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Quinoxaline Excision: A Novel Approach to Tri- and Diquinoxaline Cavitands

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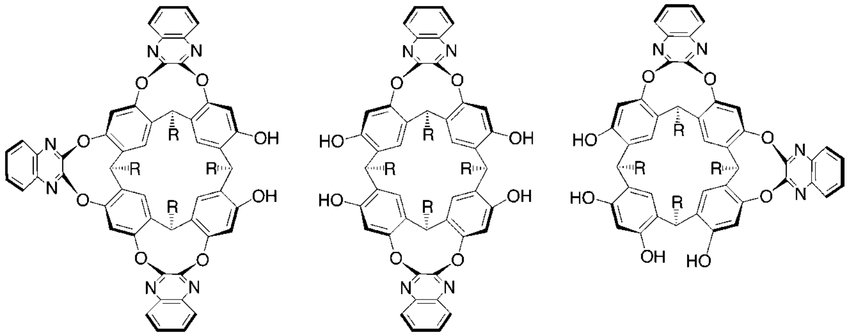
ABSTRACT



Selective excision of one or two quinoxaline units from tetraquinoxaline cavitand using catechol and base in DMF yields tri- and diquinoxaline cavitands in yields of up to 71%.

The versatility of resorcinarene-derived cavitands has generated a wealth of host molecules.[1,2] Tetraquinoxaline-spanned resorcinarene cavitands **1** were introduced by Cram in the early 1980s and have been used extensively by several groups to study host−guest interactions.[3,4] Of particular interest is the ability of these compounds to undergo a reversible thermal switch from the vase to the kite conformation as shown in Figure 1. The vase exists at temperatures of 45 °C and above, while the kite exists exclusively below −60 °C. These temperatures are affected somewhat by the identity

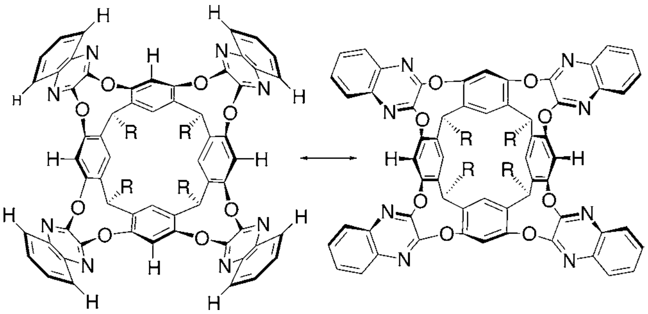


Figure 1. Reversible change of tetraquinoxaline-spanned cavitand **1** from vase to kite conformation, R = *n*-pentyl.

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(1) For reviews see: (a) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41* (20), 1488−1508. (b) Rudkevich, D. M. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 393−413. (c) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278−286. (d) Jasat, A.; Sherman, J. *Chem. Rev.* **1999**, *99*, 931−968 and references therein.

(2) Some recent examples include: (a) Paek, K.; Gutierrez-Tunstad, L. M.; Maverick, E. F.; Knobler, C. B.; Cram, D. J. *J. Inclusion Phenom. Macrocycl. Chem.* **2003**, *45* (3−4), 203−209. (b) Pirondini, L.; Stendardo, A. G.; Geremia, S.; Campagnolo, M.; Samori, P.; Rabe, J. P.; Fokkens, R.; Dalcanale, E. *Angew. Chem., Int. Ed.* **2003**, *42* (12), 1384−1387. (c) Laughrey, Z. R.; Gibb, C. L. D.; Senechal, T.; Gibb, B. C. *Chem. Eur. J.* **2003**, *9* (1), 130−139. (d) Shivanyuk, A.; Rafai Far, A.; Rebek, J., Jr. *Org. Lett.* **2002**, *4* (9), 1555−1558. (e) Barrett, E. S.; Irwin, J. L.; Turner, P.; Sherburn, M. S. *Org. Lett.* **2002**, *4* (9), 1455−1458.

(3) (a) Moran, J. R.; Ericson, J. L.; Dalcanale, E.; Bryant, J. A.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 5707−5714. (b) Moran, J.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826−5828.

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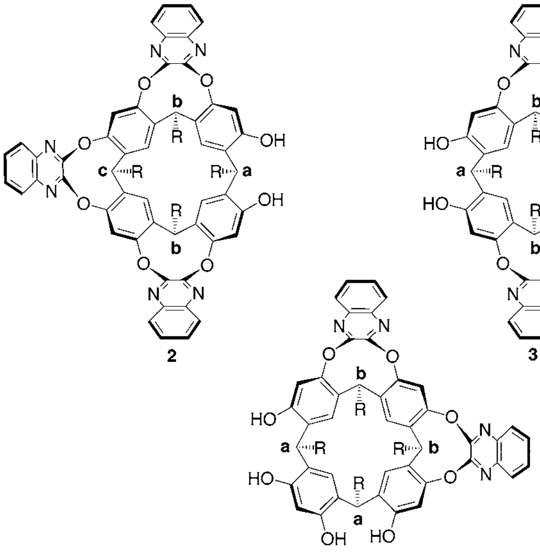


2

3

4

Figure 2. Tri- and diquinoxaline cavitands. Methine proton labels for Ha, Hb, and Hc refer to conformational studies.

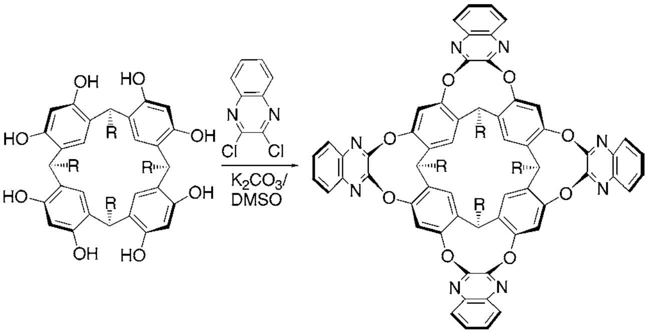
of the "R" groups.[3] Recently, Diederich reported that a tetraquinoxaline-spanned cavitand reversibly opens by addition of trifluoroacetic acid (TFA) or other acids and closes by neutralization with base in nonpolar, nonaromatic solvents.[5] In either case, conformational changes are monitored using ^{1}H NMR, optical absorption, or emission spectroscopy.

Our group required the lower quinoxaline cavitand homologues, Figure 2, as intermediates in the preparation of larger host molecules capable of conformational flexibility: triquinoxaline-spanned diol **2** and the two isomeric diquinoxaline-spanned tetrols **3** and **4** (AC- and AB-, respectively).[6]

We report here a novel approach by selective abstraction of one or two quinoxaline units from the more readily prepared tetraquinoxaline-spanned cavitand **1** that allows for greater control of the product distribution. Manipulation can produce either the triquinoxaline **2** (71%) or AC-diquinoxaline **3** (60%) as the major product in high yield. Cavitand **4**, the AB-diquinoxaline isomer, is produced in low yields of ∼11% under these conditions. Overall yields from resorcinarene of ∼56% for triquinoxaline **2** and ∼48% for AC-diquinoxaline cavitand **3** make preparative quantities of these materials readily available. Additionally, we evaluated the thermally and pH-induced conformational changes of these synthetically versatile cavitands.[6]

The synthesis of the tetraquinoxaline-spanned cavitands **1** is straightforward. A resorcin[4]arene is treated with 4−6 equiv of 2,3-dichloroquinoxaline under basic conditions to afford the desired tetraquinoxaline-spanned cavitand in yields ranging from 60 to 93%, Scheme 1.[3,4d] Throughout this paper, $R = n$-pentyl or *iso*-butyl on the resorcinarene skeleton.

Scheme 1. Synthesis of Tetraquinoxaline-spanned Cavitands. $R = n\text{-}C_5H_{11}$ or $iso\text{-}C_4H_9$.



1

Repeated attempts in our laboratory to prepare triquinoxaline-spanned cavitand **2**, in reactions parallel to Scheme 1, while applying appropriate stoichiometric restrictions of 2,3-dichloroquinoxaline and carbonate base resulted in low yields of 25−35%, although yields as high as 53% have been reported.[4d] A 35% yield of triquinoxaline cavitand ($R = C_6H_{13}$) was recently reported.[7a] Similarly, neither isomer of the diquinoxaline-spanned cavitands **3** or **4** was formed in good yields when we treated resorcinarene with 2 equiv of 2,3-dichloroquinoxaline. Complex cavitand and oligomer mixtures containing low yields (<10%) of the AC-diquinoxaline cavitand were routine. Only trace yields (<3%) of the AB-isomer were detected under these conditions. A synthesis from resorcin[4]arene recently reported 3.5% of AC- and 20.2% of AB-diquinoxaline cavitands.[7a] From 2-methyl-substituted resorcin[4]arenes, 4% of the AC- and 6% of the AB-diquinoxaline cavitands have been reported.[7b]

Accordingly, we sought to develop a reliable method to produce compounds **2**−**4** from the more readily obtained tetraquinoxaline-spanned cavitand. Observations made during our previous attempts had confirmed that all quinoxaline-containing cavitands are unstable to phenoxide nucleophiles. This provided the opportunity to explore the deliberate excision of one and then two quinoxaline units from tetraquinoxaline cavitand using an appropriate nucleophile, Scheme 2. Catechol offers two appropriately spaced oxygen atoms to efficiently attack the quinoxaline moiety, and the quinoxaline-catechol adduct formed thereby is a known, stable compound and a convenient TLC marker of reaction progress.[8]

Table 1 summarizes the results for preparation of cavitands **2**−**4**. Entries 1−3 provide results of reactions for triquin-

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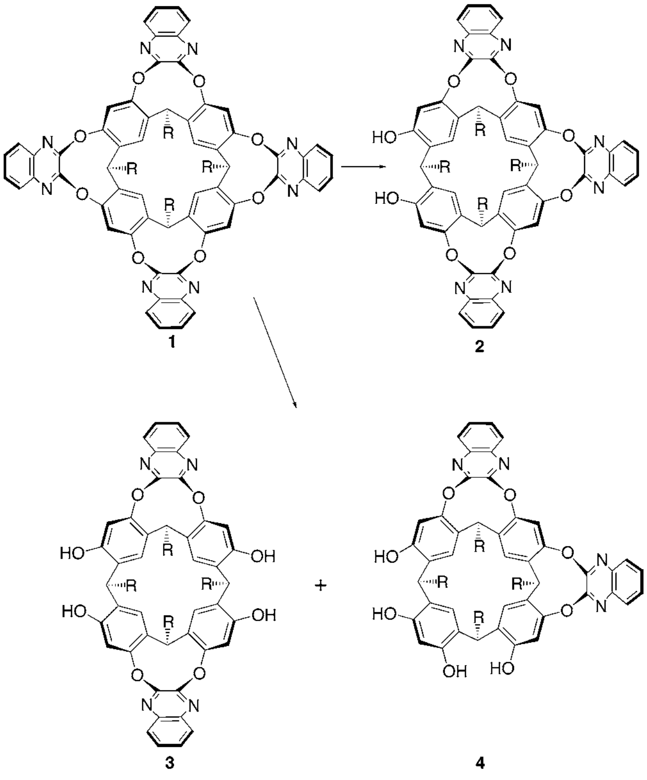
Table 1. Yields of Cavitands **1**−**4**

entry	base (equiv)	catechol equiv (*t*)	yield **1**	yield **2**	yield **3**	yield **4**
1	CsF (5)	1.1 (30 min)	10	63	9	trace
2	CsF (20)	1.1 (30 min)	6	71	trace	trace
3	K_2CO_3 (20)	1.3 (1.2 h)	0	60	12	trace
4	CsF (20)	2.3 (35 min)	0	13	35	7
5	CsF (20)	3.2 (40 min)	0	3	60	11
6	Cs_2CO_3 (20)	3.2 (1 h)	0	2	53	10
7	K_2CO_3 (20)	3.3 (1 h)	0	21	43	3
8	KF (20)	3.3 (24 h)	trace	9	38	4

oxaline-spanned cavitand **2**, while entries 4−8 refer to the preparation of diquinoxaline-spanned cavitands **3** and **4**.

Various bases were compared, with the inclusion of CsF based on related successful results in our laboratory with this base.[6] In all cases, catechol was added to a heated mixture of tetraquinoxaline-spanned cavitand and base in DMF solvent. Solubility of the tetraquinoxaline-spanned cavitand was improved at higher temperatures, and reaction times were appreciably shortened. Employment of DMF resulted in slightly cleaner reaction mixtures than did DMSO. All of the reactions were sensitive to the amount of catechol used and less so to the amount of base. Successful reactions were complete in less than 1 h. The yields reported in Table 1 are for compounds isolated after chromatography. Detailed experimental procedures are included in Supporting Information.

Scheme 2. Excision of One or Two Quinoxaline Spanners from Cavitand **1**. R = *n*-C_5H_{11} or *iso*-C_4H_9.



For the preparation of triquinoxaline-spanned cavitand **2**, entries 1 and 2, indicate that the reaction was only slightly improved with excess base, although the reaction mixtures were cleaner and the reactions somewhat faster, which influenced our choice of stoichiometry for subsequent reactions. A small amount of unreacted tetraquinoxaline-spanned cavitand usually remained, and attempts to drive the reaction to completion by adding more catechol only served to lower the yield of the desired product, entry 3. The yields of triquinoxaline-spanned cavitand ranged to 71%.

Treatment of tetraquinoxaline-spanned cavitand with 3.2−3.3 equiv of catechol efficiently excised two quinoxaline spanners to provide up to a 71% combined yield of the diquinoxaline-spanned tetrols in a notable 6:1 AC **3**:AB **4** ratio, entry 5. A statistical result in this case would provide a 1:2 AC **3**:AB **4** ratio. Use of 2.3 equiv of catechol was insufficient to provide good yields of the desired products, entry 4. These isomers were readily separable ($\Delta R_f = 0.25$) in 85:15 CH_2Cl_2/EtOAc on silica gel.

The observed regioselectivity for the diquinoxaline-spanned cavitands can be explained by the negative charge repulsion between an incoming catecholate nucleophile and the phenolate ions on a triquinoxaline-spanned intermediate. (Refer to structures in Scheme 2.) This repulsion would be greater if the nucleophile approached either quinoxaline adjacent to the phenolate ions (leading to the AB-isomer **4**) versus approach at the distal quinoxaline spanner (leading to the AC-isomer **3**). Recently, a 1:5 AC **3**:AB **4** ratio was reported from a direct synthesis of these cavitands from resorcinarene in a combined 24% yield.[7a]

The bases utilized in these studies included CsF, KF, Cs_2CO_3, and K_2CO_3. Carbonate bases served in the reactions to provide the desired product, but CsF typically offered higher yields, cleaner reaction mixtures, and faster reactions, entries 5−7. Miller and co-workers used CsF in DMF to activate catechol toward alkylation with dichloromethane to form the methylenedioxy group in high yields.[9] Potassium fluoride use required much longer reaction times with poorer results overall, entry 8. Attempts in our laboratory to directly span resorcinarene with quinoxaline using CsF were not as high yielding as with the carbonate bases.

Conformational studies were carried out for all of the quinoxaline cavitand homologues and monitored by ^1H NMR. Cram[3a] reported the temperature-dependent conformational behavior of the tetraquinoxaline-spanned cavitand

Table 2. Thermally Induced Chemical Shifts of Cavitand Methine Protons[a]

compd	solvent, v/v	δ_H [ppm] 333 K	δ_H [ppm] 193 K	$\Delta\delta$ [ppm]
1	$CDCl_3/CS_2$ 1/1	5.62	3.69	−1.93
		5.64 (Hc)	3.55	−2.09
2	$CDCl_3/CS_2$ 1/1	5.52 (Hb)	3.55	−1.97
		4.21 (Ha)	4.41	+0.20

[a] See Figure 2 for proton labels Ha, Hb, and Hc.

Table 3. pH-Induced Chemical Shifts of Methine Protons of Compounds **1**−**4** at 293 K

compd	solvent	δ_H[ppm] TFA = 0	$\delta_H(\Delta\delta)$[ppm] TFA = 0.5 M	$\delta_H(\Delta\delta)$[ppm] TFA = 1.0 M
1	$CDCl_3$	5.54	3.77 (−1.77)	
		5.57 (Hc)	3.92 (−1.65)	3.83 (−1.74)
2	$CDCl_3$	5.49 (Hb)	4.10 (−1.39)	4.02 (−1.47)
		4.24 (Ha)	4.34 (+0.1)	4.34 (+0.1)
3	$CDCl_3$	5.43 (Hb)	4.28 (−1.15)	4.07 (−1.36)
		4.35 (Ha)	4.34 (+0.01)	4.35 (0)
3	CD_2Cl_2	5.39 (Hb)	4.06 (−1.33)	3.80 (−1.59)
		4.37 (Ha)	4.39 (+0.02)	4.42 (+0.05)
4	CD_2Cl_2	5.50 (Hb)	4.04 (−1.46)	3.83 (−1.67)
		4.22 (Ha)	4.31 (+0.09)	4.34 (+0.12)

1 in which the methine protons, which are located directly below the quinoxaline units, undergo a gradual upfield chemical shift as the temperature is lowered. Below −60 °C, the kite conformation prevails with an ultimate $\Delta\delta = -1.75$ ppm for the four identical methine protons. As shown in Table 2, our results for the less symmetrical triquinoxaline cavitand **2** demonstrate that the vase-to-kite switch occurs under these conditions. The chemical shift changes ($\Delta\delta$) for the quinoxaline-affected protons Hb and Hc are of similar magnitude (−2 ppm) to those found for cavitand **1** (−1.9 ppm). Proton Ha in triquinoxaline **2** is not situated directly beneath a quinoxaline and is not affected similarly, and this is reflected in the small chemical shift of +0.20 ppm. Diquinoxaline cavitands **3** and **4** precipitated out of solution at lower temperatures in $CDCl_3$.

Similarly, we found that conformational changes for compounds **1**−**4** occurred under low-pH conditions, Table 3. The upfield chemical shift changes ($\Delta\delta$) for the quinoxaline-affected protons, Hb and Hc for compound **2**, and Hb for compounds **3** and **4**, support the vase-to-kite switch in $CDCl_3$ or CD_2Cl_2.[10] Parallel to the low-temperature studies, protons Ha (Figure 2) do not undergo the large chemical shift changes as do protons Hb and Hc. Results for analogous cavitands were reported by Diederich recently.[7a]

With the ready availability of tri- and diquinoxaline-spanned resorcinarene cavitands, work is underway in our laboratory preparing hosts that exploit these conformational abilities. This further work will be reported elsewhere.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Titrations were carried out to [TFA] = 2.0 M for cavitands **3** and **4**, resulting in an additional −0.1 ppm shift.