the best catalyst, as the acidity and the relatively low redox potential of **4** are best suited for the cyclocondensation. Replacement of the benzyloxymethyl substituents by *n*-butyloxymethyl groups did not change the yield of **2^5a** (Table 1). However, the use of less bulky leaving groups such as methoxymethyl or ethoxymethyl groups afforded very high product yields (92 and 89 %, respectively) and permitted short reaction times, even at room temperature. Free hydroxy groups (**3e**) proved to be somewhat less favorable.

Table 1: Preparation of pillar[5]arene **2^5a** by using different leaving groups CH_2OR' and OR′.



3a–e

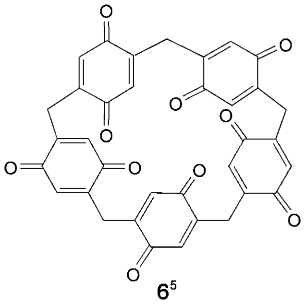
Starting compound	R′	*T* [°C]	*t* [h]	Yield of **2^5a** [%][a]
3a	Bn	41	2	75
3b	*n*Bu	41	24	75
3c	Et	RT	3–4	89
3d	Me	RT	3–4	92
3e	H	RT	5–6	84

[a] Yield of isolated product.

A detailed study of the reactions of starting compounds **3** with R = Me, Et, or *n*Bu revealed a quantitative generation of pillararenes. Apart from cyclic pentamers **2^5** as major products, higher cyclooligomers **2^n** were formed as minor components (Table 2). The overall yields of isolated products were about 97 % in each case. We used column chromatography (SiO_2, petroleum ether (b.p. 60–90 °C)/ethyl acetate 40:1) for the separation of the cyclooligomers. The hexamers **2^6a** and **2^6c** represent the first pillar[6]arenes.

Cleavage of the ether groups in **2^5** by the reaction with BBr_3 in CH_2Cl_2 (0–20 °C, 45 h) afforded compound **2^5d** having free hydroxy groups in 70 % yield. Its parent system is [1.1.1.1.1]cyclophane, which has been known for more than 20 years. However, the synthetic access to it is laborious and the overall yields are below 1 %.[12]

Even more challenging was the oxidation of **2^5**. When **2^5a** was treated with $(NH_4)_2[Ce(NO_3)_6]$, the pillarquinone **6^5** was produced (62 %, m.p. > 280 °C), representing the very first cyclooligomeric quinone.



6^5

NMR and mass spectra (MALDI-TOF) were used for the characterization of **2^5a–d**, **2^6a,c**, and **6^5**. Table 3 shows a comparison of the ^1H and ^{13}C NMR data of **3d**, **2^5a**, **2^6a**, and **6^5**. The δ values of the cyclopentamer **2^5a** and the cyclohexamer **2^6a** are very similar. The number of the signals

Table 3: ^1H and ^{13}C NMR data of **3d**, **2^5a**, **2^6a**, and **6^5** (δ values in $CDCl_3$, Me_4Si as internal standard).

Compd.		C_qO	C_q	CH	$CH_2(O)$	OCH_2	CH_3
3d	^1H			6.90	4.47	4.00	1.36
	^{13}C	150.3	126.6	112.5	69.2	64.5	15.0
2^5a	^1H			6.71	3.75	3.81	1.25
	^{13}C	149.8	128.5	115.1	29.8	63.8	15.0
2^6a	^1H			6.68	3.75	3.81	1.27
	^{13}C	150.4	127.8	115.2	30.9	64.0	15.2
6^5	^1H			6.75	3.48		
	^{13}C	186.4	143.5	135.3	26.3		

indicates a de facto D_{5h} and D_{6h} symmetry, respectively. This result is due to the rotation of the benzene rings, which, even at −50 °C, is fast in terms of the NMR time scale. Completely planar conformers would be strained, because of steric interactions. Model considerations reveal that the empty space in the center of $\mathbf{2^5}$ is about 8 Å and that for $\mathbf{2^6}$ is about 10 Å. The benzene ring rotation should decrease these cavity extensions to about 5 and 7 Å. The red cyclopentaquinone $\mathbf{6^5}$ has a similar freedom for intramolecular rotations and also yields just one each of a set of ^{1}H and ^{13}C NMR signals.

In conclusion, a novel, suprisingly simple, and quantitative preparation of pillar[5]arenes $\mathbf{2^5}$ and the first pillar[6]arenes $\mathbf{2^6}$ was found. Oxidation with $(NH_4)_2[Ce(NO_3)_6]$ afforded the first cyclooligomeric quinone $\mathbf{6^5}$. The easy access to these compounds should enable the investigation of various host–guest relationships. The differently sized cavities of $\mathbf{2^5}$ and $\mathbf{2^6}$, and the different electron densities of $\mathbf{2^5}$ and $\mathbf{6^5}$ promise distinct selectivities for organic guest molecules. Moreover, the comparison of pillar[*n*]arenes $\mathbf{2^5}$ and $\mathbf{2^6}$, and pillarquinone $\mathbf{6^5}$ with the corresponding calix[*n*]arenes and cucurbit[*n*]urils appears to be exciting.[13]

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