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Capping the upper and lower rims of calix[4]arenes by aryl dinitrile oxide reactions

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Abstract—1,3-Dipolar cycloadditions of upper- and lower-rim diallylcalix[4]arenes (**1** and **3**) with aryl dinitrile oxides provide a unique and efficient way of capping the calix[4]arenes. When dinitrile oxides reacted with 5-allylcalix[4]arene **7**, they underwent a 1,3-dipolar cycloaddition on one side and an electrophilic substitution on the other side, which led to a novel type of asymmetric calix[4]arenes (**9** and **12**).
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Modification on the upper or lower rims of calix[4]-arenes enhances the accommodative ability of these molecules, and allows the inclusion of larger guest molecules.[1–3] We have been interested in the design of new chromogenic[4] and fluorogenic chemosensors. In the latter theme, we have developed a method of attaching aryl isoxazoline or isoxazole units onto the upper or lower rims of calix[4]arenes by 1,3-dipolar cycloadditions.[5]

Restriction of the conformational mobility of calix[4]-arenes by upper-rim bridges has been shown to highly enhance its affinity towards neutral guests.[6] Judging from molecular modelling, we envisaged it highly likely that a double 1,3-dipolar cycloaddition could be operated on the bis-allylcalix[4]arenes, and thus, may form a cap on the upper or lower rims of the macrocycles. Our synthetic strategy for novel capping on calix[4]-arenes involves double cycloadditions between bis-dipoles (aryl dinitrile oxides) and bis-dipolarophiles (5,17-di-allyl- or 25,27-diallyloxycalix[4]arenes). Although double cycloaddition methodologies have been exploited in the syntheses of crown ether macrocycles,[7] silamacro-cycles,[8] and bis-calix[4]arenes,[9] most of them resulted in 2+2 macrocyclizations. As described below, our work is

quite unique because most of the systems studied here exhibited 1+1 macrocyclizations.

The 1,3-dipolar cycloaddition reaction of isophthaldi-nitrile oxide[8] with 25,27-diallyloxycalix[4]arene **1**[1a] in methanol was studied first using a method reported previously.[10] After refluxing for 24 h, the reaction underwent a 1+1 double cycloaddition to give **2** (in 27%), which has an aryl-1,3-diisoxazoline cap on the lower rim of calix[4]arene (Scheme 1). To our disappointment, the reaction of terephthaldinitrile oxide[8] with lower rim diallyloxycalix[4]arene **1** under similar reaction condition gave only an inseparable complex mixture.

The structure of **2** was confirmed spectroscopically, and it was further determined by an X-ray crystallography analysis (see Supplementary data).[11,12]

The 1,3-dipolar cycloaddition reaction of 5,17-diallyl-calix[4]arene **3** with isophthaldinitrile oxide was studied

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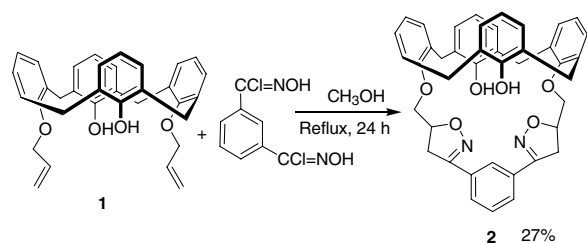
Scheme 1. Capping of lower rim diallyloxycalix[4]arene **1**.

next. The reaction after 24 h of reflux in methanol gave a 1+1 cycloadduct **4** in 29% yield. Whereas reaction of **3** with terephthaldinitrile oxide gave 1+1 upper rim capped calix[4]arene diastereomers **5** and **6** in ca. 2:1 ratio (Scheme 2).[11,12]

The structures of cycloadducts **4**–**6** were confirmed spectroscopically. Furthermore, the structures of the two upper-rim capped products **4** and **5** were confirmed by X-ray crystallography analysis (Fig. 1).[12]

After successfully capping the lower and upper rim diallylcalix[4]arenes **1** and **3** by double 1,3-dipolar cyclo-

additions, we extended this methodology for upper and lower rim mono allyl calix[4]arenes **7** and **8**,[1a] with a hope to synthesize 'clamshell' type calix[4]arene dimers.[13]

The reaction of terephthaldinitrile oxide with 5-allylcalix[4]arene **7** in ethanol did not give the expected 2+1 'clamshell' bis-calix[4]arene adduct **10**. Instead, we obtained 18% yield of an interesting asymmetric capped calix[4]arene **9**, which contained both an isoxazoline and an oxime moiety (Scheme 3).

It is noteworthy that host **9** becomes asymmetric from the reaction of two symmetrical reagents. The ^{1}H NMR of **9** reveals that all the four methylene bridges and the four phenolic groups are in different chemical environments (see Supplementary data). The structure of **9** was further confirmed by an X-ray crystallography analysis (Fig. 2).

Compound **9** might have arisen from two concurrent reactions: (1) 1,3-dipolar cycloaddition of one nitrile oxide with upper rim allyl group, and (2) an electrophilic substitution of another nitrile oxide on the *para*-position of distal phenol group. Scheme 4 provides a possible pathway for the formation of **9** through a zwitterionic

Scheme 2. Capping of upper rim diallylcalix[4]arene **3**.

Scheme 3. The reaction of terephthaldinitrile oxide with 5-allylcalix[4]arene **7**.
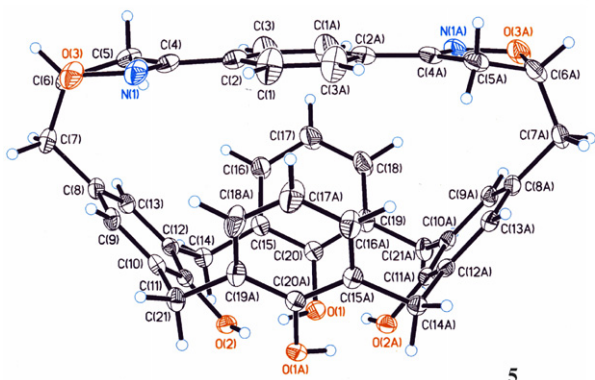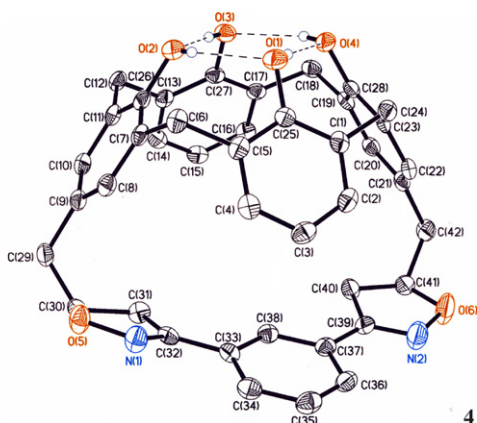
Figure 1. Single crystal X-ray structures of **4** and **5**.
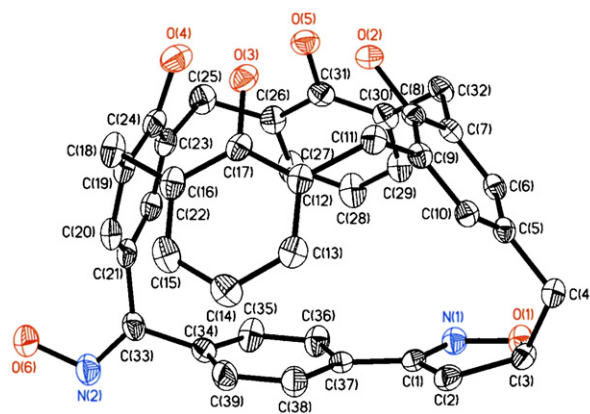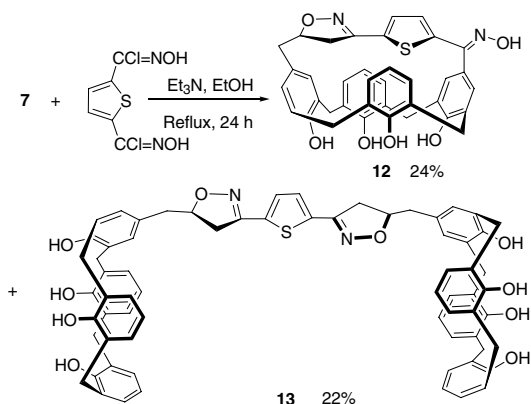
Figure 2. Single crystal X-ray structure of **9**.[12]
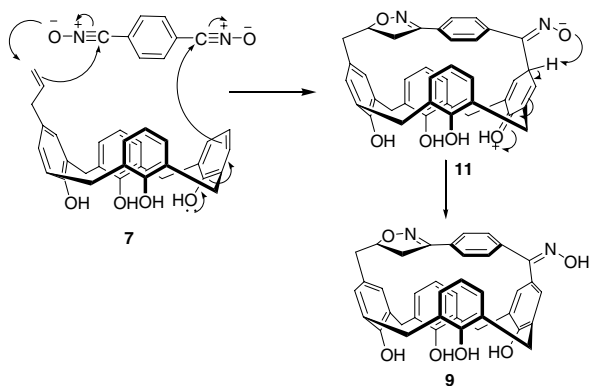
Scheme 4. Possible mechanism for the formation of **9**.

Scheme 6. The reaction of **8** with terephthaldinitrile oxide.

intermediate **11**. Although, oxime formation has been reported by the reactions of nitrile oxides with aromatic compounds,[14] indoles,[15] uracil,[16] styrene and indenes,[17] and a similar zwitterionic intermediate was proposed by others,[17] however, it has never been formed in such a stereo fashion.
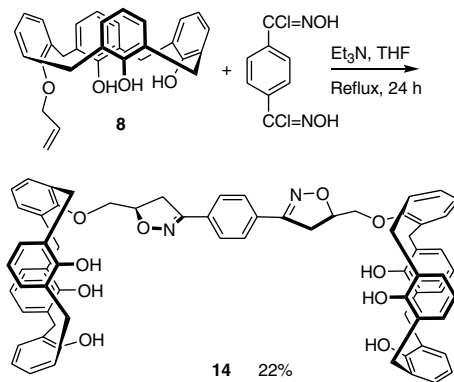
Due to the novel observation, we wish to know the scope and generality of this reaction type; therefore; the cycloaddition reaction of 5-allylcalix[4]arene **7** was extended to heteroaryl dinitrile oxide. The reaction of thiophene-2,5-dinitrile oxide with **7** gave not only the isoxazoline-oxime compound **12** (in 24%), but also the expected bis-calix[4]arene **13** in 22% yield (Scheme 5).[18] Compound **12** exists as an inseparable mixture of *E* and *Z* isomers based on ^{1}H NMR spectra.[18]

The reaction of lower rim 25-allyloxycalix[4]arene **8**[1a] with terephthaldinitrile oxide in THF gave bis-calix[4]-arene **14** in 22% yield via a 2+1 cycloaddition (Scheme 6).

In summary, we have described here a convenient and efficient method for capping the upper and lower rim of calix[4]arenes by double 1,3-dipolar macrocycloadditions. Unexpected asymmetric isoxazoline-oxime compounds were observed in the cycloaddition reactions of aryl dinitrile oxides with 5-allylcalix[4]arene. Further

investigations on the optimization of reaction conditions to control the cycloaddition fashion and the ring opening reactions of calix[4]arene-isoxazolines to multifunctional calix[4]arenes are in progress in our laboratory.

Acknowledgements

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tetlet.2006.09.070.

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Scheme 5. The reaction of thiophene-2,5-dinitrile oxide with 5-allylcalix[4]arene **7**.

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11. General procedures for the synthesis of capped calix[4]-arenes **2**, **4–6**: To a well stirred solution of calix[4]arene **1** or **3** (1 mol equiv) and substituted aryl dihydroximoyl chloride (1.2 mol equiv) in methanol (100 mL, 4 mM), excess triethylamine (10 equiv) was slowly added. The reaction mixture was stirred at reflux for 24 h. The solvent was removed under reduced pressure; the residue obtained was purified over silica gel column to give the respective cycloadducts **2**, **4–6**. The major difference in ^{1}H NMR between **5** and **6** is on the chemical shift of their hydroxy protons: which is δ 9.95 for **5** but is 9.74 for **6**.
Spectral data for **2**: $R_f = 0.2$ (EA/Hexane = 1/2); ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.15 (s, 1H), 7.58 (dd, $J = 7.5$ Hz and 1.3, 2H), 7.41 (t, $J = 7.5$ Hz, 1H), 7.10–7.03 (m, 4H), 6.79–6.67 (m, 3H), 6.47–6.37 (m, 5H), 5.08–5.04 (m, 2H), 4.88 (s, 1H), 4.43 and 3.32 (ABq, $J = 14.2$ Hz, 4H), 4.36 (s, 1H), 4.11 and 3.32 (ABq, $J = 13.7$ Hz, 4H), 4.02–3.93 (m, 4H), 3.83–3.61 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 157.0 (Cq), 152.9 (Cq), 152.8 (Cq), 152.7 (Cq), 133.3 (Cq), 131.7 (Cq), 130.4 (Cq), 129.8 (Cq), 129.1 (Cq), 129.0 (CH), 128.9 (CH), 128.9 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 124.4 (CH), 119.4 (CH), 118.8 (CH), 78.8 (CH), 78.1 (CH$_2$), 37.3 (CH$_2$), 30.4 (CH$_2$), 29.9 (CH$_2$); FAB-MS *m/z*: 666 (M+H$^+$, 68); HR FAB-MS *m/z*: Calcd for C$_{42}$H$_{36}$N$_2$O$_6$ 664.2573, found 664.2577.

12. Crystal structure data for **2**: C$_{44}$H$_{43}$N$_2$O$_8$, $M = 727.80$, monoclinic, $a = 11.0874(5)$ Å, $\alpha = 90°$, $b = 11.8544(6)$ Å, $\beta = 96.216(2)°$, $c = 28.6896$ (13) Å, $\gamma = 90°$, $V = 3748.6(3)$ Å^3, $T = 150(1)$ K, space group $P2_1/c$, $Z = 4$, $\mu = 0.089$ mm^{-1}, 29,164 reflections collected ($R1 = 0.0708$, $wR2 = 0.1680$), 6597 independent reflections (R(int) = 0.0605, $R1 = 0.0999$, $wR2 = 0.1861$). Crystal structure data for **4**: C$_{44}$H$_{37}$Cl$_3$N$_2$O$_7$, $M = 812.11$, monoclinic, $a = 11.9873(4)$ Å, $b = 35.0966(16)$ Å, $c = 8.9562(5)$ Å, $\alpha = 90°$, $\beta = 97.735(2)°$, $\gamma = 90°$, $V = 3733.7(3)$ Å^3, $T = 150(1)$ K, space group $P2_1/c$, $Z = 4$, $\mu = 0.303$ mm^{-1}, 34,966 reflections collected ($R1 = 0.0738$, $wR2 = 0.1688$), 8585 independent reflections (R(int) = 0.0719, $R1 = 0.1163$, $wR2 = 0.1948$).
Crystal structure data for **5**: C$_{42.50}$H$_{38}$N$_2$O$_{6.50}$, $M = 680.75$, tetragonal, $a = 9.6341(4)$ Å, $\alpha = 90°$, $b = 9.6341(4)$ Å, $\beta = 90°$, $c = 35.9266(14)$ Å, $\gamma = 90°$, $V = 3334.6(2)$ Å^3, $T = 150(1)$ K, space group $P4_12_12$, $Z = 4$, $\mu = 0.092$ mm^{-1}, 22,260 reflections collected ($R1 = 0.0741$, $wR2 = 0.1687$), 2948 independent reflections (R(int) = 0.0913, $R1 = 0.0810$, $wR2 = 0.1728$).
Crystal structure data for **9**: C$_{40.50}$H$_{40}$N$_2$O$_{7.50}$, $M = 674.74$, monoclinic, $a = 35.5191(3)$ Å, $\alpha = 90°$, $b = 9.6250(1)$ Å, $\beta = 91.2989(4)°$, $c = 19.8381(2)$ Å, $\gamma = 90°$, $V = 6780.34(11)$ Å^3, $T = 150(1)$ K, space group $C2/c$, $Z = 8$, $\mu = 0.091$ mm^{-1}, 55,371 reflections collected ($R1 = 0.0696$, $wR2 = 0.2036$), 7786 independent reflections (R(int) = 0.0626, $R1 = 0.0977$, $wR2 = 0.2351$).

Crystallographic data for the four structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication. Their CCDC numbers are **2** (CCDC 611611), **4** (CCDC 611612), **5** (CCDC 611613), and **9** (CCDC 611614), respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44-1223-336033, e-mail: data_request@ ccdc.cam.ac.uk.

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18. Procedures for the synthesis of calix[4]arenes **12** and **13**: Triethylamine (10 equiv) was slowly added to a mixture of 5-allylcalix[4]arene **7** (1 mol equiv) and 2,5-thiophene dihydroximoyl chloride (0.5 mol equiv) in EtOH (50 mL). After reflux for 24 h followed by chromatographic separation, the reaction gave **12** and **13** in 24% and 22% yield, respectively. Spectral data for **12**: $R_f = 0.5$ (EA/hexane/CHCl$_3$ = 1/1/1); ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.31 (br s, 8H), 8.01 (br s, 1H), 7.28–6.63 (m, 24H), 5.00–4.92 (m, 2H), 4.30–4.15 (m, 8H), 3.55–3.42 (m, 8H), 3.28–3.13 (m, 2H), 2.56–2.41 (m, 2H), 2.24–2.15 (m, 1H), 2.04–1.95 (m, 1H), 1.72–1.52 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 151.0 (Cq), 149.9 (Cq), 149.7 (Cq), 148.6 (Cq), 148.4 (Cq), 146.3 (Cq), 143.7 (Cq), 134.4 (Cq), 133.8 (Cq), 133.3 (Cq), 131.6 (Cq), 131.3 (Cq), 131.1 (Cq), 131.0 (Cq), 130.6 (Cq), 130.0 (Cq), 129.8 (Cq), 129.2 (Cq), 129.1 (Cq), 128.9 (CH), 128.9 (Cq), 128.8 (Cq), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.1 (CH), 128.1 (Cq), 127.6 (Cq), 127.6 (Cq), 127.3 (Cq), 127.3 (Cq), 126.2 (CH), 125.9 (CH), 123.8 (CH), 121.9 (CH), 121.6 (CH), 80.5 (CH), 80.2 (CH), 41.9 (CH$_2$), 41.8 (CH$_2$), 37.6 (CH$_2$), 37.4 (CH$_2$), 31.7 (CH$_2$), 31.3 (CH$_2$), 31.2 (CH$_2$), 31.1 (CH$_2$), 31.0 (CH$_2$), 30.9 (CH$_2$), 30.8 (CH$_2$), 30.7 (CH$_2$); FAB-MS *m/z*: 631 (M+H$^+$, 14), 613 (M$^+$–OH, 14), 460 (100); HR FAB-MS *m/z*: Calcd for [M+H$^+$] C$_{37}$H$_{31}$N$_2$O$_6$S 631.1903, found 631.1898.
Spectral data for **13**: $R_f = 0.73$ (EA/hexane/CHCl$_3$ = 1/1/ 1); ^{1}H NMR (300 MHz, CDCl$_3$): δ 10.19 (s, 8H), 7.07–7.05 (m, 14H), 6.93 (s, 4H), 6.76–6.70 (m, 6H), 4.94–4.82 (m, 2H), 4.24 (br s, 8H), 3.52 (br s, 8H), 3.27–3.18 (m, 2H), 3.00–2.87 (m, 4H), 2.70–2.63 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 151.9 (Cq), 148.8 (Cq), 148.7 (Cq), 147.6 (Cq), 134.3 (Cq), 130.2 (Cq), 129.8 (CH), 129.0 (CH), 128.9 (2CH), 128.5 (Cq), 128.2 (2Cq), 128.1 (Cq), 128.0 (CH), 122.3 (CH), 122.2 (CH), 82.6 (CH), 39.9 (CH$_2$), 39.8 (CH$_2$), 31.7 (CH$_2$); FAB-MS *m/z*: 1095 (M+H$^+$, 17), 614 (14), 460 (100); HR FAB-MS *m/z*: Calcd for C$_{68}$H$_{58}$N$_2$O$_{10}$S 1094.3812, found 1094.3822.