Tetrahedron Letters 56 (2015) 4824–4828

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Cavitands with inwardly and outwardly directed functional groups

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ARTICLE INFO

*Article history:*
Received 29 April 2015
Revised 16 June 2015
Accepted 24 June 2015
Available online 29 June 2015

*Keywords:*
Cavitand
Pyridine *N*-oxide
Triquinoxaline-spanned resorcinarene
Supramolecular capsule
Silane

ABSTRACT

The synthesis of novel triquinoxaline-spanned cavitands with selectively oriented functional groups is described. In one instance a pyridine *N*-oxide functionalized cavitand was prepared as an exclusive isomer. We investigated its reactivity and formation of host–guest complexes. These imply that electronic aspects may influence guest inclusion and reaction progress more than steric details.



Functionalized resorcin[4]arene cavitands are synthetic receptors providing a deep, vase-like space in which small molecules can reside. Recent advances have introduced intro- or extroverted functionality, typically through the functionalization of one of the four quinoxaline-walls.[1–3] The remaining three walls, while chemically inert, serve as a platform for host–guest recognition events. Diederich and co-workers deployed cavitands as an elegant redox-switch.[4] Rebek and co-workers report that the functionalized cavitands act as hydrophobic nano environments that can accelerate,[5] and catalyze[6] organic reactions presumably due to stabilization of labile reaction intermediates.[7] Indeed, these are reminiscent of natural supramolecular receptors which serve as incredibly well-organized chemical space. The binding sites of enzymes, poly-peptides, and RNA strands can fold around a substrate, and in the folded state the conformation changes according to the guest, and the functionality converges on the substrate.[8,9] Thus, there are parallels between synthetic and natural systems, though the former lack most of the complexity of the latter. Cavitand receptors can therefore play an important role to understand facets of their natural counterparts and perhaps will one day serve as a powerful platform for new modes of chemical catalysis and reactivity. To do so the preparation of in- and out-directed reactive centers will have to advance. Thus far inwardly directed functionalization has been underrepresented owing to synthetic difficulty.[10] Overcoming this intrinsic problem would expand the possibilities and significance of functionalized chemical space and perhaps allow supramolecular chemistry to make more significant inroads in the synthetic community.[11]

Recently, we have reported the synthesis of functionalized cavitands with allylsilanes.[12] The reaction of **1** in Scheme 1 with allyl(dichloro)methylsilane yielded isomeric mixtures of in- and outwardly directed allyls. 34% of the inward and 27% of the outward directed allyl were isolated, although the separation was not easy. Nevertheless this successful isolation enabled us to determine that the introverted ally has slightly higher reactivity than the extroverted one toward *m*CPBA, a not fully understood result at this time.

It appeared to us that other synthetic modification would be possible and would amplify the potential of mono-functionalized cavitands. Herein we expand on our initial Letter preparing R,R′-silanes: where R = R′ = phenyl; R = Me, R′ = $(CH_2)_3Cl$; R = Me, R′ = $(CH_2)_3OAc$; R = Me, R′ = $(CH_2)_3CN$. We report on the isolation of inward versus outward orientation of R′ and find that the isolation of these materials is readily performed. Finally, we have identified that 2-(dibromomethyl)pyridine can be used to prepare an outwardly oriented pyridine that follows from earlier precedent.[13] Subsequent oxidation gives rise to the *N*-oxide compound, while the pyridine ring resides outside the cavitand, the *N*-oxide group clearly has access to the internal space. The following reactions show that a chlorotrimethylsilane (TMSCl) forms host–guest complex via interaction with the *N*-oxide group.

The reaction of **1** with freshly prepared (2-pyridil)dibromomthane proceeded to give **2** in 31% yield (Scheme 2).

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http://dx.doi.org/10.1016/j.tetlet.2015.06.072
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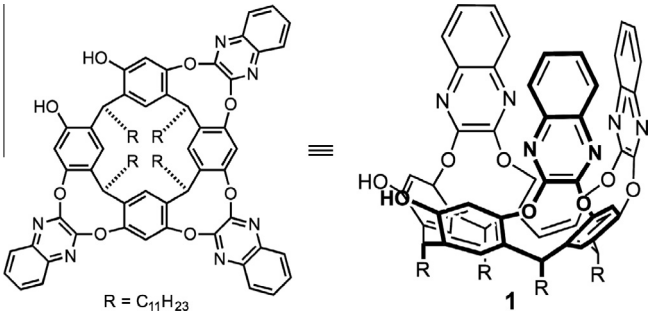



**Scheme 1.** Triquinoxaline-spanned resorcin[4]arene **1**.

Although two isomers (inward and outward) might have been formed during the reaction, TLC and $^1$H NMR spectra surprisingly showed the exclusive formation of single isomer of **2**.[13,14] Subsequent oxidation with mCPBA yielded *N*-oxide **3** in 76%. The molecular structures of **2** and **3** were determined by the chemical shifts of the pyridinyl methine hydrogen ($H^a$ in Fig. 2) as compared to control compounds **4** and **5** (Fig. 1). As depicted in Figure 2, $H^a$ of **2**, **3**, **4**, and **5** appear at 5.03, 5.32, 6.74, and 7.39 ppm, whereas other protons $H^b$–$H^e$ had mostly comparable chemical shifts. The resultant differences in the chemical shifts between **2** and **4**, or **3** and **5** are summarized in Figure 3; the remarkable upfield-shifts more than 1.0 ppm were observed only in the pyridinyl methine, $H^a$ of **2** and **3**.[15] This clearly indicates these $H^a$ are enclosed by the interior space; and thus the pyridine group is outside.[16] While the precise direction of the *N*-oxide group of **3** has not been determined, we predict that it will be inwardly directed most of the time. Instances in which the negatively charged oxygen points to an adjacent wall, or when it rotates completely outside and is flanked by phenyl ethers would be higher in energy. Indeed an AM1 minimized structure was subjected to a torsion scan rotating about the methine-pyridyl bond using mm+ revealed a global minimum with oxygen inwardly directed and a relative minima with oxygen outward (see Supplementary materials). These two conformations were then subjected to B3LYP/6-31G* minimization and single point energy were calculated (B3LYP/6-311G**). The inwardly directed oxygen is 5.3 kcal/mol more stable than the outwardly directed conformer. This would place it inward 99.9% of the time.

Portions of the $^1$H NMR spectra of **2** and **3** in deuterated benzene are shown in Figure 4. Those in [D8]toluene, [D10]-*p*-xylene, [D10]-*o*-xylene, and [D12]mesitylene are summarized in Supplementary materials (Figs. 1S and 2S). The vase conformation predominates at room temperature in [D6]benzene and [D8]toluene, as the CH methine protons that are located directly below the quinoxaline units are situated in the mid-field region.[17] The spectra in [D6]benzene and [D8]toluene are clear with sharp peaks, yet the spectra in [D10]-*p*- and [D10]-*o*-xylene are obscure with broad peaks. Finally, the signals in [D12]mesitylene are too broad to assign; that is, [D12]mesitylene is larger in size than

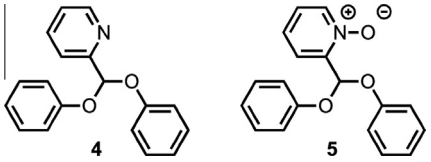



**Figure 1.** Pyridine **4** and pyridine *N*-oxide **5**.

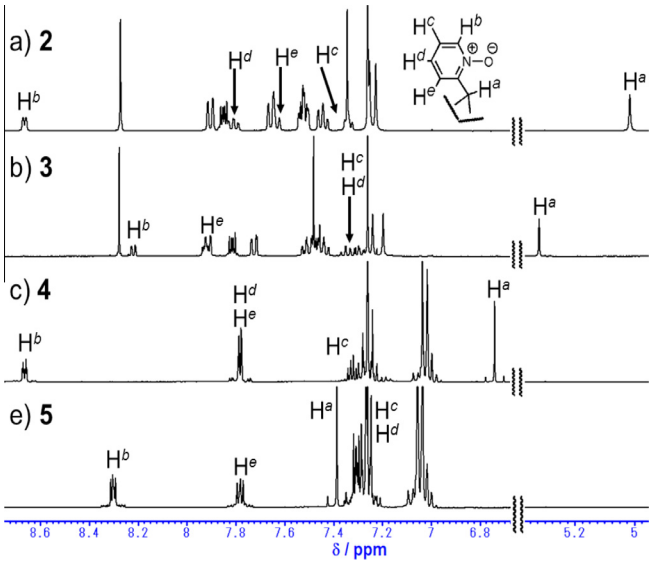
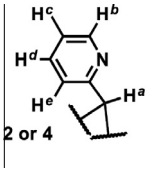
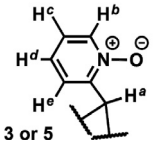



**Figure 2.** Mid- and upfield of the $^1$H NMR spectra for (a) pyridine cavitand **2**, (b) *N*-oxide cavitand **3**, (c) pyridine model compound **4** and (d) *N*-oxide model compound **5** (400 MHz, $CDCl_3$). The each resonance labeled alphabetically corresponds to protons $H^a$–$H^e$.



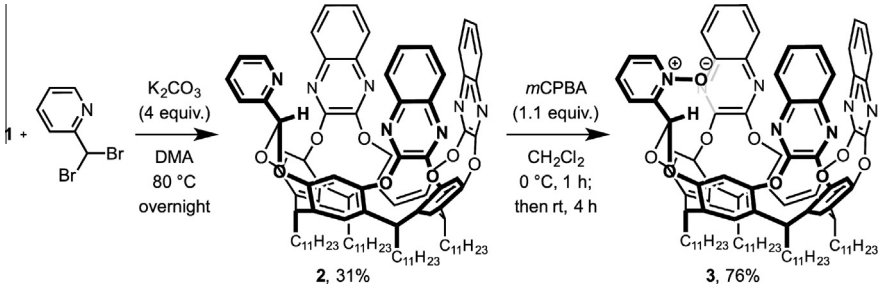

| | $H^a$ | $H^b$ | $H^c$ | $H^d$ | $H^e$ |
|---|---|---|---|---|---|
| $\Delta\delta$ | -1.7 | 0 | 0 | +0.16 | 0 |




| | $H^a$ | $H^b$ | $H^c$ | $H^d$ | $H^e$ |
|---|---|---|---|---|---|
| $\Delta\delta$ | -2.1 | -0.10 | 0 | +0.10 | +0.14 |

**Figure 3.** The differences in the chemical shifts ($\Delta\delta$) in $CDCl_3$ between **2** and **4**, and **3** and **5**. The values are standardized as ($\delta$ of **2**)−($\delta$ of **4**), and ($\delta$ of **3**)−($\delta$ of **5**).

[D6]benzene and [D8]toluene, and thus it cannot fit inside the cavity. The quinoxaline substructures in mesitylene would be not arranged in order to equilibrate between the vase and kite form, and consequently the moieties are randomly floating.[12]




**Scheme 2.** Synthesis of pyridine **2** and pyridine *N*-oxide **3**.

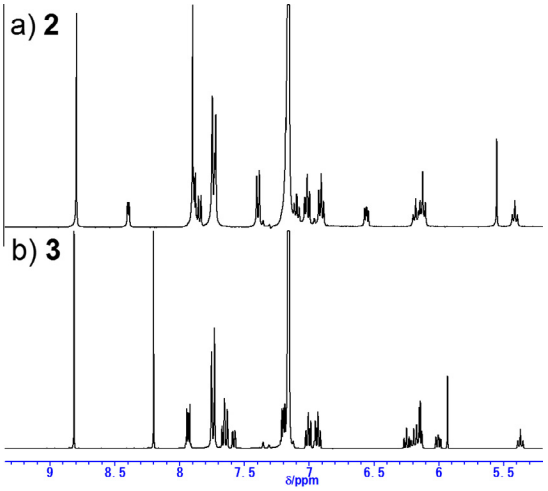



**Figure 4.** Portions of the $^{1}$H NMR spectra in [D6]benzene for a) pyridine cavitand **2**, and b) *N*-oxide cavitand **3**.

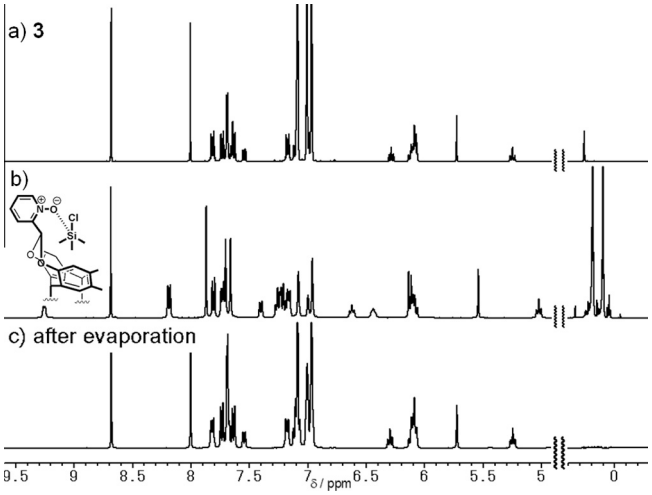



**Figure 5.** Portions of the $^{1}$H NMR spectra for (a) **3** and (b) host–guest complex obtained upon addition of TMSCl (5 equiv) to **3**, and (c) the residue obtained upon evaporating volatiles from the mixtures in (b) (400 MHz, [D8]toluene).

With a workable protocol for preparing **3** (Figs. 2 and 4), we envisaged the *N*-oxide as an oxidant for transforming haloalkanes into carbonyl compounds.[18] The *N*-oxide **3** could be designed to achieve size-selective oxidation: first, the cavity size-selectively acquires the haloalkane, then the *N*-O moiety performs nucleophilic attack to the carbon of C-X, and finally an external base deprotonates to afford the corresponding carbonyls. Thus, several haloalkanes were tested as guest substrates; however, even iodomethane ($CH_3I$) that is highly reactive and smallest haloalkane was neither oxidized nor was there any evidence of encapsulated or even interaction with the reactive *N*-oxide center. Indeed in a variety of deuterated solvents no significant changes were noted upon addition of methyl iodide.

Is a hollow of the cavity too narrow for receiving iodomethane? This seems unlikely given past successes with larger guests. Is there something about the stereoelectronics preventing interaction? Does the congested environment prevent access to a suitable transition state?

We explored other guests to gain a deeper understanding of the behavior of host **3**.[19] When 5 equiv of TMSCl were added, we noted significant changes to the $^{1}$H NMR spectra consistent with reaction at the oxygen center. Indeed the proton at C2 on pyridine moves drastically downfield to 9.3 ppm from a starting point of 7.5 ppm, as well as methyl groups on TMSCl shift upfield (Fig. 5). In addition, $^{29}$Si NMR data for the mixture showed two peaks of 30.1 ppm for free TMSCl and 7.22 ppm for the host–guest complex (see Supplementary materials). We imagined that a covalent bond between oxygen and silicon was formed, however extraction with aqueous washing and evaporation yielded material with identical NMR to pure **3**.

We observed similar behavior with dimethylallylsilylchloride. In these experiments one peculiarity emerged, significant upfield shifts of the guest were not observed for either of these two silyl guests (Table 1). When compared to the control compound pyridine *N*-oxide, the magnitude of upfield shift of the TMSCl or dimethylallylsilylchloride methyl groups is nearly identical. Lacking this tells tale feature of guest inclusion due to magnetic shielding of the aromatic surfaces, we reacted **3** with the larger triisopropylsilylchloride (TIPSCl) and no changes were noticed in the NMR for either of the reactants. To the best of our knowledge, such a selective encapsulation has never been reported so far. These differences in behavior based on size support the inwardly directed orientation of the *N*-oxide group. Nevertheless more information is needed in light of no significant changes in chemical shift of the guests that do interact.

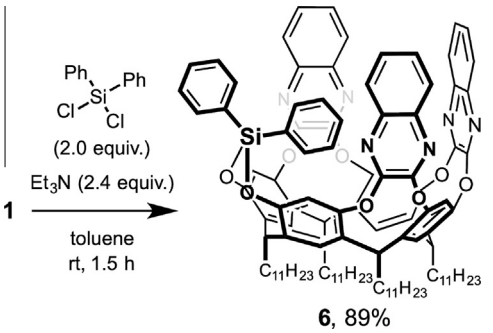
**Table 1**
Comparison of changes in chemical shift of silyl methyl protons of bound guests with control compound pyridine *N*-oxide and host 3[a]

| Guest | Δδ, pyridine *N*-oxide | Δδ, **3** |
|---|---|---|
| $ClSi(CH_3)_3$ | −0.083[b] | −0.088[c] |
| $ClSi(CH_2CH{=}CH_2)(CH_3)_2$ | −0.097[b] | −0.051[c] |

[a] Change is calculated compared to free guest in [D8]toluene, negative number implies upfield shift.
[b] The value is standardized as (δ of bound guest with pyridine *N*-oxide)−(δ of free guest).
[c] The value is standardized as (δ of bound guest with **3**)−(δ of free guest).

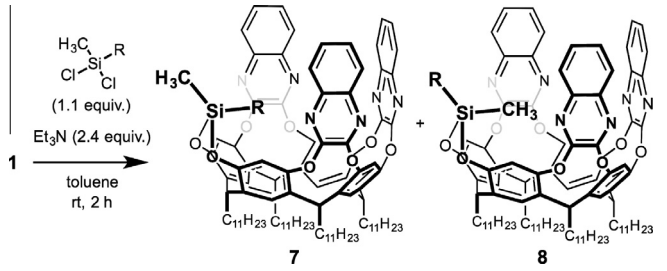
In addition to pyridine and pyridine *N*-oxide functionalized cavitands, we had continued interest in expanding the scope of earlier with dimethylsilyl[20] and silylmethylallyl functionalized cavitands.[12] We find that the bulky $Cl_2SiPh_2$ reacts smoothly with **1** to give **6** in 89% yield (Scheme 3). This is somewhat unexpected as aromatic containing moieties such as in the synthesis of **2** and the case of phenyl in Rebek group,[13a] resist placement inwardly directed. With two identical phenyl groups on silicon—we do not give the cavitand a choice to discriminate, but likely the silyl attachment center affords possibilities that carbon as in **2** does not. While **6** lacks practical applications toward synthetic chemistry, reactions with other silyl reagents begin a more interesting story.

As shown in Table 2, reactions of silyl reagents $Cl_2Si(CH_3)R$ with **1** afforded both introverted **7a–e** in comparable yields with



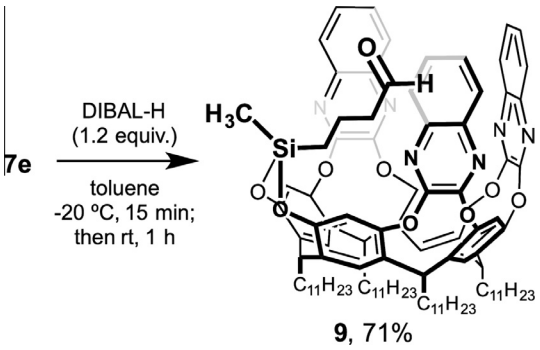

**Scheme 3.** The reaction of **1** with $Cl_2SiPh_2$ to give **6**.

**Table 2**
Reaction of 1 with $Cl_2Si(CH_3)R$




| Entry | R | Compound, yield[a] (%) | |
|---|---|---|---|
| | | 7 | 8 |
| 1 | $-CH{=}CH_2$ | **7a**, 48[b] | **8a**, 52[b] |
| 2 | $-CH_2CH{=}CH_2$ | **7b**, 34 | **8b**, 27 |
| 3 | $-CH_2CH_2CH_2Cl$ | **7c** 32 | **8c**, 34 |
| 4 | $-CH_2CH_2CH_2OAc$ | **7d**, 34 | **8d**, 33 |
| 5 | $-CH_2CH_2CH_2CN$ | **7e**, 22 | **8e**, 20 |

[a] Isolated yields.
[b] The yields were determined by $^1H$ NMR owing to inseparable mixtures of **7a** and **8a**.




**Scheme 4.** DIBAL-H reduction of **7e** to give the introverted aldehyde **9**.

extroverted **8a**–**e**. Except in the cases where R = vinyl (unseparable) and allyl (challenging), the separation of **7** and **8** (**c**–**e**) proceeded readily.[21] These latter 3 compounds, in particular **7c**, **7d**, and **7e** afford new opportunities to place reactive centers in close proximity to receptor bound small molecule guests.

Furthermore, while the variety of alkyl substituted chlorosilanes may be limited, but alkyl chloride, acetate, and nitrile provide a breadth of possibilities for functional group interconversion. In one example we convert the inwardly directed nitrile **7e** to the corresponding aldehyde in high yield using DIBAL-H (Scheme 4). The reaction proceeded despite the fact that the nitrile is likely encumbered with three quinoxaline-walls.[22,23] These suggest that the steric congestion is not a cause for concern, and that the space may be tolerable to catalyze reactions.[24] Likely our early lack of reaction of **3** with $CH_3I$ stems from electronic effects of the *N*-oxide, or perhaps electrostatic repulsion of the halide.

In summary, these new class of mono-functionalized cavitands, including pyridine, *N*-oxide, alkyl chloride, alkyl acetate, alkyl nitrile, and alkyl aldehyde present a wide variety of new chemical possibilities with cavitands. While we envisioned **3** as a size selective host for oxidation of alkyl halides, this goal has not yet materialized. Nevertheless the combined features of restricted space that the three walls provide in conjunction with a variety of spatially controlled functional group makes for an interesting class of compounds for future study. Toward the goal of size selective catalysis, the opportunity to study reactive intermediates though transition state stabilization is another application. Further synthetic developments of host molecules for improving chemical transformations are ongoing and will be reported in shortly.

## Acknowledgments

We thank Japan Society of the Promotion of Science for an Invitational Fellowship (Long-term, L-15528, M.P.S.). We thank Dr. Toshiyuki Iwai and Dr. Takatoshi Ito for assistance with HRMS.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.06.072.

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21. Upfield shift of alkyl groups on the Si atom is a characteristic of these silicon cavitands; for example, in $C_7D_8$, 6.66–6.64 ppm (m, 3H, Si–CH(CHC*H*)$_2$C*H*) for **6**, −0.80 ppm (t, *J* = 15.4, 5.4 Hz 2H, SiC*H*$_2$CH=CH$_2$) for **7b**, −1.3 ppm (s, 3H, SiC*H*$_3$) for **8b**, −0.84 ppm (t, *J* = 8.4 Hz 2H, SiC*H*$_2$CH$_2$) for **7c**, −1.41 ppm (s, 3H, SiC*H*$_3$) for **8c**, −0.88 ppm (t, *J* = 8.3 Hz 2H, SiC*H*$_2$CH$_2$) for **7d**, −1.41 ppm (s, 3H, SiC*H*$_3$) for **8d**, −0.92 ppm (t, *J* = 8.6 Hz 2H, SiC*H*$_2$CH$_2$) for **7e**, −1.46 ppm (s, 3H, SiC*H*$_3$) for **8e**.
22. The resultant aldehyde moiety was still enfolded because its proton of C*H*O was upfield-shifted in 8.87 ppm (toluene-$d_8$) compared with conventional chemical shift ~10 ppm.
23. In our previous Letter Ref. 12, the encumbered interior-allyl group was more reactive than non-crowded exterior-one.
24. Based on a previous Letter (Ref. 12), we anticipate interior nitrile **7e** should be more reactive than exterior **8e**.