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Efficient synthesis of lower rim α-hydrazino tetrazolocalix[4]arenes via an Ugi-azide multicomponent reaction

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ABSTRACT In this study we have developed an efficient synthesis of α-hydrazino tetrazolocalix[4]arene derivatives in good yields under mild conditions via an Ugi-azide multicomponent reaction. Metal ion binding properties of one of the α-hydrazino

tetrazolocalix[4]arenes (**7a**) as the model compound were also investigated, revealing that compound **7a** exhibit the highest binding toward Ni(II).

INTRODUCTION

Calixarenes, produced by condensation of p-substituted phenols with aldehydes, have been applied in diverse areas.[1] Calixarenes are versatile macromolecules which can be used for the synthesis of multivalent/multifunctional ligands [2] The easy accessibility and functionalization at their wide and narrow rims have made them ideal candidates for studying noncovalent interactions involved in many biological processes.[3] Calixarenes can also be used as metal-selective ionophores by virtue of coordinating functional groups at their wide rims.

The presence of nitrogen-rich functional groups such as tetrazole derivatives on the calixarene skeleton has drawn more and more attention in fields of molecular recognition and host-guest chemistry.

Tetrazoles represent an important class of nitrogen heterocyclic compounds and their derivatives have possessed a broad range of biological activities in both medicinal and pharmaceutical fields.[4] Besides their well-known applications in medicinal chemistry, pharmacology, materials chemistry, and organocatalysis, they are also of interest as ligands in coordination chemistry due to the presence of four nitrogen atoms in the tetrazole ring.[5] The ability of two phenolic OH groups to provide more coordination sites and maintain the cone conformation led to the increasing importance of lower rim 1,3-disubstitutedcalix[4]arenes.[6] An interesting example in this respect is the synthesis of tetrazoles and para-substituted phenylazo-coupled calix[4]arenes as highly sensitive chromogenic sensors for Ca^{2+} by 1,3-dipolar cycloaddition of oxyacetonitrile azocalix[4]arenes activated with trimethylsilyl azide.[7] Another fascinating example is the

synthesis of the lower rim 1,3-tetrazole-functionalised calix[4]arene by reaction of the 5,11,17,23-tetra-tert-butyl-25,27-dicyanomethoxy-26,28-dihydroxycalix[4]arene with sodium azide and triethylammonium chloride that acts as an ionophore for lanthanoid cations, forming luminescent complexes.[5b]

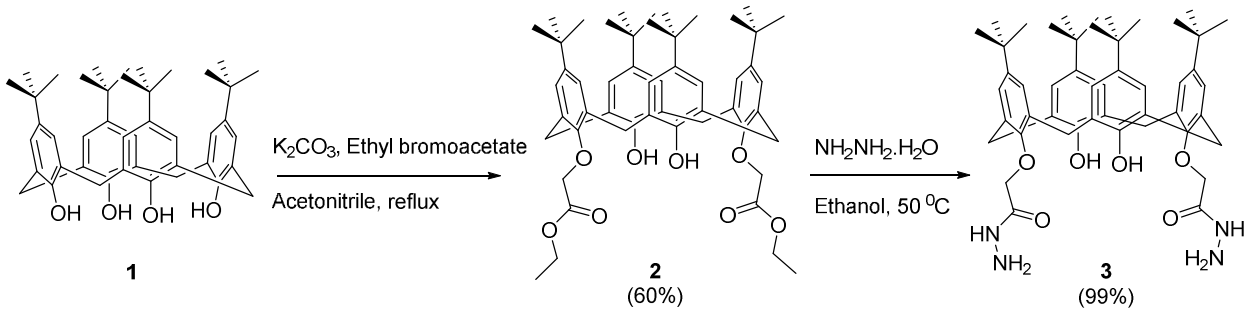
As part of our interest in the synthesis of functionalized calixarenes, we have reported synthesis of a number of functionalized calixarenes by using through multi-component reactions.[8] Multicomponent reactions (MCRs) are compelling strategies for rapid generation of diverse sets of complex molecules.[9] Among the MCRs, the isocyanide-based multicomponent reactions (IMCRs) by virtue of their synthetic potential, their inherent atom efficiency, convergent nature, ease of implementation, and the generation of molecular diversity, have attracted considerable attention of organic chemists, medical chemists and pharmacologists worldwide.[10] Despite their undeniable advantages in the field of combinatorial chemistry, the synthetic utility of IMCRs toward the synthesis of functionalized calixarenes is rather under-represented.[11]

In this paper, we propose a versatile synthesis of the lower rim α-hydrazinotetrazolocalix[4]arenes based on the Ugi-azide multicomponent reaction. The presence of numerous nitrogen atoms making a bidentate bonding mode likely for metal ion complexation.

RESULTS AND DISCUSSION

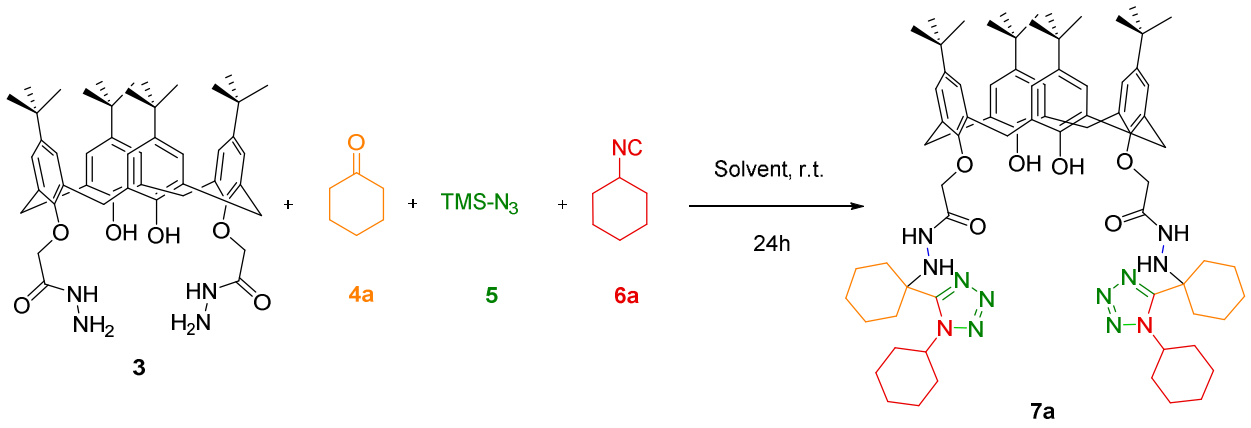
The basic precursor of our investigation, calixarene dihydrazide **3**, was prepared in good yield using the previously reported synthetic procedures.[12]

Scheme 1. Synthesis of calixarene dihydrazide **3**.



At the outset of this study, our efforts were focused on finding appropriate reaction conditions to perform the proposed reaction. We commenced our study of Ugi-azide reaction by using calixarene dihydrazide **3**, cyclohexanone, cyclohexyl isocyanide, and trimethylsilyl azide. The results are summarized in Table **1**. The use of ethanol, acetonitrile, tetrahydrofuran, and dichloromethane in place of methanol as the reaction solvent decreased the yield of the desired product (entries 2-5).

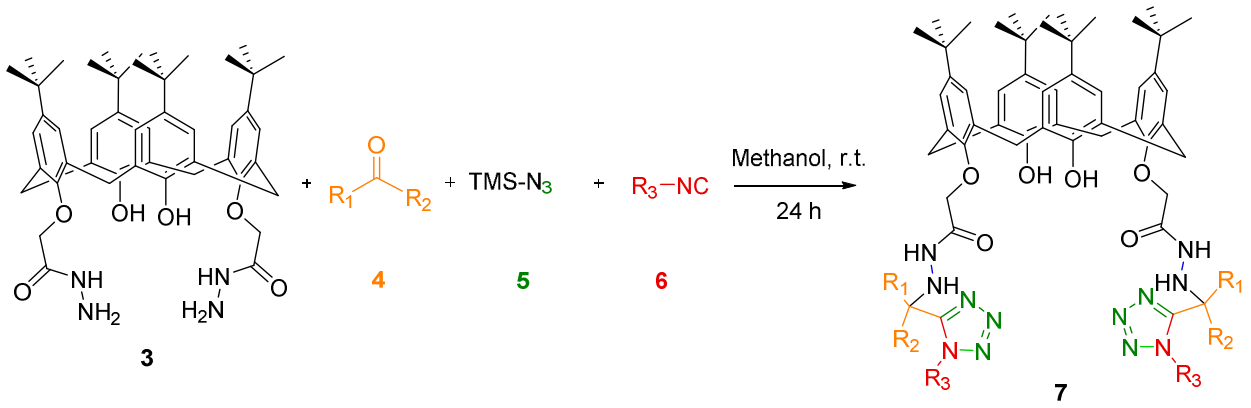
Table 1. Optimization of the reaction conditions.



Entry	Solvents	Yield of **7a** (%)
1	Methanol	80
2	Ethanol	72
3	Acetonitrile	54
4	Tetrahydrofuran	40
5	Dichloromethane	30

Furthermore, when TMS-N_3 in the reaction was replaced by NaN_3 we could isolate only 30% of **7a**. To further demonstrate the efficiency of the Ugi-azide reaction based on calixarene dihydrazide **3**, the scope of the reaction with various ketones and isocyanides were explored and the results obtained are summarized in Table **2**.

Table 2. Scope of Ugi-azide reaction of calixarene dihydrazide **3**.



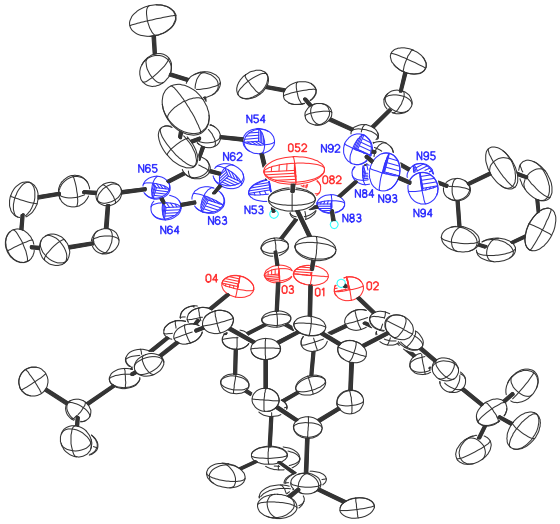
Entry	Ketones	Isocyanides	Yield of **7** (%)	Entry	Ketones	Isocyanides	Yield of **7** (%)
1	**4a**	**6a**	**7a**, 80	6	**4c**	**6b**	**7f**, 65
2	**4a**	**6b**	**7b**, 72	7	**4d**	**6a**	**7g**, 76
3	**4b**	**6a**	**7c**, 68	8	**4d**	**6b**	**7h**, 67
4	**4b**	**6b**	**7d**, 58	9	**4e**	**6a**	**7i**, 70
5	**4c**	**6a**	**7e**, 73	10	**4e**	**6b**	**7j**, 61

The products have been characterized using the spectroscopic techniques, and their IR, ^{1}H NMR, ^{13}C NMR, and UHPLC–TOFMS spectroscopic data confirm the proposed structures. All

the synthesized compounds exist in the cone conformation as the signals of bridging methylene carbons all appear at about 31 ppm in their ^{13}C NMR spectra.[13]

Due to the presence of two chiral centers in compounds **7g-7j**, diastereomeric products are possible. The structure of one of the compounds **7g** has also been established by single crystal X-ray diffraction analysis (Figure 1). The crystal structure of compound **7g** shows the presence of the both diastereomers in a 60:40 ratio. In 60% of the molecules in this specific crystal the configuration of the asymmetric carbon atom C85 is the same as for the asymmetric carbon C55. In 40% of the molecules it is the opposite one. That means, there are indeed different stereoisomers.

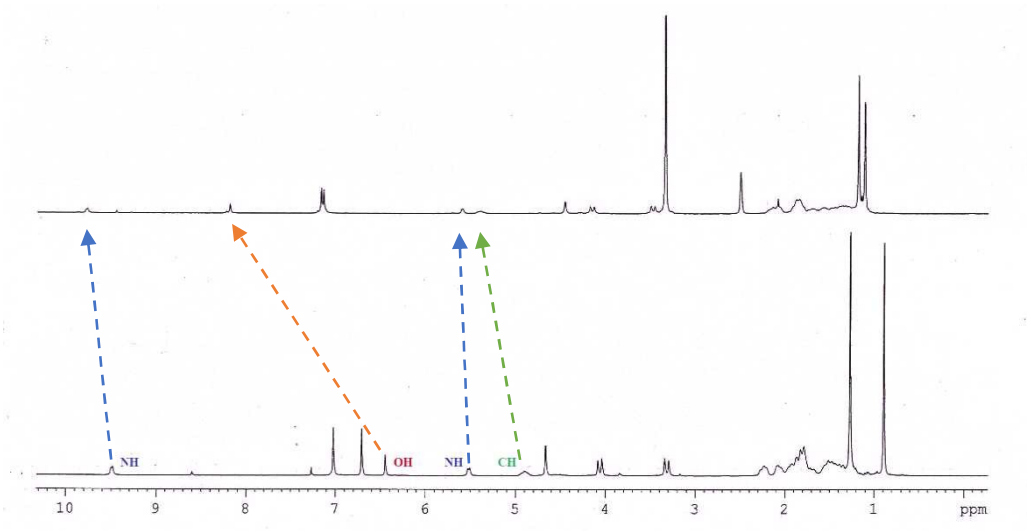
Figure 1. ORTEP view of the major diastereomer of compound **7g**.



The strength of this process lies in the simple one-step synthesis of bidentate nitrogen rich calixarene ligands through an Ugi-azide multicomponent reaction with easy workup and purification procedures. To gain some insights into the intramolecular hydrogen bonding occurring in these compounds, the ^{1}H NMR spectra of **7a** as the model compound in $CDCl_3$ and DMSO-d_6 was obtained. Significant downfield shifts of the CH proton directly attached to the

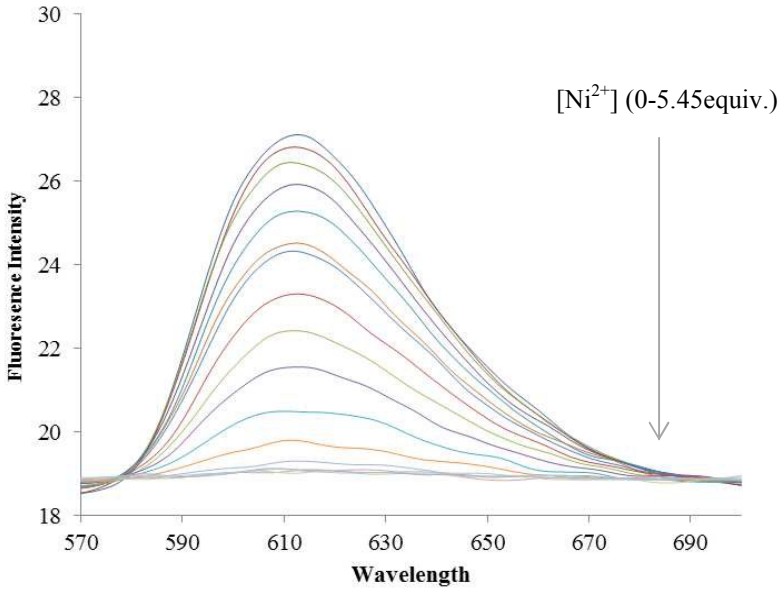
nitrogen of the tetrazole (~0.5 ppm), and OH protons (~1.65 ppm) indicating that both the tetrazole and OH groups participate in significant hydrogen-bonding interactions in nonpolar solvent (Figure 2).

Figure 2. Comparison of ^{1}H NMR spectra of compound **7a** in DMSO-d_6 (above) and $CDCl_3$ (below).



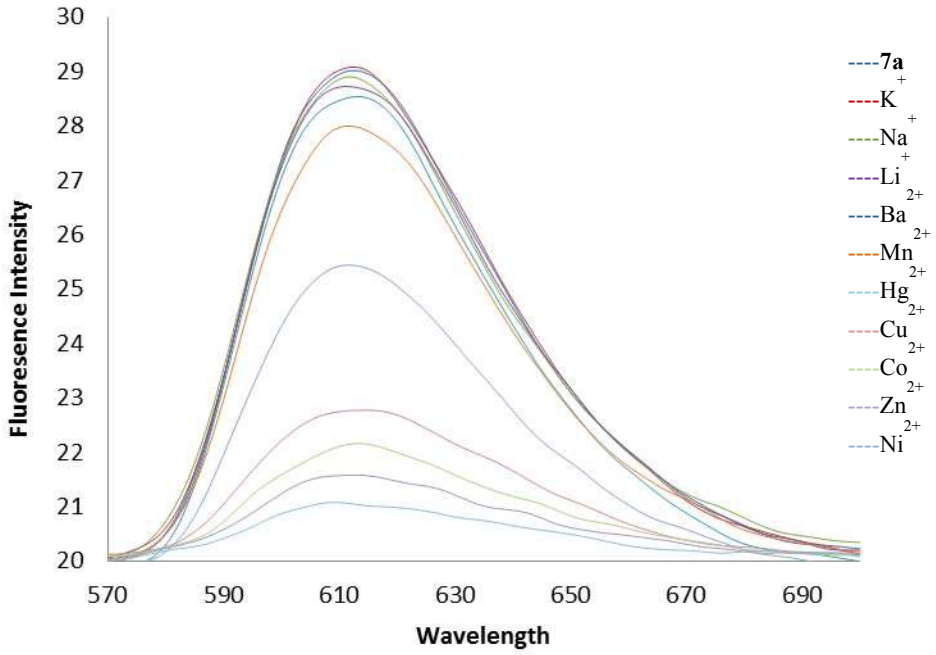
The metal-binding sites on the synthesized compounds are the nitrogen and oxygen atoms. Therefore, we further investigated the metal cation binding properties of the newly synthesized receptor **7a** as the model compound by fluorescence titration with cations as metal perchlorates (Li^{+}, Na^{+}, K^{+}, Ba^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and Hg^{2+}), and the desired compound demonstrated the highest binding affinity toward Ni(II) to form a Ni(II)-**7a** complex, resulting in prominent fluorescence quenching is shown in figure **3**.

Figure 3. Fluorescence spectra of **7a** in response to the presence of Ni^{2+} ions (0 to 5.45 equiv.) in MeCN; λex = 280 nm.



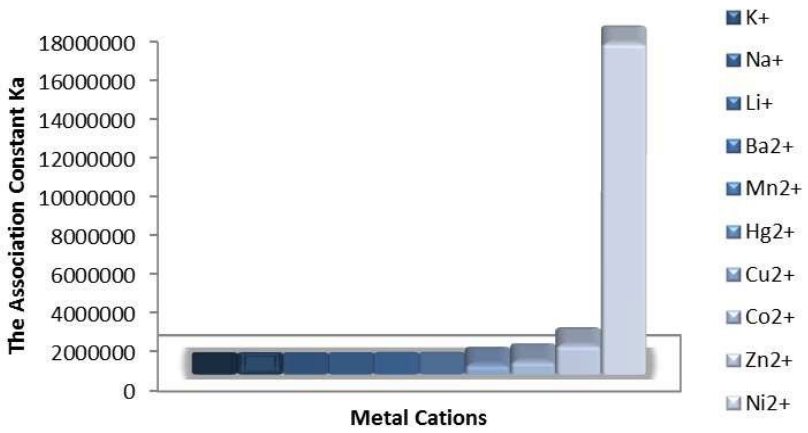
The fluorescence spectrum of **7a** (λex = 280 nm, The molar extinction coefficient ε = 9340.66 $M^{-1}cm^{-1}$) in CH_3CN exhibited two characteristic emission bands at 309 nm and 612 nm. The strong 309 nm band is characteristic of the aromatic core of the calixarene.[14]

Figure 4. Fluorescence intensity changes of compound **7a** in MeCN upon addition of 1 equiv. of various metal perchlorates; λex = 280 nm.



As shown, the fluorescence of compound **7a** was almost completely quenched by $Ni(ClO_4)_2$. The binding constant of compound **7a** with Ni^{2+} was calculated by non-linear least square curve fitting (SigmaPlot Version 10.0), and the corresponding association constant K_a was found to be 1.70×10^7 M^{-1} (Table 3).[15]

Table 3. The association constants of **7a** with metal cations (1:1 binding model) in CH_3CN.

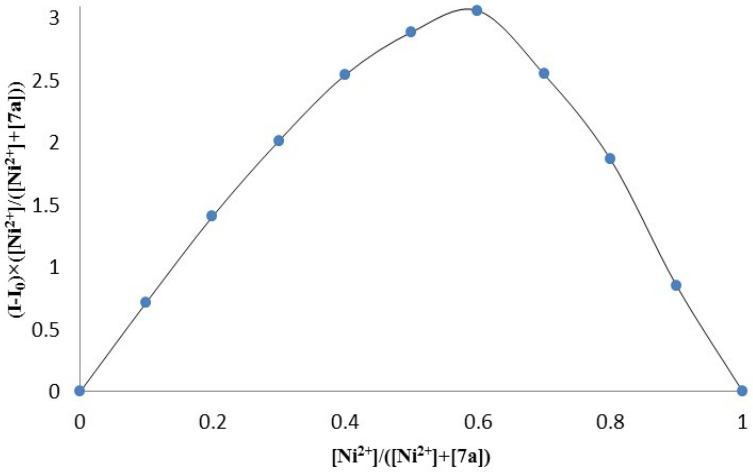


Cation	K_a (M^{-1})	Cation	K_a (M^{-1})
K^+	1560	Hg^{2+}	15100
Na^+	1640	Cu^{2+}	422000
Li^+	2480	Co^{2+}	599000
Ba^{2+}	4290	Zn^{2+}	1430000
Mn^{2+}	7767	Ni^{2+}	17000000

Job plots analysis and ESI-MS spectra show that **7a** and Ni(II) form a 1:1 Ni(II)-**7a** complex (Figure 5). Peaks in the ^1H NMR spectra of compound **7a** with Ni^{2+} (1:1) decreased in signal intensities, culminating in substantial broadening and subsequent disappearance of the

resonances ascribable to the compound **7a**. These results, provide evidence that **7a** and Ni(II) form a 1:1 Ni(II)-**7a** complex.

Figure 5. The Job plot for the complexation of **7a** with Ni^{2+} in CH_3CN



To test the highest binding affinity of compound **7a** with Ni^{2+}, competitive experiments were carried out in the presence of Ni^{2+} at 1 equiv. mixed with Li^{+}, Na^{+}, K^{+}, Ba^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and Hg^{2+} at 1 equiv., no significant variation was found by comparison with and without the other metal ions besides Ni^{2+}. This means that compound **7a** has the highest binding affinity for Ni^{2+} ions.

In contrast to many fluorescent sensors for heavy and transition metal ions detection like Hg^{2+}, Ag^{+}, Cd^{2+}, Pb^{2+}, Cr^{3+}, etc, reports concerning fluorescent sensors for Ni^{2+} detection are scarce.[16] Fluorescent sensors for Ni^{2+} detection are often based on small molecules, and encounter serious interference problems from other heavy and transition metal ions.[17] This study opens up new opportunities for the design of efficient, fast and inexpensive synthesis of fluorescent sensor libraries based on the calixarene unit.

CONCLUSION

In summary, an operationally simple Ugi-azide multicomponent reaction protocol was developed for the preparation of lower rim α-hydrazino tetrazolocalix[4]arene derivatives in good yields under mild conditions. The scope of this reaction was expanded to include various ketones and isocyanides. A detailed investigation of the metal ion binding properties of the model compound **7a** is performed mainly by the fluorometric titration approach, revealing that compound **7a** exhibit the highest binding toward Ni(II). Future efforts in our laboratories are aiming to develop new and efficient multicomponent reaction protocols for rapidly synthesis of large libraries of functionalized calixarene derivatives and will be reported in due course.

EXPERIMENTAL SECTION

All solvents and reagents were commercially available. NMR spectra were recorded on a Bruker DRX-300 AVANCE 300 MHz spectrometer. All chemical shifts are reported in the standard δ notation of parts per million. UHPLC-TOF mass spectra using electrospray ionisation were recorded with an Agilent 1290 Infinity UHPLC and an Agilent 6550 iFunnel Q-TOF. Fluorescence emission spectra were measured on a A JASCO FP-6500 spectrofluorometer. UV/Vis spectra was measured on a PerkinElmer LAMBDA 35 UV/Vis spectrophotometer.

General procedure for the synthesis of lower rim α-hydrazino tetrazolocalix[4]arenes: A solution of calixarene dihydrazide 3 (0.2 mmol) and ketone 4 (0.5 mmol) in 2 mL MeOH was stirred for 2 h, then trimethylsilyl azide 3 (0.5 mmol) and isocyanide 4 (0.5 mmol) were added. The mixture was stirred for 24 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane, 1:3), the solvent was removed under vacuum, and the residue was precipitated by addition of 3 mL of EtOH and 1 mL of H_2O. The precipitate was filtered off and then recrystallized from ethanol.

7a: Yield: 80%, mp: 223-225 °C; IR (KBr, ν, cm^{-1}): 3056, 2953, 2863, 1673, 1549, 1482, 1425, 1266, 1194, 1104, 1036, 896, 749; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, *t*-Bu, 18H); 1.27 (s, *t*-Bu, 18H); 1.44 (m, CH_2, 12H); 1.81 (m, CH_2, 20H); 2.06 (m, CH_2, 4H); 2.24 (m, CH_2, 4H); 3.32 (d, *J* = 13.4 Hz, $ArCH_2Ar$, 4H); 4.06 (d, *J* = 13.4 Hz, $ArCH_2Ar$, 4H); 4.66 (s, OCH_2, 4H); 4.90 (m, CH, 2H); 5.52 (d, *J* = 5.7 Hz, NH, 2H); 6.45 (s, OH, 2H); 6.71 (s, ArH, 4H); 7.02 (s, ArH, 4H); 9.49 (d, *J* = 5.5 Hz, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 21.9, 24.8, 24.9, 25.3, 25.5, 30.8, 31.6, 31.8, 33.0, 33.2, 33.4, 33.6, 33.8, 33.9, 57.9, 58.7, 59.4, 74.5, 125.3, 125.9, 127.3, 131.9, 142.9, 147.9, 149.2, 149.6, 155.7, 167.5; UHPLC–TOFMS (ESI) m/z: calcd for $C_{74}H_{105}N_{12}O_6$: 1257.8275 $[M+H]^+$; found 1257.8297, calcd for $C_{74}H_{104}N_{12}NaO_6$: 1279.8094 $[M+Na]^+$; found 1279.8117.

7b: Yield: 72%, mp: 161-163 °C; IR (KBr, ν, cm^{-1}): 3320, 3056, 2963, 2864, 1685, 1544, 1481, 1427, 1266, 1196, 1120, 1039, 898, 743; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, *t*-Bu, 18H); 1.27 (s, *t*-Bu, 18H); 1.37-1.41 (m, CH_2, 2H); 1.58 (m, CH_2, 6H); 1.63 (s, *t*-Bu, 18H); 1.94-1.98 (m, CH_2, 4H); 2.12-2.16 (m, CH_2, 4H); 2.34-2.37 (m, CH_2, 4H); 3.30 (d, *J* = 13.4 Hz, $ArCH_2Ar$, 4H); 4.11 (d, *J* = 13.4 Hz, $ArCH_2Ar$, 4H); 4.71 (s, OCH_2, 4H); 5.55 (d, *J* = 5.9 Hz, NH, 2H); 6.35 (s, OH, 2H); 6.68 (s, ArH, 4H); 7.00 (s, ArH, 4H); 9.27 (d, *J* = 5.7 Hz, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 25.3, 30.8, 30.9, 31.6, 33.8, 33.7, 34.7, 60.4, 63.5, 74.6, 76.6, 125.2, 125.8, 127.2, 131.9, 142.6, 147.7, 149.4, 149.5, 158.1, 167.7; UHPLC–TOFMS (ESI) m/z: calcd for $C_{70}H_{100}N_{12}NaO_6$: 1227.7781 $[M+Na]^+$; found 1227.7803.

7c: Yield: 68%, mp: 228-230 °C; IR (KBr, ν, cm^{-1}): 3394, 3305, 3056, 2961, 2863, 1690, 1549, 1485, 1426, 1359, 1267, 1190, 1102, 1039, 894, 743 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, *t*-Bu, 18H); 1.24-1.27 (m, CH_2, 4H); 1.27 (s, *t*-Bu, 18H), 1.68-1.71 (bs, CH_3, CH_2, 14H); 1.78 (m, CH_2, 14H); 3.31 (d, *J* = 13.3 Hz, $ArCH_2Ar$, 4H); 4.11 (d, *J* = 13.3 Hz, $ArCH_2Ar$, 4H); 4.72 (s,

OCH_2, 4H); 4.72-4.78 (m, CH, 2H); 5.45 (d, J = 5.1 Hz, NH, 2H); 6.40 (s, OH, 2H); 6.69 (s, ArH, 4H); 7.02 (s, ArH, 4H); 9.50 (d, J = 4.9 Hz, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 24.8, 25.4, 30.8, 31.5, 31.6, 33.0, 33.8, 33.9, 56.4, 59.2, 74.4, 76.6, 125.2, 125.8, 127.3, 131.9, 142.7, 147.8, 149.4, 149.5, 157.0, 168.3; UHPLC–TOFMS (ESI) m/z: calcd for $C_{68}H_{97}N_{12}O_6$: 1177.7649 $[M+H]^+$; found 1177.7665, calcd for $C_{68}H_{96}N_{12}NaO_6$: 1199.7468 $[M+Na]^+$; found 1199.7488.

7d: Yield: 58%, mp: 162-164 °C; IR (KBr, ν, cm^{-1}): 3312, 3056, 2968, 2867, 1684, 1546, 1482, 1429, 1357, 1268, 1190, 1123, 1039, 895, 746; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, *t*-Bu, 18H); 1.27 (s, *t*-Bu, 18H); 1.59 (s, *t*-Bu, 18H); 1.75 (s, CH_3, 12H); 3.27 (d, J = 13.3 Hz, $ArCH_2Ar$, 4H); 4.14 (d, J = 13.3 Hz, $ArCH_2Ar$, 4H); 4.76 (s, OCH_2, 4H); 5.51 (bs, NH, 2H); 6.26 (s, OH, 2H); 6.66 (s, ArH, 4H); 7.01 (s, ArH, 4H); 9.45 (s, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.1, 27.7, 30.6, 30.8, 31.4, 31.6, 33.8, 58.7, 63.3, 74.6, 76.6, 125.1, 125.7, 127.3, 131.7, 142.6, 147.8, 149.4, 149.5, 159.0, 168.4; UHPLC–TOFMS (ESI) m/z: calcd for $C_{64}H_{93}N_{12}O_6$: 1125.7336 $[M+H]^+$; found 1125.7328, calcd for $C_{64}H_{92}N_{12}NaO_6$: 1147.7155 $[M+Na]^+$; found 1147.717.

7e: Yield: 73%, mp: 220-222 °C; IR (KBr, ν, cm^{-1}): 3310, 3051, 2936, 2865, 1702, 1594, 1549, 1480, 1356, 1296, 1269, 1198, 1125, 1098, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, CH_3, 12H); 0.89 (s, *t*-Bu, 18H); 1.29 (s, *t*-Bu, 18H); 1.35-1.39 (m, CH_2, 4H); 1.68-1.72 (m, CH_2, 4H); 1.72-1.83 (m, CH_2, 10H); 2.00-2.07 (m, CH_2, 6H); 2.14-2.19 (m, CH_2, 4H); 3.33 (d, J = 13.4 Hz, $ArCH_2Ar$, 4H); 4.08 (d, J = 13.4 Hz, $ArCH_2Ar$, 4H); 4.65 (s, OCH_2, 4H); 5.02 (m, CH, 2H); 5.53 (d, J = 4.7 Hz, NH, 2H); 6.50 (s, OH, 2H); 6.72 (s, ArH, 4H); 7.04 (s, ArH, 4H); 9.40 (d, J = 4.7 Hz, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.7, 25.0, 25.5, 26.3, 30.8, 31.6, 33.1, 33.8, 33.9, 59.6, 62.9, 74.6, 76.6, 125.3, 125.9, 127.2, 131.8, 142.9, 148.0, 149.3, 155.1, 167.5; UHPLC–

TOFMS (ESI) m/z: calcd for $C_{72}H_{105}N_{12}O_6$: 1233.8275 $[M+H]^+$; found 1233.8293, calcd for $C_{72}H_{104}N_{12}NaO_6$: 1255.8094 $[M+Na]^+$; found 1255.8112.

7f: Yield: 65%, mp: 161-163 °C; IR (KBr, ν, cm^{-1}): 3310, 3057, 2965, 2865, 1682, 1542, 1480, 1427, 1268, 1268, 1190, 1121, 1036, 896, 745; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84-0.89 (t, CH_3, 12H); 0.87 (s, *t*-Bu, 18H); 1.29 (s, *t*-Bu, 18H); 1.64 (s, *t*-Bu, 18H); 2.21 (q, CH_2, 8H); 3.31 (d, *J* = 13.4 Hz, $ArCH_2Ar$, 4H); 4.12 (d, *J* = 13.4 Hz, $ArCH_2Ar$, 4H); 4.72 (s, OCH_2, 4H); 5.61 (d, *J* = 5.4 Hz, NH, 2H); 6.22 (s, OH, 2H); 6.68 (s, ArH, 4H); 7.03 (s, ArH, 4H); 9.26 (d, *J* = 5.2 Hz, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.1, 27.9, 30.8, 30.9, 31.5, 31.6, 33.8, 64.2, 64.7, 74.6, 76.6, 125.2, 125.8, 127.4, 131.7, 142.8, 147.8, 149.4, 149.6, 156.8, 167.5; UHPLC–TOFMS (ESI) m/z: calcd for $C_{68}H_{100}N_{12}NaO_6$: 1203.7781 $[M+Na]^+$; found 1203.7803.

7g: Yield: 76%, mp: 225-227 °C; IR (KBr, ν, cm^{-1}): 3305, 3054, 2981, 2867, 1696, 1546, 1476, 1354, 1267, 1196, 1099, 1038, 897, 819, 744, 560; ^1H NMR (300 MHz, $CDCl_3$, mixture of two diastereomers (60:40)) δ 0.83-0.96 (m, CH_3, 12H, mixture); 0.88 (s, *t*-Bu, 18H, major); 0.89 (s, *t*-Bu, 18H, minor); 1.04-1.09 (m, CH_2, 4H, mixture); 1.29 (s, *t*-Bu, 18H, mixture); 1.34- 1.40 (m, CH_2, 4H, mixture); 1.67-1.83 (m, CH_2, 16H, mixture); 1.91-2.09 (m, CH_2, 6H, mixture); 2.21-2.25 (m, CH_2, 2H, mixture); 3.30-3.35 (m, $ArCH_2Ar$, 4H, mixture); 4.07-4.12 (m, $ArCH_2Ar$, 4H, mixture); 4.56-4.76 (m, OCH_2, 4H, mixture); 5.01 (m, CH, 2H, mixture); 5.46 (d, *J* = 5.0 Hz, NH, 2H, mixture); 6.34 (s, OH, 1H, minor); 6.44 (s, OH, 2H, major); 6.49 (s, OH, 1H, minor); 6.71 (s, ArH, 4H, mixture); 7.04 (s, ArH, 4H, mixture); 9.30 (d, *J* = 5.0 Hz, NH, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6, 7.7, 14.3, 16.8, 16.9, 24.9, 25.4, 26.6, 30.8, 31.5, 31.6, 33.0, 33.3, 33.8, 33.9, 36.3, 59.5, 62.6, 62.7, 74.5, 76.6, 125.3, 125.8, 125.9, 127.2, 127.3, 131.7, 131.8, 142.7, 142.8, 142.9, 147.9, 149.3, 149.4, 155.3, 155.4, 167.6, 167.7; UHPLC–TOFMS (ESI) m/z: calcd for $C_{74}H_{109}N_{12}O_6$: 1261.8588 $[M+H]^+$; found 1261.8604, calcd for $C_{74}H_{108}N_{12}NaO_6$: 1283.8407

$[M+Na]^+$; found 1283.8426. **Crystallographic analysis** colourless crystal (polyhedron), dimensions 0.110 x 0.080 x 0.050 mm3, crystal system triclinic, space group P , Z=2, a=15.0078(8) Å, b=15.5458(8) Å, c=18.4958(10) Å, alpha=99.5345(15) deg, beta=101.1917(16) deg, gamma=113.0196(14) deg, V=3754.1(3) Å3, rho=1.116 g/cm3, T=200(2) K, Thetamax= 22.464 deg, radiation Mo Kalpha, lambda=0.71073 Å, 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 4.95and a completeness of 99.9% to a resolution of 0.93 Å, 48309 reflections measured, 9743 unique (R(int)=0.0512), 6476 observed ($I > 2\sigma$ (I)), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS1 based on the Laue symmetry of the reciprocal space, mu=0.07mm-1, Tmin=0.95, Tmax=1.00, structure refined against F2 with a Full-matrix least-squares algorithm using the SHELXL (Version 2014-3) software 2, 980 parameters refined, hydrogen atoms were treated using appropriate riding models, except those at the hetero atoms, which were refined isotropically (except H54 at N54, that couldn't be considered at all),goodness of fit 1.06 for observed reflections, final residual values R1(F)=0.088, wR(F2)=0.255 for observed reflections, residual electron density -0.37 to 0.78 eÅ-3. CCDC 1025095 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

7h: Yield: 67%, mp: 163-165 °C; IR (KBr, ν, cm^{-1}): 3318, 3050, 2960, 2860, 1682, 1541, 1479, 1427, 1260, 1190, 898, 743; ^1H NMR (300 MHz, $CDCl_3$, mixture of two diastereomers (52:48)) δ 0.73-0.75 (m, CH_3, 6H, mixture); 0.86 (s, *t*-Bu, 18H, major); 0.87 (s, *t*-Bu, 18H, minor); 0.92-0.98 (m, CH_2, 4H, mixture); 1.17-1.28 (m, CH_3, 6H, mixture); 1.28 (s, *t*-Bu, 18H, mixture); 1.64 (s, *t*-Bu, 18H, major); 1.66 (s, *t*-Bu, 18H, minor); 1.91-1.99 (m, CH_2, 2H, mixture); 2.06-2.19 (m,

CH_2, 4H, mixture); 2.29-2.34 (m, CH_2, 2H, mixture); 3.28-3.34 (m, $ArCH_2Ar$, 4H, mixture); 4.09-4.31 (m, $ArCH_2Ar$, 4H, mixture); 4.59-4.84 (m, OCH_2, 4H, mixture); 5.56 (s, NH, 2H, major); 5.57 (s, NH, 2H, minor); 6.03 (s, OH, 1H, minor); 6.24 (s, OH, 2H, major); 6.30 (s, OH, 1H, minor); 6.66 (s, ArH, 4H, minor); 6.72 (s, ArH, 4H, major); 7.01 (s, ArH, 4H, minor); 7.03 (s, ArH, 2H, major); 7.04 (s, ArH, 2H, major); 9.30 (m, NH, 2H, mixture); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.0, 8.2, 14.1, 17.2, 28.6, 29.7, 30.7, 30.8, 31.4, 31.6, 33.8, 37.9, 64.0, 64.5, 74.7, 76.6, 125.1, 125.2, 125.7, 127.0, 127.2, 127.3, 127.5, 131.6, 131.6, 131.7, 147.8, 149.3, 149.5, 156.8, 156.9, 167.6; UHPLC–TOFMS (ESI) m/z: calcd for $C_{70}H_{104}N_{12}NaO_6$: 1231.8094 $[M+Na]^+$; found 1231.8115.

7i: Yield: 70%, mp: 221-223 °C; IR (KBr, ν, cm^{-1}): 3394, 3309, 3056, 2960, 2863, 1689, 1547, 1483, 1426, 1360, 1267, 1194, 1099, 1040, 899, 741; ^1H NMR (300 MHz, $CDCl_3$, mixture of two diastereomers (54:46)) δ 0.86 (s, *t*-Bu, 18H, major); 0.87 (s, *t*-Bu, 18H, minor); 0.87 (s, CH3, 6H, mixture); 1.15-1.4 (m, CH_3, CH_2, 8H, mixture); 1.27 (s, *t*-Bu, 18H, minor); 1.28 (s, *t*-Bu, 18H, major); 1.52-1.67 (m, CH_2, 4H, mixture); 1.71 (br, CH_2, 4H, mixture); 1.78-1.87 (m, CH_2, 10H, mixture); 1.92-2.07 (m, CH_2, 4H, mixture); 3.24-3.51 (m, $ArCH_2Ar$, 4H, mixture); 4.03-4.18 (m, $ArCH_2Ar$, 4H, mixture); 4.32-4.89 (m, CH, OCH_2, 6H, mixture); 5.45 (br, NH, 2H, minor); 5.53 (br, NH, 2H, minor); 6.08 (s, OH, 1H, minor); 6.26 (s, OH, 2H, major); 6.35 (s, OH, 1H, minor); 6.66 (s, ArH, 4H, major); 6.68 (s, ArH, 4H, minor); 6.98 (s, ArH, 4H, major); 7.02 (s, ArH, 4H, major); 9.38 (br, NH, 2H, major); 9.45 (br, NH, 2H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3, 8.4, 21.8, 21.9, 24.8, 25.4, 30.8, 31.6, 32.8, 33.0, 33.8, 59.2, 59.3, 59.8, 59.9, 74.6, 76.6, 125.0, 125.2, 125.6, 125.7, 125.8, 125.9, 127.0, 127.2, 127.4, 127.6, 131.7, 131.9, 142.6, 142.9, 147.7, 147.8, 149.5, 149.5, 149.6, 155.9, 156.2, 168.2, 168.3; UHPLC–

TOFMS (ESI) m/z: calcd for $C_{70}H_{101}N_{12}O_6$: 1205.7962 $[M+H]^+$; found 1205.7976, calcd for $C_{70}H_{100}N_{12}NaO_6$: 1227.7781 $[M+Na]^+$; found 1227.7795.

7j: Yield: 61%, mp: 160-162 °C; IR (KBr, ν, cm^{-1}): 3309, 3055, 2967, 2866, 1687, 1546, 1476, 1357, 1269, 1193, 1121, 1039, 902, 820, 739, 583; ^1H NMR (300 MHz, $CDCl_3$, mixture of two diastereomers (52:48)) δ 0.76-0.85 (m, CH_3, 6H, mixture); 0.85 (s, *t*-Bu, 18H, mixture); 1.28 (m, *t*-Bu, 18H, mixture); 1.27-1.30 (m, CH_3, 3H, mixture); 1.57 (s, *t*-Bu, 18H, major) 1.58 (s, *t*-Bu, 18H, minor); 1.77-1.84 (m, CH_3, 3H, mixture); 1.98-2.20 (m, CH_2, 4H, mixture); 3.20-3.49 (m, $ArCH_2Ar$, 4H, mixture); 3.96-4.24 (m, $ArCH_2Ar$, 4H, mixture); 4.45-4.94 (m, OCH_2, 4H, mixture); 5.07-5.68 (br, NH, 2H, mixture); 5.99 (s, OH, 1H, minor); 6.19 (s, OH, 2H, major); 6.35 (s, OH, 1H, minor); 6.64 (s, ArH, 4H, major); 6.65 (s, ArH, 4H, minor); 6.91-7.06 (m, ArH, 4H, mixture); 9.38 (s, NH, 2H, mixture); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3, 8.4, 24.1, 24.3, 27.7, 29.8, 30.7, 30.8, 31.3, 31.4, 31.6, 32.1, 32.3, 33.8, 61.7, 63.5, 63.6, 74.6, 76.6, 125.0, 125.1, 125.2, 125.4, 125.7, 125.8, 125.9, 126.9, 127.1, 127.4, 127.6, 131.5, 131.6, 131.8, 142.6, 147.7, 149.2, 149.4, 149.5, 149.6, 157.7, 157.9, 168.1, 168.3; UHPLC–TOFMS (ESI) m/z: calcd for $C_{66}H_{96}N_{12}NaO_6$: 1175.7468 $[M+Na]^+$; found 1175.7486.

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