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New strapped calix[4]pyrrole based receptor for anions

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ABSTRACT

Calix[4]pyrrole bearing catechol-derived diether strap linked via alkyl chains has been synthesized and characterized for the first time. The strap with 1,2-diether link is providing a relatively constrained geometry on its side of the calix[4]pyrrole moiety. As a result only one isomer (*cis*-type) of the receptor formed during reaction. The crystal structure reveals two molecules of methanol bound to the host. This calix[4]pyrrole also exhibits enhanced binding towards halide anions compared to simple calix[4]pyrrole apart from showing binding towards dihydrogenphosphate and acetate ions. The association constants are quite similar to that found for orcinol strapped calix[4]pyrrole towards halide anions in general, but having a higher preference for chloride than bromide ion in particular. Further it shows very strong preference towards fluoride ion.

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1. Introduction

Calix[4]pyrrole **1** is a tetrapyrrolic macrocycle known for more than hundred years [1]. However, recently it was observed that it can also act as a host for both anions and neutral molecules [2]. These attributes are of great attraction to researchers in the last two decades. In order to modulate the anion binding behavior of the macrocycle, a large number of derivatives have been reported by varying functional groups at the *meso*-carbons and β -pyrrole position(s) and also by inversion of core (using N-confused pyrrole approach) [3]. Enhanced binding could be achieved through single side strapping of calix[4]pyrrole moiety by Lee's group [4] and further detailed studies were carried out in association with Sessler's group [5]. These calix[4]pyrroles were strapped using flexible straps via 1,3-linkage to benzene derivatives and 2,5-heteroarenes having diester, diether and diamide based alkyl chains [5,6]. Furthermore porphyrins, binaphthol and coumarin were also used as probes to study their binding abilities [7]. These strapped derivatives possess large binding domains which help in modulating their properties [4-7]. These receptors apart from displaying enhanced binding toward halides; show some selectivity toward fluoride and chloride ions.



Recently, Gale and co-workers reported a 1,2,3-triazole strapped calix[4]pyrrole along this line via click chemistry, which acts as a good membrane transporter towards chloride ion [8a]. Very recently Gale's group reported another sets of strapped calix[4]pyrroles where, two 1,2,3-triazoles were bridged through alkyl chains of different length to tune their transport properties [8b]. Among the strapped calix[4]pyrroles, only the furan strapped calixpyrrole found to bind two methanol molecules [5c] whereas in case of 3 one methanol bind to two adjacent NHs of the calix[4]pyrrole moiety in 1,2-alternate fashion and the other one H-bonded to another macrocycle in the solid state. In case of the bis-triazole derivative, an additional methanol molecule is bound to one of the already H-bonded methanol [8b]. Here, we wish to report the synthesis of a new calix[4]pyrrole with flexible catechol-derived diether strap on one side, its structure and anion binding properties. This mode of strapping is expected to possess a

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relatively constrained binding domain and hence may display some interesting host guest chemistry.

2. Experimental

2.1. Materials

All analytical reagents were purchased from commercial sources and used as received and all solvents were dried and purified as described by Armarego and Chai [9].

2.2. Methods

NMR spectra were recorded on a BRUKER-AVANCE 400 MHz FT NMR spectrometer at room temperature. Mass spectral determinations were carried out using Shimadzu-LCMS-2010 mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300. Crystal data was collected on Oxford Gemini A Ultra diffractometer with dual source. The binding constants were measured by isothermal titration calorimetry studies using the instrument VP-ITC from MicroCal, LLC, MA, USA.

2.3. Synthesis

2.3.1. Synthesis of 7-[2-(6-oxo-heptyloxy)phenoxy]-2-heptanone (5)

A mixture of catechol (330 mg, 3 mmol) and K₂CO₃ (4.14 g, 30 mmol) in acetone (80 mL) was stirred well for about 1 h, and then 7-bromo-2-heptanone [10] (2.89 g, 15 mmol) was added. The mixture was refluxed for 3 days and then filtered and solvent was removed. The crude product was purified by column chromatography over silica gel with increasing ratio of ethyl acetate in hexane. The excess bromoketone is removed first (15% ethyl acetate in hexane) and the desired product was collected as the next major band and vacuum dried to give compound **5** as a viscous liquid which solidifies when kept in refrigerator (700 mg; 70%). IR (neat): v (cm⁻¹) 2944–2865, 1715; ¹H NMR (CDCl₃): δ in ppm 6.88 (s, 4H), 3.98 (t, 4H, *J* = 12 Hz), 2.46 (t, 4H, *J* = 16 Hz), 2.14 (s, 6H), 1.82 (m, 4H), 1.65 (m, 4H), 1.50 (m, 4H); ¹³C NMR (CDCl₃): δ in ppm 209.00, 149.23, 121.28, 114.36, 69.06, 43.7, 29.95, 29.24, 25.75, 25.64. LC–MS *m*/*z*, M+H: 335.4 (Calc. for C₂₀H₃₁O₄+H = 335.2).

2.3.2. Synthesis of 1,2-bis[6,6-di (pyrrol-2-yl)heptyloxy]benzene (6)

To a mixture of **5** (650 mg; 1.94 mmol) and pyrrole (5.35 mL; 77.72 mmol), trifluoroacetic acid (150 μ L; 1.94 mmol) was added at about 60 °C. The mixture was stirred for about 1.5 h and the



Scheme 1. Reagents and reaction conditions: (i) 7-bromo-2-heptanone, K₂CO₃, dry acetone, reflux; (ii) pyrrole, TFA, 60 °C; and (iii) acetone, BF₃-etherate, room temperature.



Fig. 1. Ortep diagram of **4**·(MeOH)₂ with the displacement ellipsoid drawn at 35% probability level, showing 1,2-alternate conformation of pyrrole units and the two bound methanol molecules (left) and orientation of the strap with respect to the calix[4]pyrrole moiety (right). Hydrogen atoms, disordered atoms and methanol molecules (for right only) have been omitted for clarity.



Fig. 2. Hydrogen bonding pattern of compound 4 (MeOH)₂. Here disordered atoms were removed for clarity.

reaction was quenched with triethylamine (1 mL). Excess reagents were removed under reduced pressure to get the crude product, which was purified by column chromatography over silica gel (10% ethyl acetate in hexane) to obtain the pure product **6** (1 g, 65%). IR (neat): v (cm⁻¹) 3341, 2926–2870; ¹H NMR (CDCl₃): δ in ppm 7.59 (s, 4H), 6.98 (s, 4H), 6.56 (s, 3H), 6.17–6.13 (m, 9H), 4.03 (t, 4H), 2.04 (t, 4H), 1.8 (m, 4H), 1.6 (s, 6H), 1.4 (m, 4H), 1.35 (m, 4H); ¹³C NMR (CDCl₃): δ in ppm 149.20, 138.37, 121.28, 117.26, 114.34, 107.58, 104.78, 69.27, 41.06, 38.99, 29.26, 26.58, 26.42, 24.17; LC–MS m/z (M+H) : 567.6 (Calc. for C₃₆H₄₆N₄O₂+H = 567.4).

2.3.3. Synthesis of strapped calix[4]pyrrole (4)

To a solution of **6** (750 mg; 1.32 mmol) and acetone (150 mL), BF₃·OEt₂ (1 µL; 0.38 mmol) was added. The solution was stirred at room temperature for 10 min, after which product formation was confirmed by TLC. The reaction was quenched by triethylamine (1 mL) and solvent was removed. The crude mass was subjected to column chromatography over silica gel (10% ethyl acetate in hexane) to obtain the product as a colored species, which upon subsequent washing with methanol yielded the pure macrocycle **4** as an off white powder (27 mg, 8%). ¹H NMR (CDCl₃): δ in ppm 7.42 (s, 4H), 6.89 (s, 4H), 5.94 (m, 8H), 3.97 (t, 4H, *J* = 16 Hz), 1.95 (t, 4H, *J* = 16 Hz), 1.82 (s, 4H), 1.68 (s, 6H), 1.52–1.50 (m, 16H), 1.24 (m, 4H); ¹³C NMR (CDCl₃): δ in ppm 149.42, 137.73, 136.9, 121.31, 114.37, 104.31, 103.69, 69.23, 41.48, 39.47, 35.63, 30.24, 29.50, 28.53, 26.68, 25.37; LC–MS *m/z* (M–H): 645.75 (Calc. for C₄₂H₅₄N₄O₂–H = 645.42).

Table 1

Association constant K_a , and thermodynamic parameters for the binding of anions with **4** as measured by ITC (isothermal titration calorimetry) at 303 K in acetonitrile using the corresponding tetrabutlyammonium salts (TBA) and fluoride as the trihydrate.

TBA-salt	K _a	ΔG (kcal mol ⁻¹)	ΔH (kcal mol ⁻¹)	T∆S (kcal mol ⁻¹)
Chloride [11a]	1.37×10^{6}	-8.51	-7.43	1.08
Bromide [11b]	$3.1 imes 10^4$	-6.24	-7.1	-0.86
Fluoride ^a	1.17×10^{6}	-8.42	-6.27	2.15
Chloride	2.12×10^{6}	-8.78	-11.2	-2.42
Bromide	1.95×10^4	-5.97	-12.39	-6.42
Acetate	1.28×10^5	-7.09	-10.45	-3.36
Dihydrogenphosphate	1.07×10^5	-6.97	-14.48	-7.51

^a Measured in 0.5% water in acetonitrile.

3. Results and discussion

The desired strapped calix[4]pyrrole **4** was synthesized in three steps from catechol (Scheme 1) following Lee's method [5a]. However, we have to modify the reaction conditions in order to get the optimal yields. For example, reaction of catechol with 7-bromo-2-heptanone to obtain **5** was very sluggish and needed very long time to undergo completion. Increasing the scale of reaction needed further increase of time and the completion of reaction



Fig. 3. ITC of 4 with TBAF in 0.5% water in acetonitrile.



Fig. 4. ¹H NMR competition experiment in acetonitrile-d₃: (1) free host 4; (2) 4 with 1 equiv. of TBACl; and (3) 4 with 1 equiv. each of TBACl and TBAF-3H₂O.

was always monitored by thin layer chromatography. Use of DMF as solvent and higher temperature led to decrease in yield along with decomposition of the excess bromoketone used (which could be reused otherwise). Conversion of 5 to 6 was smooth. However, the condensation of **6** with acetone yielded the desired macrocycle **4** (8%) exclusively as the *cis*-isomer only in 10 min. Longer reaction time not only reduced the yield further but also, led to coloration of the product which was not possible to remove by methanol washing; however there was no indication of the formation of the transisomer. All the compounds were characterized by ¹H NMR, ¹³C NMR spectroscopy and mass analysis. Single crystal obtained by slow evaporation of 4 from dichloromethane and methanol mixture, when subjected to X-ray diffraction analysis, not only established the structural integrity but also revealed few interesting attributes of the macrocycle (Fig. 1). The macrocycle 4 found to bind two methanol molecules, where one was bound to the NHs of calixpyrrole moiety by hydrogen bonding and the other one Hbonded to the remaining two pyrrolic NHs directed towards the strap and oxygens of catechol moiety (Fig. 2). This type of host guest behavior for strapped calix[4]pyrroles was so far not reported for the benzene-based derivatives [4–7] and only recently observed in case of furan strapped derivative [5c]. Compound 4 adopts a 1,2-alternate conformation for pyrrole units with the catechol based strap slightly tilted towards one-half of the calix[4]pyrrole unit.

The anion binding properties of 4 were studied by ¹H NMR titration technique using acetonitrile- d_3 as the solvent. The anions were used as their corresponding tetrabutylammonium (TBA) salts. Preliminary study with halides shows that **4** converted to its bound form with \sim 1.2 equiv. of fluoride, chloride or bromide anions and the complexation follow slow exchange kinetics on NMR time scale, and hence the binding constants could not be evaluated (Supplementary data). However, it can be concluded that the complexes follow 1:1 stoichiometry. Further, iodide does not show any binding to the host. We carried out isothermal titration calorimetry (ITC) in acetonitrile (HPCL grade obtained from Aldrich used as such) solvent at 303 K to evaluate the association constants. In all cases we observed exothermic host guest complexation that is compensated to some extent by unfavorable entropy contribution (Table 1). Except for the fluoride ion, in which case binding measurement was carried out using 0.5% water in acetonitrile as the solvent which give reproducible data for evaluation of association constant (Fig. 3). This can be explained by taking note that fluoride remains in hydrated form in aqueous acetonitrile and hence its binding to the host led to the increase in the entropy contribution. Compared to 1 large enhancement of association constants were observed for all anions in case of 4 [11]. However when compared with 2 (although it was measured using rigorously dried acetonitrile), we found **4** has a relatively higher affinity towards chloride and lesser towards bromide ion [5a]. Assuming that slight change in condition can led to serious error in evaluation of binding affinity, still we could come to the above conclusion as it is already known presence of water can only decrease the K_{a} . Though the $K_{\rm a}$ for fluoride appears to be lesser than chloride (Table 1), this may be attributed to the presence of water. We attempted to determine the $K_{\rm a}$ value for fluoride following competitive experiment using ¹H NMR spectroscopy [4], but when equimolar ratio of fluoride anion was added to already complexed chloride solution (1:1 M ratio in CD₃CN), we observed complete ejection of chloride ions with the onset of signals corresponding to fluoride complex exclusively (Fig. 4). Therefore, exact K_a in pure acetonitrile could not be evaluated. However we can still assume that the K_a for fluoride must be higher than the diester strapped calix[4]pyrrole (highest so far reported to our knowledge) in which case a 6.3:1 ratio of fluoride to chloride complexation observed, although it was measured in DMSO- d_6 [3]. Moreover, we can further conclude that the role played by the aromatic CH in **2** and other related systems towards anion binding (although large shift on CH signal upon encapsulation of anion was observed) may not be significant [5-7]. Moreover, the relatively constrained binding domain due to the catechol derived strap could stabilize the fluoride and chloride more effectively than the bromide. Further we observe moderately strong association constant toward acetate and dihydrogenphosphate (Table 1), which was not reported for other related strapped calix[4]pyrroles. This may be attributed to the additional hydrogen bonding of oxygen atoms of catechol (already we observed in methanol adduct) to the periphery of the anions which might be at appropriate structural environment. Only very recently Gale's group reported a bistriazole strapped calix[4]pyrrole which also shows binding towards a larger set of anions through a highly flexible strap [8b].

4. Conclusions

In this work we have prepared a new catechol derived strapped calix[4]pyrrole where the binding domain is more constrained compared to the earlier reported ones by slightly optimizing Lee's method. Due to the unique structural environment, this receptor hosts two methanol molecules in solid state which was not observed before for the benzene derived strapped derivatives. This observation also led us to believe that suitable design of strap can also enhance the binding towards neutral guest molecules apart from anions. Presently we are exploring this aspect in details. Compound **4** displays relatively higher affinity towards chloride than bromide ion compared to **2** along with very strong preference for fluoride ion. Further we could calculate reliable K_a for **4** towards fluoride using 0.5% water in acetonitrile using ITC. Compound **4**

also displays reasonably high association constant towards acetate and dihydrogenphosphate ion.

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Appendix A. Supplementary material

NMR spectral data and ITC data are available as Supplementary Material at www.elsevier.com. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2011.02.004.

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