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Tiara[*n*]uril: a glycoluril-based macrocyclic host with cationic walls

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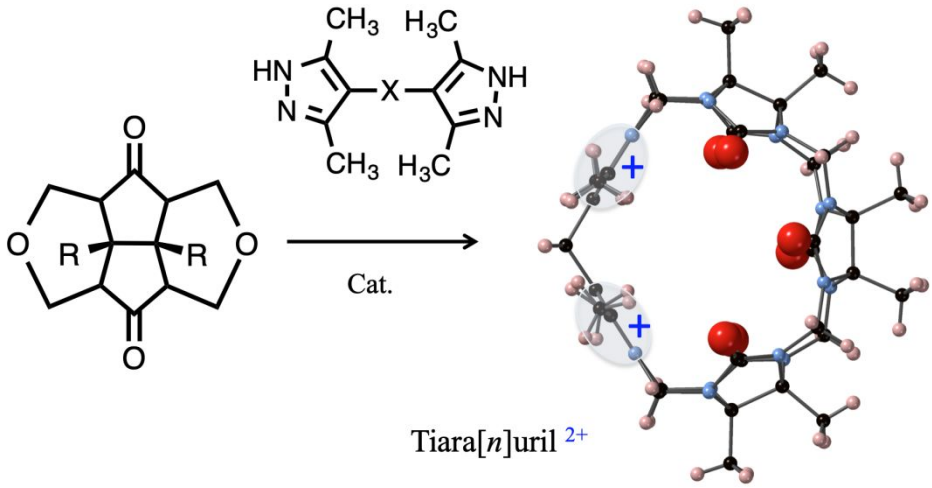


Abstract

The synthesis of new cationic macrocyclic host molecules is described. These macrocycles are comprised of glycoluril oligomers linked to two pyrazolium groups, which form part of a cationic wall facing into their cavities. A number of derivatives have been prepared with an objective to increasing the cavity size and each new product has been fully characterized. Preliminary investigations of pK_as of $Me_{10}Tu[3]^{2+}$ and an interaction of L-glutamine, indicate a potential for binding anionic molecules that also carry H-bond donor groups.

Introduction

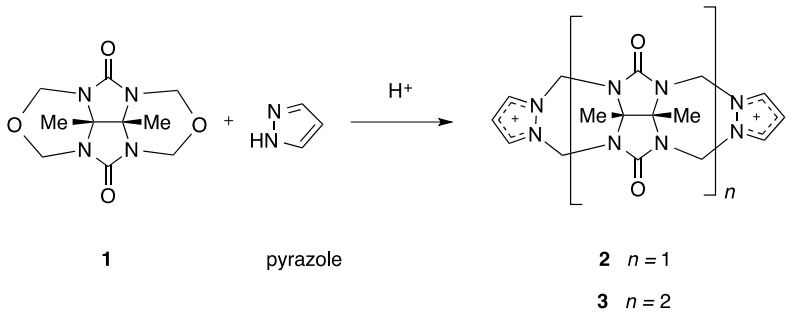
The most common glycoluril based macrocyclic host is cucurbit[*n*]uril (Q[*n*]), which has found utility in numerous chemical applications.[1-18] Various derivatives of Q[*n*] have also been reported such as inverted forms or a catalogue of methylene linked mismatches leading to interesting new hosts but none of these examples carry a positive charge within their cavities.[1,2]

Another macrocyclic host which is essentially an inverted cyclic oligomer of glycolurils known as bambus[*n*]uril (Bu[*n*]) has the distinction of having an electropositive cavity capable of effective anion binding in water.[19] Anion binding in Q[*n*] has mostly been confined to examples where a cation (H^+ or metal ion) resides at

their portals and an anion is bound within the cavity.[20] Here in, we report the synthesis of a new water-soluble cyclic oligomer with a cavity, which has cations built into its walls and hence has the potential to bind anions and/or electronegative groups within its cavity through screening from the solvent (water).

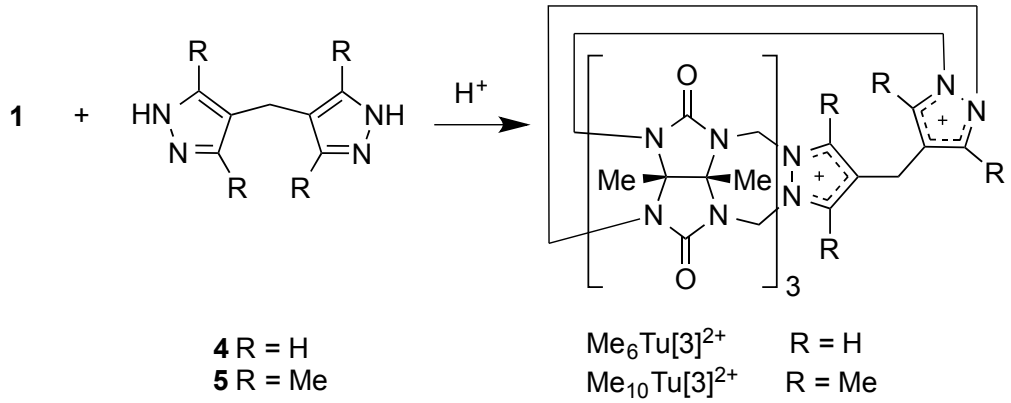
Results and Discussion

While investigating the use of pyrazole as a formaldehyde scavenger under acidic conditions as an approach to removing methylene groups from glycoluril diethers, we discovered the facile condensation reaction between pyrazole and dimethylglycoluril diether **1** that affords the pyrazolium adducts **2** and **3** (Scheme 1). This reaction was very clean consuming all starting diether **1** to give products **2** and **3** in a ratio of ~1.8:1 respectively.



Scheme 1. The condensation reaction between diether **1** and pyrazole.

As we have a particular interest in macrocyclic hosts this result then led us to investigate the potential to synthesize a macrocycle where the two pyrazole rings were linked, eg dipyrazole methane **4**.[21] Under the same acidic conditions as above, the diether **1** condenses to furnish the macrocycle, $Me_6Tu[3]^{2+}$, containing a single dipyrazolium moiety (Scheme 2). Purification on cation exchange resin gave the major product as the dipyrazolium macrocycle, $Me_6Tu[3]Cl_2$ in 60% yield.



Scheme 2. The acid catalyzed condensation reaction between diether **1** and dipyrazole methanes **4** or **5** forms the macrocycles $Me_6Tu[3]^{2+}$ and $Me_{10}Tu[3]^{2+}$ respectively.

This molecule contains a cavity, where one side of the molecular cavity is a concave wall in an arc composed of three glycoluril moieties and the remaining wall of pyrazolium ions provides two adjacent planar facets completing the cavity. While this molecular structure appears to bear some resemblance to an analogue of cucurbituril[22] its chemical properties do not, and as a consequence we have named this molecule tiara[*n*]uril (Tu[*n*]). The molecular shape loosely resembles a tiara, with the carbonyl O of the wall of glycolurils jewelling the front and the dipyrazolium wall forming the band at the back (Figure 1). As will become clear in the remaining discussion the *n* refers to the number of repeating glycolurils.

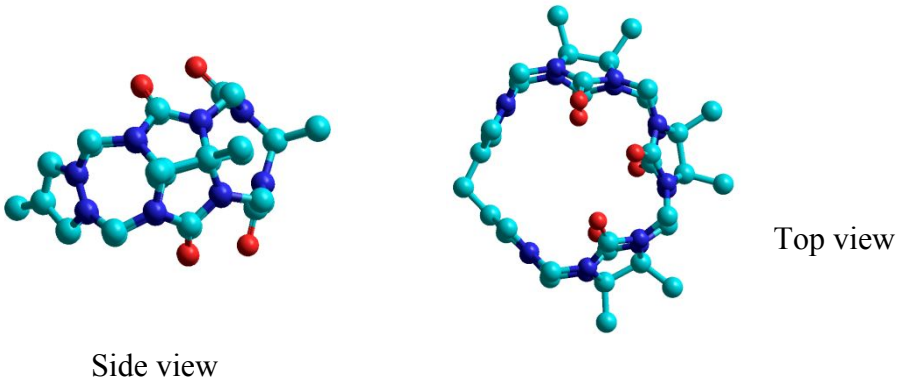


Figure 1. The hydrogen atoms and the counter ions have been omitted to clearly show the skeleton of the molecular model of $Me_6Tu[3]$ emphasizing the resemblance to a tiara.

We soon found that while this molecule was stable to acidic and near neutral conditions it was not stable to basic conditions including weakly basic (aqueous

NaOAc). This was evident by the occurrence of multiple resonances in the ^{1}H NMR spectra of basic solutions aged by 24 h. Base sensitivity was overcome by replacing dipyrazole methane **4** in the reaction process, with the methyl substituted dipyrazole **5**.[21] The efficiency of macrocyclization was unchanged affording $Me_{10}Tu[3]^{2+}$ (Scheme 2, R = Me). Optimal yields of 65% were achieved by a reaction process with a two-portion addition of the diether **1**, which minimized the formation of decamethylcucurbit[5]uril,[23] a by-product in this reaction.

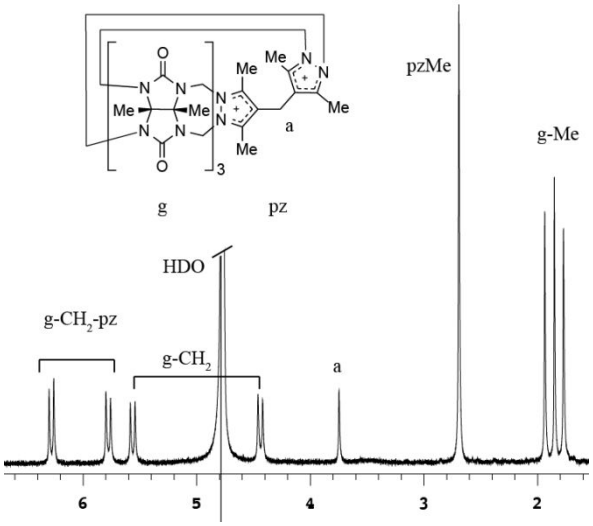
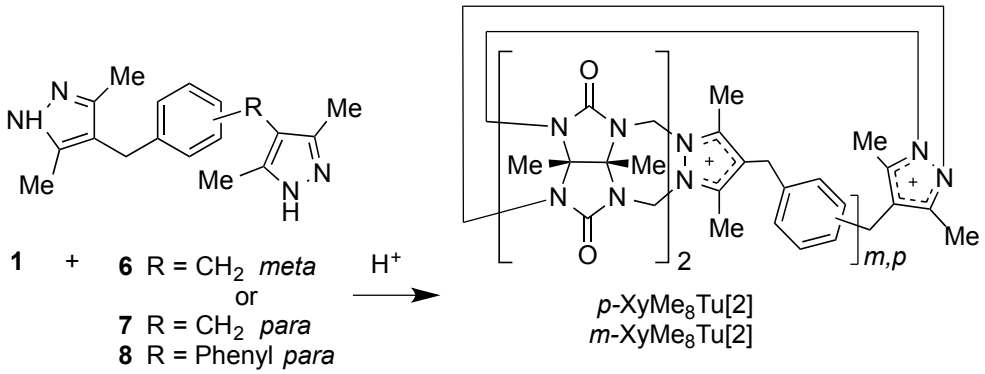


Figure 2. The ^{1}H NMR spectrum of $Me_{10}Tu[3]Cl_2$ in D_2O with assignment of the significant resonances.

The symmetry of $Me_{10}Tu[3]^{2+}$ was evident from the ^{1}H NMR spectrum with 3 distinct sets of proton resonances characteristic for the macrocycle. The magnetically nonequivalent methylenes at the center of the glycoluril oligomer moiety (g-CH_2) and those between the pyrazolium groups and the ends of the glycoluril oligomer moiety (g-CH_2-pz) show clearly define doublets at δ 6.25, 5.78, 5.56, 4.44 ppm, with integral ratios 4:4:4:4 (Figure 2). The two upfield doublets (g-CH_2) show similar chemical shifts to methylene proton resonances for cucurbit[*n*]uril[24] consistent with a macrocycle and two adjacent glycoluril moieties. The remaining protons of $Me_{10}Tu[3]^{2+}$, all appear as singlets at δ 3.75, 2.69, 1.94, 1.85 and 1.77 ppm (respectively CH_2 at **a**; four chemically identical methyl groups on the pyrazolium moieties; three singlet resonances for three pairs of methyl groups on the glycoluril moieties). ESMS also gave a double charged ion at *m/z* 406.3 consistent with this

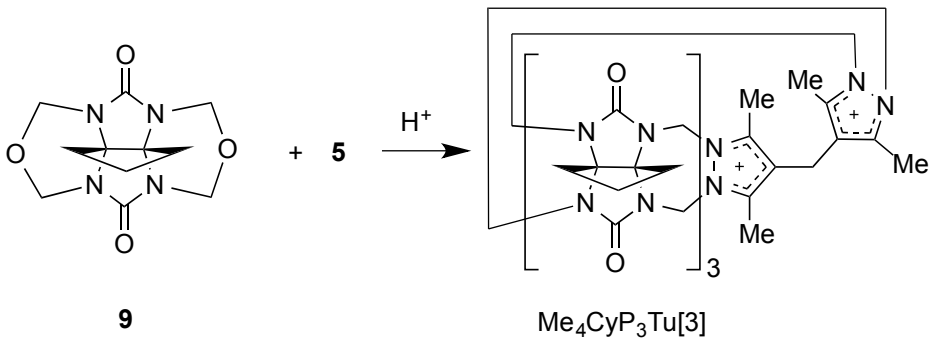
dicationic structure, further substantiated through elemental analysis for $C_{33}H_{40}N_{16}O_6Cl_2.11H_2O$. Additional support for this structure came from a single crystal X-ray diffraction of the salt $Me_{10}Tu[3](PF_6)_2$, crystalized from MeOH/H_2O.[25] These crystals showed the $Me_{10}Tu[3]^{2+}$ molecule in two different orientations at ~90° to each other and one has a molecule of MeOH at its cavity center lying parallel to the equatorial plane and aligned with the longest cavity dimension (~ 5.9 Å van der Waals radii included, Supporting Information Figure S18-21). The other $Me_{10}Tu[3]^{2+}$ only has an H_2O at each of its portals. The MeOH at the cavity center provides an indication of the molecular occupation capacity for $Me_{10}Tu[3]^{2+}$. While an anion may be expected to occupy the cavity, the PF_6^- ion is too large (5.10 Å) to pass through the portal opening (dia. ~ 2.1 Å). Interestingly the MeOH orientation in either occupancy states within the cavity, finds the electronegative O (O0BA) in close proximity to the pyrazolium ions (~ 3 Å) indicating a dipole-ion interaction. The portals of the MeOH occupied cavities are each capped by H_2O molecules, which are H-bonded to the C=Os of the portals. The H atom of MeOH (H0BA) is H-bonded to the O atom of the water cap (O0AA) and not to the portal C=O .

The absence of Tu[*n*] homologues larger than *n* = 3 was intriguing and as a cursory study this aspect to Tu synthesis was explored further with two approaches. The first was to modify the dipyrazole by inserting a spacer moiety between the pyrazoles such as dipyrazoles **6**, **7** and **8** (Scheme 3).[26,27] The second was to use an alternatively substituted glycoluril such as cyclopentanoglycoluril **9** (Scheme 4), which is known to have the propensity to favour higher homologues in the synthesis of cyclopentanocucurbit[*n*]uril.[28]



Scheme 3. The acid catalyzed condensation reaction between diether **1** and dipyrazole xylyl derivatives **6** or **7** to form the macrocycles *p*-$XyMe_8Tu[2]^{2+}$ and *m*-$XyMe_8Tu[2]^{2+}$ respectively. Extended dipyrazolylbiphenyl **8** gave no macrocyclic products.

It was found that the *meta*-xylylpyrazole **6** afforded a new cationic macrocycle *m*-$XyMe_8Tu[2]$ and increasing the distance between pyrazolyl ends with the para derivative **7** (~ 5.4 to 8.2 Å; Figure S13) gave *p*-$XyMe_8Tu[2]$ where both were linked by only two glycoluril moieties (Scheme 3). Despite of the reduction in the number of glycoluril moieties and based upon molecular models the cavity size has not changed. However, the shape of the cavity was slightly modified (Supporting Information Figure S17). It is not clear why both the *m*- and *p*-xylyldipyrazole derivatives **6** and **7** form Tu[2]s. It was anticipated that the significantly greater distance between the pyrazole ends of **7** would facilitate the formation of Tu[$n > 2$]$^{2+}$. In contrast, the dipyrazolylbiphenyl **8**[27] with its pyrazole ends further apart gave only intractable polymeric material, evident as broad resonances by ^{1}H NMR.



9 $Me_4CyP_3Tu[3]$

Scheme 4. The acid catalyzed condensation reaction between diether **9** and dipyrazole **5** to form the macrocycle $Me_4CyP_3TU[3]^{2+}$

The second approach toward higher homologues involved the use of cyclopentanoglycoluril diether **9**[28] and its condensation with dipyrazole **5**. This afforded $Me_4CyP_3Tu[3]$ but again only three glycoluril moieties were introduced (Scheme 4). While the cavity size remains the same, this provided another example of a Tu[3] except with alternative substitution on the glycoluril moieties.

The solubility of $Me_{10}Tu[3]Cl_2$ in pure water is relatively high at 73 g/L and it was of interest to determine if the positively charged pyrazolium walls of the cavity in

combination with the arc of C=O's had any binding potential. It was anticipated that this space could facilitate a function as an anion or an electronegative group receptor,[29] supported by the H-bonding acceptor potential of the arc of C=O's. Hence anions such as HSO_4^- and amino acids were considered. It was anticipated that buffering effects should occur if a binding association was present. $Me_{10}Tu[3](HSO_4)_2$ was readily prepared from $Me_{10}Tu[3]Cl_2$ dissolved in concentrated H_2SO_4 followed by precipitation from dry Et_2O and recrystallization. A titration of aliquots of hydroxide revealed a buffer region consistent with a pK_a ~ 3 for HSO_4^- with no distinction between the two mole equiv. of the anion (pK_a of HSO_4^- alone = 1.99).[30] Modeling[31] indicates that at least one HSO_4^- can be accommodated within the cavity of $Me_{10}Tu[3]^{2+}$, however, it can not be concluded that this pK_a effect is specifically due to cavity encapsulation. The recrystallized chloride salt $Me_{10}Tu[3]Cl_2$ was determined to have a pK_a of 3.4, indicating the first of two host dependent pK_as. In addition, $Me_{10}Tu[3]^{2+}$ irrespective of the anion has a second pK_{a2} of 11.1, which relates to the acidity of the methyl groups on the pyrazolium moieties (pK_a titration curves, Figure S9-10). The acidity of these methyl groups is further supported by deuterium exchange, where the four methyl groups become methyl-d_3 within 7 h (DO^- /D_2O 0.54 M, Figure 3). A ^2H NMR spectrum further substantiates the exchange, with the CD_3 resonances occurring slightly isotope shifted to 2.66 ppm (Supporting Information Figure S8).

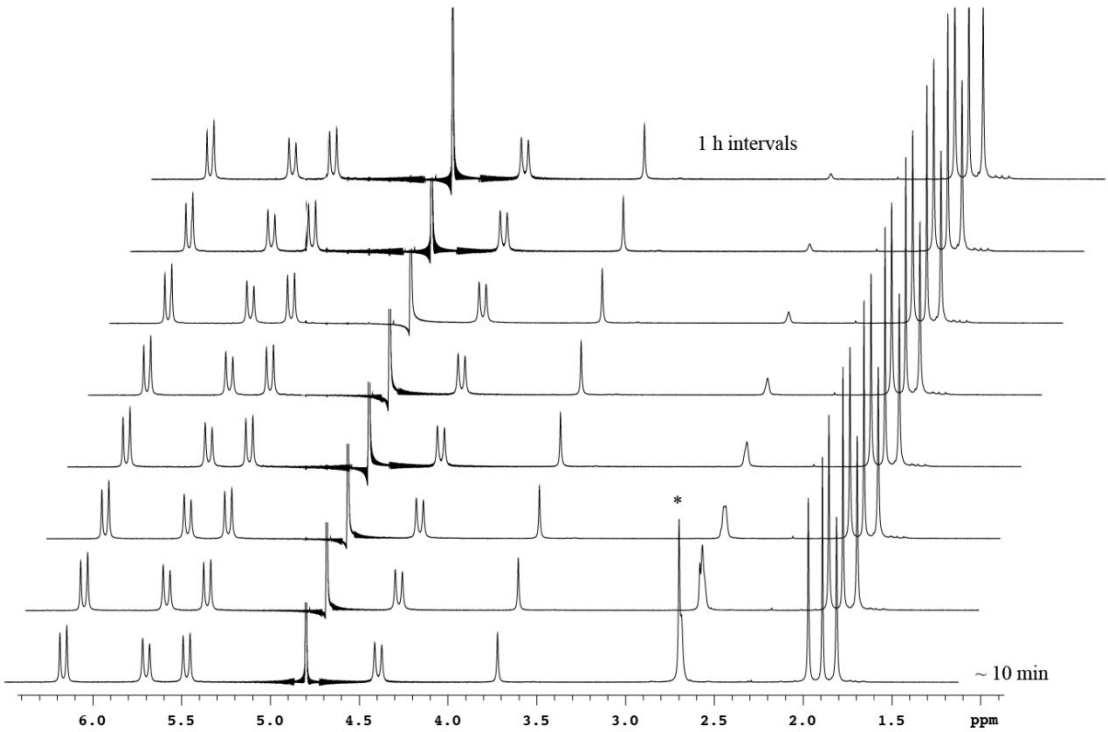


Figure 3. ^{1}H NMR time course of $Me_{10}Tu[3]Cl_2$ (20mM) in D_2O after the addition of NaOD/D_2O 0.54 M. The mark (*) indicates the pyrazole methyl resonance, which decreases as the protons are exchanged with deuterium.

As a preliminary exploration of association of an organic molecule through ion-ion and H-bond interaction, an aqueous buffered solution of $Me_{10}Tu[3]^{2+}$ (pH 6.6) was added to L-glutamine in the same buffer. The sensitivity of circular dichroism (CD) and a potential for induced chirality through association was expected.[32] CD spectra showed a significant maxima red shifted (4 nm) to 210 nm and a positive increase in molar ellipticity ([θ] = 1.2 and 2.9) following the addition of 2 and 2.25 mole equiv. of $Me_{10}Tu[3]^{2+}$ respectively. This was an interesting result though we remain cognizant of the other competing ions of Cl^- from $Me_{10}Tu[3]Cl_2$ and the phosphate in the buffer. A binding constant was then determined for the association between L-glutamine and $Me_{10}Tu[3]^{2+}$ through competitive displacement of the fluorescent anionic dye sodium 6-(p-toluidino)-2-naphthalenesulfonate (TNS). The association constant for L-glutamine@ $Me_{10}Tu[3]^{2+}$ was found to be ~ 2.2 x10^2 M^{-1} assuming a binding ratio of 1:1 (Supporting Information).

^{1}H NMR spectra of $Me_{10}Tu[3]^{2+}$ in buffered D_2O (pD 6.6) with the addition of L-glutamine showed no significant change in proton resonances of either the host or the guest. Given that the binding affinity was in the order of 10^2 M^{-1} and the anticipated that association would be at the portal, a resonance shift was not expected. If cavity encapsulation was to occur it would most likely be the $–CO_2^-$, and H-bonding from the $–NH_3^+$ to the carbonyls. Under this circumstance the resonance of protons exterior and near the portals would result in very small or insignificant chemical shifts consistent with our finding.

Conclusion

We have demonstrated a relatively facile synthesis of a new family of glycoluril-based macrocycles that have incorporated into their walls pyrazolium moieties. Their structures create cationic cavities furnished with potential H-bond acceptors as C=O arcs, both at the top and bottom of their portals. A measurable interaction between $Me_{10}Tu[3]^{2+}$ and HSO_4^- or L-glutamine has been shown through an increase in the pK_a for the first, and changes in the CD spectra for the amino acid. A greater number of examples of H-bond donor anion associations with novel tiarauril macrocycles is required to establish their potential but the indicators mentioned above and the MeOH

bound in the cavity in the solid state, suggest that further exploration would be fruitful.

We have demonstrated that substitution variations can be included either on the glycoluril moiety or between the pyrazolium groups, which conceivably indicates chemical opportunities yet to be realized. The attainment of larger cavities with various substitutions, warrants further investigation and will be the subject of our future work.

Experimental Section

Instrumentation

NMR spectra were recorded at 400 and 100 MHz respectively for the nuclei ^{1}H and ^{13}C. Chemical shifts for each nuclei were respectively reported with the solvent at the internal standard HDO 4.78 ppm and with external dioxane 67.19 ppm.

Synthesis of glycoluril dipyrazolium products 2 and 3

Dimethyl glycoluril diether **1** (1.0 g, 3.94 mmol) and pyrazole (0.55 g, 7.92 mmol), were added together and mixed as a fine powders. To this mixture was added 32% HCl (2.5 mL). The mixture was stirred at 50 °C for 30 min and then the temperature was gradually increased to 80 °C and maintained overnight. The temperature was increased to 95 °C and heating continued for an additional 5 hr. After cooling the acid was removed via rotary evaporation and the residue examined by ^{1}H NMR which showed two main products in a ratio of ~1.8:1. Purification was achieved by cation exchange chromatography (Dowex X50) eluting with 0.5 M HCl and 45% formic acid. The separate fractions were precipitated from water with NH_4PF_6 and the PF_6 salts were recrystallized from water/acetonitrile.

*Dipyrazolium **2*** obtained as colorless needles (998 mg, 63%) Mp dec. 206 °C ^{1}H NMR (DMSO-d_6): δ 1.97 (6H, s), 6.07 (4H, d, J = 15.6 Hz), 6.30 (4H, d, J = 15.6 Hz), 6.82 (2H, s), 8.70 (4H, s). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6): δ 17.3, 55.3, 78.0, 108.3, 140.1, 153.3. MS (ES): *m/z* 178 ($M^{2+}/2$). Anal. Calcd for $C_{16}H_{20}N_8O_2\ (PF_6)_2.CH_3CN$ (687.3680): C, 31.45; H, 3.37; N, 18.34. Found: C, 31.68; H, 3.36; N, 18.03.

*Dipyrazolium **3*** obtained as a colorless crystalline solid (254 mg, 21%) Mp > 250 °C ^{1}H NMR (CH_3CN-d_3/D_2O 6:1) δ 1.75 (3H, s), 1.81 (3H, s), 4.30 (2H, d, J = 16.4 Hz), 5.42 (2H, d, J = 16.4 Hz), 5.76 (4H, d, J = 15.6 Hz), 6.29 (4H, d, J = 15.6 Hz), 6.72

(2H, t, J = 2.8 Hz), 8.34 (4H, d, J = 2.8 Hz). $^{13}C\{^{1}H\}$ NMR (CH_3CN-d_3/D_2O 6:1): δ 17.3, 17.5, 45.3, 56.3, 78.17, 78.19, 108.8, 140.0, 154.6. MS (ES) *m/z* 275.3 (M^{2+}/2). Anal. Calcd for $C_{24}H_{30}N_{12}O_4$ $(PF_6)_2$ (840.5085): C, 34.30; H, 3.60; N, 20.00. Found: C, 34.49; H, 3.49; N, 20.26.

Synthesis of dipyrazole derivatives

1,1'-Di(3,5-dimethylpyrazol-4-yl)methane

3,5-Dimethylpyrazole (7.4 g, 77.1 mmol), tetrabutylammonium chloride (950 mg), 50% NaOH (65 mL) and DCM (130 mL) were combined. The mixture was refluxed for 8 hr with vigorous stirring. After cooling to RT the organic phase was collected, dried over anhydrous K_2CO_3 and the solvent removed *in vacuo* to give a viscous liquid (9.85 g) that was dissolved in 48% HBr solution (50 mL). The solvent was reduced to near dryness using the rotary evaporator to obtain a crystalline residue (sometimes the HBr salt remained as a viscous yellow liquid). Adding acetone (50 mL) to the oil and allowing the solution to stand overnight at RT afforded off white crystals. The crystals were collected by decantation to give bis(3,5-dimethyl-1H-pyrazol-1-yl)methane HBr salt.

The HBr salt was placed in a reaction flask and in an oven which was heated to 200 °C (the flask was open and vented into a fume cupboard). At the desired temperature, the entire crystalline white solid melted then turned into an off white solid. The temperature was maintained at 200 °C for 1hr before cooling to RT. The off-white solid was dissolved in water and solid NaOH was added until pH 10 was obtained. The solid suspension which formed was collected by filtration and dried under vacuum, to give an off white solid (6.03 g, 77% overall yield). No further purification was required for the next step. The physical properties were identical to those reported.[21,34]

The synthesis of *α,α'-bis(3,5-dimethylpyrazol-4-yl)-p-xylene* (**8**), *α,α'-bis(3,5-dimethylpyrazol-4-yl)-m-xylene* (**9**) and 4, 4*'-bis((3,5-dimethylpyrazol-4-yl)methyl)biphenyl* (**7**) were prepared following the typical procedure outlined below for **8**:

4, 4*'-Bis((3,5-dimethylpyrazol-4-yl)methyl)biphenyl* (**7**)

The physical data was consistent with that previously reported.[35] Mp >300 °C

α,α'-Bis(3,5-dimethylpyrazol-4-yl)-p-xylene (**8**)

α,α'-dibromo-*p*-xylene (264 mg,1.00 mmol) dissolved in anhydrous THF (20 mL) was added to NaH (60% oil dispersion) (90 mg, 2.25 mmol) at 0 °C under an inert atmosphere. Acetylacetone (225 mg, 2.25 mmol) in THF (20 mL) was then added dropwise to the mixture and upon completion the temperature was allowed to increase to RT over 30 min. The reaction mixture was then heated at reflux overnight. After cooling to RT the solution was poured into water, neutralized and the organics were extracted using DCM. The DCM extracts were dried over $MgSO_4$ and the solvent removed in vacuo leaving a viscous liquid. The crude tetraone (2.00 g, 7.57 mmol) was dissolved in MeOH (40 mL) and 50% hydrazine solution (50%) (1.0 mL, 15.9 mmol) was added. The mixture was stirred at 50 °C for 24 h before the MeOH was removed using a rotary evaporator. The residue was washed with water to yield the desired dipyrazole **8** as a colorless solid. The physical data was consistent with that previously reported.[26,27,34] Mp >290 °C

α,α'-Di(3,5-dimethylpyrazol-4-yl)-m-xylene (**9**)

The physical data was consistent with that previously reported.[27] Mp >300 °C

General procedure for the synthesis of Tu[n] derivatives

Typical example: A mixture of a dipyrazole (1.0 mmol) and a glycoluril diether (2.00 mmol) were ground together to form a fine powder before 32% HCl (2 mL) was added at RT. After 30 min the temperature was increased to 50 °C and maintained at that temperature for 90 min. The temperature of the reaction mixture was then increased to 90 °C. After 2 hr an additional portion of glycoluril diether (1.00 mml) was added and the mixture was left at 90 ° C overnight. After cooling the acid was removed via rotary evaporation and the residue examined by ^{1}H NMR for maximum product formation. The crude mixture was purified using cation exchange chromatography eluting with 0.5 M HCl and 45% formic acid. The products thus obtained were crystallized as the chloride from water or water/acetonitrile.

$Me_6Tu[3]Cl_2$

This compound was prepared as described in the general procedure from 4,4'-dipyrazolylmethane **4**[21b] (1.31 mmol,) and dimethylglycoluril diether **1** (2.62 mmol)

to give after purification a colorless crystalline product (396 mg, 60% relative to **1**). ^{1}H NMR (D_2O): δ □ 1.80 (6H, s), 1.74 (6H, s), 1.63 (6H, s), 3.74 (2H, s), 4.30 (4H, d, *J* = 16.0 Hz), 5.39 (4H, d, J = 16.0 Hz), 5.81 (4H, d, J = 16.0 Hz), 6.29 (4H, d, *J* = 16.0 Hz), 8.25 (4H, s). ^{13}C{^{1}H} NMR (D_2O): δ 16.3, 16.9, 17.3, 43.8, 55.0, 76.9, 77.2, 78.0, 119.8, 137.9, 155.0. MS (ES): *m/z* 378.2 (M^{2+}/2). HRMS (ES-TOF) calculated for $C_{33}H_{40}N_{16}O_6Cl$ (M^+) 791.3005, found 791.3004.

$Me_{10}Tu[3]Cl_2$

This compound was prepared as described in the general procedure from dipyrazole **5** (1.31 mmol) and diether **1** (2.62 mmol) to give the *product* as a colorless crystalline solid (461 mg, 65%)

^{1}H NMR (D_2O): δ □1.79 (6H, s), 1.88 (6H, s), 1.96 (6H, s), 2.72 (12H, s), 3.77 (2H, s), 4.46 (4H, d, *J* = 16.0 Hz), 5.59 (4H,d , *J* = 16.0 Hz), 5.80 (4H,d, *J* = 16.0 Hz), 6.30 (4H, d, *J* = 16.0 Hz). ^{13}C{^{1}H} NMR (D_2O): δ 10.9, 16.4, 16.9, 17.7, 43.9, 51.5, 76.8, 77.03, 77.9, 146.5, 154.8. UV (H_2O) λ_{max} 235 nm, ε = 14701. MS (ES): *m/z* 406.3 (M^{2+}/2). Anal. Calcd for $C_{37}H_{48}N_{16}O_6Cl_2.9H_2O$ (1045.8683): C, 42.49; H, 6.36; N, 21.43. Found: C, 42.58; H, 6.06; N, 21.60.

$Me_{10}TU[3](HSO_4)_2$

This salt was prepared by dissolving $Me_{10}TU[3]Cl_2$ in a minimum volume of conc H_2SO_4. After a few min allowing the expulsion of HCl the sulfate salt was then precipitated by the addition of dry diethyl ether. Collecting by filtration and washing with additional dry ether and then ethanol to give a dry colorless solid. Recrystallized for water/acetonitrile. By ^{1}H and ^{13}C{^{1}H} NMR the sulfate was identical to the chloride form. Calcd for $C_{37}H_{48}N_{16}O_6.2HSO_4^-.6H_2O$ (1115.1265): C, 39.85; H, 5.42; N, 20.10; S, 5.75. Found: C, 39.82; H, 5.47; N, 19.87; S, 5.72.

$Me_4CyP_3Tu[3]$

This compound was prepared as described in the general procedure from dipyrazole **5** (504 mg, 2.47 mmol) and cyclopentanoglycoluril diether **6** (1.97 g, 7.41 mmol) to give after purification the *product* (454 mg, 20% relative to **5**).

^{1}H NMR (D_2O): δ 1.75 – 1.78 (2H, t), 1.95 - 1.98 (4H, m), 2.27 – 2.30 (4H, t), 2.37 – 2.42 (8H, m), 2.72 (12H, s), 3.78 (4H, s), 4.42 (4H, d, *J* = 16 Hz), 5.56 (4H, d, *J* = 16

Hz), 5.86 (4H, d, J = 16 Hz), 6.34 (4H, d, J = 16 Hz). $^{13}C\{^1H\}$ NMR (D_2O): δ 10.8, 15.8, 22.5, 23.3, 33.8, 35.1, 37.2, 45.9, 52.2, 83.4, 83.8, 85.2, 146.5, 155.0, 155.6. MS (ES): *m/z* 424.2 (100 [M^{2+}/2]). HRMS (ES-TOF) calculated for $C_{40}H_{48}N_{16}O_6$ (M^{2+}) 424.1971, found 424.1970.

m-XyMe$_8$Tu[2]

This compound was prepared as described in the general procedure from the *m*-xylyl dipyrazole **9** (500 mg, 1.70 mmol) and diether **1** (864 mg, 3.40mmol) to give after purification the product (125 mg, 16%).

^1H NMR (D_2O): δ 1.81 (6H, s), 1.93 (6H, s), 2.41 (12H, s), 3.77 (4H, s), 4.50 (2H, d, J = 16 Hz), 5.46 (2H, d, J = 16 Hz), 5.65 (4H, d, J = 16 Hz), 6.20 (4H, d, J = 16 Hz), 6.74 (1H, s), 7.38 (3H, b s). MS (ES): *m/z* 354.4 (100, [M^{2+}/2]. HRMS (ES-TOF) calculated for $C_{36}H_{44}N_{12}O_4$ (M^{2+}) 354.1804, found 354.1808.

p-XyMe$_8$Tu[2]

This compound was prepared as described in the general procedure from the *p*-xylyl dipyrazole **8** (500 mg, 1.70 mmol) and diether **1** (864 mg, 3.40 mmol) to give after purification the product (331 mg, 25%).

^1H NMR (D_2O): δ 1.85 (6H, s), 2.01 (6H, s), 2.61 (12H, s), 3.82 (4H, s), 4.42 (2H, d, J = 16 Hz), 5.50 (2H, d, J = 16 Hz), 5.68 (4H, d, J = 16 Hz), 6.22 (4H, d, J =16 Hz), 7.22 (4H, s). $^{13}C\{^1H\}$ NMR (D_2O): δ 9.7, 16.3, 16.9, 27.3, 44.6, 51.3, 76.4, 77.4, 120.0, 128.3, 138.1, 145.2, 154.3. MS (ES): *m/z* 354.3 (100, [M^{2+}/2]. HRMS (ES-TOF) calculated for $C_{36}H_{44}N_{12}O_4$ (M^{2+}) 354.1804, found 354.1802.

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Supporting Information Statement

^1H and $^{13}C\{^1H\}$ NMR spectra of purified compounds includes **2**, **3**, $Me_6Tu[3]Cl_2$, $Me_{10}Tu[3]Cl_2$, m-$XyMe_8Tu[2]Cl_2$, p-$XyMe_8Tu[2]Cl_2$ and $Me_{10}Tu[3]Cl_2$. A ^2H NMR spectrum of the crude deuterium exchange product d_{12}-$Me_{10}Tu[3]Cl_2$. CD spectra of L-glutamine with $Me_{10}Tu[3]Cl_2$ are provided, and plots for pK_a measurements of $Me_{10}Tu[3]Cl_2$ and $Me_{10}Tu[3](HSO_4)_2$. X-ray crystallographic data and the CIF file.

The Supporting Information is available free of charge on the ACS Publications website.

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