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Tetrahedron Letters 49 (2008) 2772–2775
Tetrahedron Letters

A chloride selective sensor based on a calix[4]arene possessing a urea moiety

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Received 31 December 2007; revised 22 February 2008; accepted 25 February 2008
Available online 29 February 2008

Abstract

New calix[4]arene derivative **1** of 1,3-*alternate* conformation with a ureido moiety has been synthesized in high yield and examined for its anion recognition abilities towards anions such as fluoride, chloride, bromide, iodide, nitrate and acetate by ^{1}H NMR and UV–vis spectroscopy. The results show that receptor has strong binding affinity for chloride ions. A chloride ion selective electrode (ISE) was also formed which showed excellent selectivity over all the other anions tested. The limit of detection is 2.51×10^{-5} mol dm^{-3}.

The selective recognition of anions play an important role in biology, medicine, catalysis and in the environment.[1,2] Among the biologically relevant anions, chloride sensing is important in clinical diagnosis,[3,4] environmental monitoring[5] and industrial applications.[6,7] Further, chloride ions play an important role in maintaining potentials across cell membranes and misregulation of chloride transport through cell membranes by chloride channels is the cause of cystic fibrosis.[8] The transport of chloride as HCl by prodigiosins through biological lipid bilayer membranes has been shown to uncouple lysosomal vacuolar type ATPases.[9] Thus, keeping in view these applications across diverse areas, the development of synthetic chloride receptors is an emerging topic in supramolecular chemistry.

We have recently reported calix[4]arene and thiacalix[4]arene based receptors which were selective for soft metal ions[10] and anions.[11] In continuation of our research on the design and synthesis of calix[4]arene and thiacalix[4]arene based receptors, we have now designed and synthesized a chloride ion selective sensor **1** based on calix[4]arene of 1,3-*alternate* conformation which has a urea moiety for the interaction with anions. The presence of electron-withdrawing groups would be expected to increase the acidity of the urea protons and hence enhance their anion binding ability through hydrogen bonding. The results show that compound **1** has strong binding affinity for chloride ions as proved by UV and NMR studies. A chloride ion selective electrode has also been formed which showed excellent selectivity over all the other anions tested. There are some examples of receptors for chloride ions, based on calixarenes[12] and different other scaffolds,[13] however, to the best of our knowledge the chloride ion selective electrode based on a calix[4]arene bearing a urea moiety has not been reported. There are examples of calixarene based ionophores as ISE's for sensing of anions such as carbonate,[14] hydrogensulfite[15] and nitrate.[16] While this work was in progress, Diamond co-workers reported[17] a chloride selective optical sensor based on calix[4]arene having urea moieties.

Condensation of calix-1,3-diamine **2**[11a] in the 1,3-*alternate* conformation with 2.0 mol equiv of *p*-nitrophenylisocyanate in refluxing dichloromethane gave urea **1** in 87% yield (Scheme 1).[18] The product separated as a pure solid after adding hexane to the dichloromethane solution, and gave a satisfactory elemental analysis after single crystallization.

The structure of **1** was confirmed from its spectroscopic and analytical data. The IR spectrum of **1** showed a C=O

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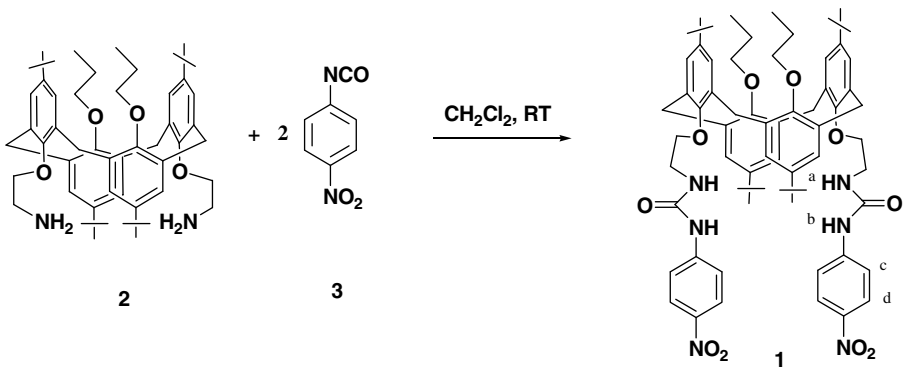
doi:10.1016/j.tetlet.2008.02.133



Scheme 1. Synthesis of urea derivative **1**.

stretching band at 1636 cm^{-1}. The FAB mass spectra showed a parent ion peak at 1147 (M^++1) corresponding to a 1:2 condensation product. The ^1H NMR spectrum of **1** showed two singlets (18H each) at δ 1.16 and 1.27 ppm corresponding to the *tert*-butyl protons, three triplets (4H each) at δ 3.18, 3.30 and 3.45 ppm corresponding to the OCH_2 protons, and two singlets (4H each) at δ 7.02 and 7.03 ppm corresponding to the aromatic protons, and one broad signal and a singlet (2H each) at δ 5.76 and 7.65 ppm for the amido protons. The bridging methylene protons of **1** appeared as a singlet at δ 3.84 ppm. The appearance of a singlet for the bridging methylene protons in the ^1H NMR data suggests a 1,3-*alternate* conformation for **1**. Receptor **1** contains four urea NH groups as H-bond donors for anions and two *p*-nitrophenyl groups for monitoring the anion-binding event.

To evaluate the binding ability of calix[4]arene receptor **1** towards different anions, we carried out NMR and UV–vis experiments and prepared solid state ion-selective electrodes. The anion recognition via hydrogen bonding interactions and deprotonation can be easily monitored by anion-complexation induced changes in NMR and UV–vis spectra. The stoichiometries of the complexes formed between the anions and the host were determined from Job's plot.

Addition of different anions as their tetrabutylammonium salts to a solution of receptor **1** in $CDCl_3$ resulted in complexation induced shifts of various protons of **1** (Table 1). The urea protons NH_a and NH_b of **1** experienced a large downfield shift of 0.96 ppm and 1.70 ppm, respectively, in the presence of 1.0 mol equiv of tetrabutylammonium chloride in $CDCl_3$. The H_c protons of the nitrophenyl moiety were also shifted downfield by +0.16 ppm. This can be accounted for by the formation of hydrogen bonds between the partially charged urea oxygen and the H_c protons of the *p*-nitrophenyl moiety. The other aromatic proton, H_d was shifted upfield by 0.10 ppm. This upfield shift results from an increase in the electron density on the phenyl ring due to the enhanced anionic character of the urea nitrogen. In the presence of other anions such as bromide, iodide and nitrate, the NH_a and NH_b protons undergo relatively smaller downfield shifts of 0.79, 0.65 and 0.83 ppm and 1.36, 0.84 and 1.24 ppm, respectively (Table 1), while the H_c protons undergo downfield shift of 0.12, 0.07 and 0.12 ppm, respectively. The H_d protons undergo upfield shift of −0.09, −0.08 in the case of bromide and iodide, and downfield shift of 0.06 ppm in the case of nitrate. This indicates that the complex between **1** and anions like chloride, bromide, iodide and nitrate is formed by multiple hydrogen bonding. Further, the greater downfield proton shifts in the case of chloride ions indicate strong hydrogen bonding between **1** and chloride ions. The stoichiometries of the complexes formed between **1** and different anions were determined by Job's method of continuous variation and found to be 2:1 (receptor:anion) for chloride and 1:1 (receptor:anion) for bromide, iodide and nitrate ions, respectively.

Table 1
^1H NMR induced shifts ($\Delta\delta$ in ppm) in **1** upon complexation with various tetrabutylammonium anions (F^-, Cl^-, Br^-, I^-, NO_3^- and OAc^-)

Entry	Anion	Change in chemical shift of protons of **1** on adding anions			
		H_c	H_d	NH_a	NH_b
1	F^-	0.14	−0.11	[a]	[a]
2	Cl^-	0.16	−0.10	0.96	1.70
3	Br^-	0.12	−0.09	0.79	1.36
4	I^-	0.07	−0.08	0.65	0.84
5	NO_3^-	0.12	0.06	0.83	1.24
6	OAc^-	0.14	−0.11	[a]	[a]

[a] Signals disappeared.

On the other hand, addition of tetrabutylammonium fluoride/tetrabutylammonium acetate to a solution of compound **1** in $CDCl_3$ resulted in the disappearance of the urea proton signals, NH_a and NH_b. This clearly indicates that fluoride/acetate interactions with compound **1** occur and that the kinetics of fluoride/acetate exchange is on NMR time scale. The H_c protons of the *p*-nitrophenyl moiety shifted downfield by 0.14 ppm while the H_d protons shift upfield by 0.11 ppm, respectively.

The urea derivative **1** (5×10^{-5} M) shows an absorption band at 329 nm in the UV spectrum in the absence of anions. Upon the addition of increasing amounts of chloride ions to the solution of receptor **1**, the absorption peak at 329 nm gradually moves to a longer wavelength finally reaching a maximum value at 342 nm (Fig. 1). Fitting the

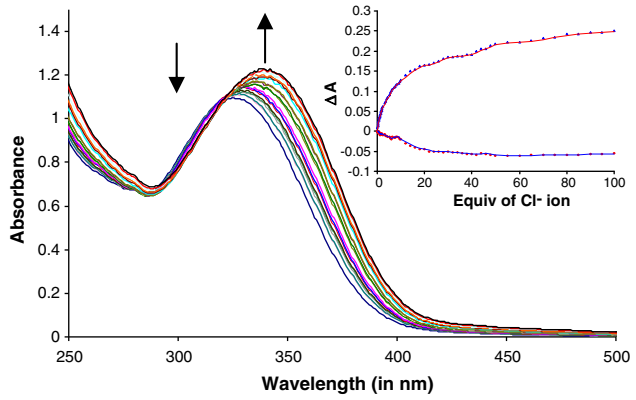


Fig. 1. UV–vis absorption spectra of compound **1** (5×10^{-5} M) upon the addition of tetrabutylammonium chloride (0–100 equiv) in THF. Inset showing the binding isotherm at selected wavelengths, 300 nm (◇) and 342 nm (Δ).

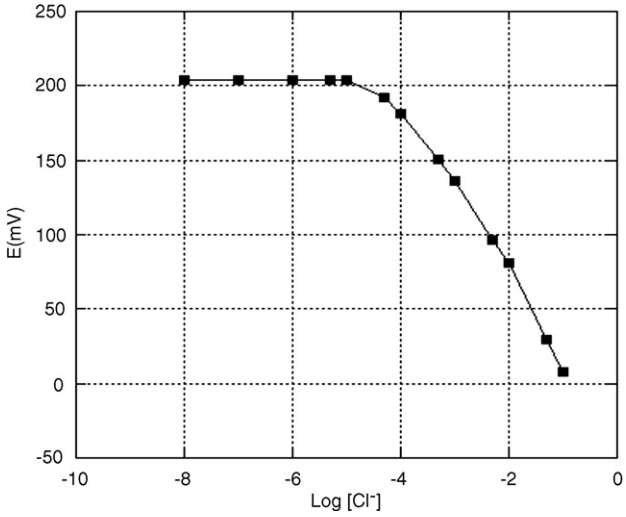


Fig. 2. Potential response curve for the **1**: chloride ion-selective electrode.

changes in the UV–vis spectra of compound **1** using the nonlinear regression analysis program SPECFIT[19] gave a good fit and demonstrated that a 2:1 stoichiometry (host: guest) was the most stable species in the solution with a binding constant of $\log \beta_{21} = 6.54(\pm 0.16)$.

On the other hand, in the presence of anions such as bromide, iodide and nitrate, the absorption band changed from 329 nm to 337, 333 and 331 nm, respectively. Fitting the changes in the UV–vis spectra of compound **1** with bromide, iodide and nitrate, using SPECFIT[19] gave good fits with binding constants of $\log \beta_{11} = 3.05(\pm 0.02)$, $3.31(\pm 0.16)$ and $3.12(\pm 0.05)$ for bromide, iodide and nitrate, respectively.

Thus, from the NMR and UV–vis studies it may be concluded that chloride ions selectively complex with **1** in comparison to other anions. Based on the results of these binding studies we envisaged that it should be possible to construct chloride ion selective PVC membranes based on **1**. Thus, a sensor membrane for **1** was prepared and assembled as previously reported from our laboratory for silver ions.[10a] The composition of this membrane is listed in Table 2. The PVC membrane of the anion receptor generated a stable potential when placed in contact with sodium chloride solution. The emf response of the membrane in the presence of a wide range of chloride ion solutions is shown in Figure 2. The electrodes demonstrate a linear response for Cl^- in the concentration range from 1.0×10^{-5} to 1.0×10^{-1} mol dm^{-3}. The limit of detection was 2.51×10^{-5} mol dm^{-3}.

The slope of the plot was approximately −55.69 mV/dec of concentration which indicates the near Nerstian nature of the electrode. The response time of the membrane was measured at different concentrations and was found to be less than 20 s and no change was observed up to 5 min. Potentials were measured periodically at a fixed concentration and the standard deviation of ten identical measurements was ±2 mV. The dependence of the membrane potentials on pH was studied at 1.0×10^{-2} mol dm^{-3} chloride ion concentration. The potential remained constant from pH 3.3 to 6.9 which may be taken as the operational pH range of the sensor. The most important feature of an ion selective electrode is its response to its primary ion in the presence of various other anions. This is measured in terms of the potentiometric selectivity coefficient ($K^{pot}_{A,B}$) which was evaluated by the fixed interference method at 1.0×10^{-2} mol dm^{-3} concentrations of various interfering ions. Table 3 shows the potentiometric selectivity coefficient data of the urea derivatized *p-tert*-butylcalix[4]arene based PVC membrane electrode for interfering anions relative to chloride ions. $K^{pot}_{A,B}$ was fairly low for all the anions tested which indicates that there is no interference present with the determinant ion (Cl^-).

The electrode assembly was tested as an indicator electrode to determine the end-point in the potentiometric titration of Ag^+ with a standard solution of sodium chloride. A 20 ml solution of 1.0×10^{-2} mol dm^{-3} silver nitrate was titrated against 1.0×10^{-2} mol dm^{-3} sodium chloride solution. The sharp rise in the potential indicates the end-point (Fig. 3).

In conclusion, calix[4]arene based uriedo receptor **1** in 1,3-*alternate* conformation was synthesized in high yield. Complexation studies by ^{1}H NMR and UV spectroscopy were carried out towards different anions and it was found

Table 2
Composition and response characteristics of the chloride ion selective sensor

PVC (mg)	Plasticiser (mg)	*n*-Butyl-3-methylimidazolium hexafluorophosphate (mg)	Ionophore (mg)	Internal solution (M)	Linear range (M)	Detection limit (M)	Slope (mV/dec)
40.1	29.2	25.5	8.2	1.0×10^{-2}	1.0×10^{-1}–5.0×10^{-5}	2.51×10^{-5}	−55.69

Table 3
Selectivity coefficient values of chloride ion selective electrode **1**

Secondary ions	NO_2^-	Tartrate	Citrate	CO_3^{2-}	HCO_3^-	OAc^-	NO_3^-	NCS^-	SO_4^{2-}	OH^-	F^-	N_3^-	ClO_4^-	Br^-	I^-
$\log K^{pot}_{A,B}$	−3.00	−3.75	−4.31	−3.65	−2.70	−3.00	−2.60	−1.40	−4.00	−2.10	−2.65	−2.50	−2.70	−1.30	−1.80

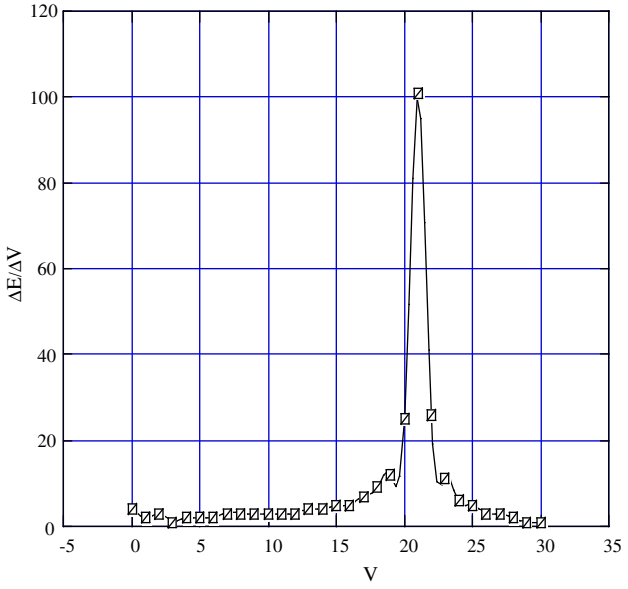


Fig. 3. Derivative curve for the titration of 1.0×10^{-2} M Ag^+ solution with 1.0×10^{-2} M NaCl solution.

that the receptor shows selectivity for chloride ions. The receptor can be used to form a chloride selective PVC membrane. The chloride selectivity is due to the formation of strong hydrogen bonds between the urea moieties and the chloride ions.

Acknowledgements

We are thankful to CSIR (New Delhi) for financial support [project no. 01(1934)/04/EMR-II]. J.N.B. is thankful to CSIR for a senior research fellowship. We are also thankful to the Central Drug Research Institute (CDRI), Lucknow, for FAB mass spectra, DST for support under FIST programme, UGC for SAP programme and Guru Nanak Dev University for providing research facilities.

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18. *Synthesis of 5,11,17,23-Tetra-tert-butyl-25,27-bis(p-nitrophenylureido ethoxy)-26,28-dipropoxy-calix[4]arene* **1**: To a solution of 5,11,17,23-tetra-*tert*-butyl-25,27-bis(2-aminoethoxy)-26,28-dipropoxycalix[4]arene **2** (81.8 mg, 0.10 mmol) in dry CH_2Cl_2 was added *p*-nitrophenyl isocyanate **3** (36.1 mg, 0.22 mmol). The resulting mixture was stirred at room temperature. After completion of the reaction (TLC, 6 h) the solvent was removed under vacuum. The residue was recrystallised from dichloromethane and hexane (1:5) to give a yellow solid. Yield (0.10 g, 87%). Mp 234 °C. IR ν_{max} (KBr, cm^{-1}) 3360, 1636; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.09 (d, $J = 9.6$ Hz, 4H, *p*-NO_2ArH), 7.65 (s, 2H, NH), 7.45 (d, $J = 9.6$ Hz, 4H, *p*-NO_2ArH), 7.03 (s, 4H, ArH), 7.02 (s, 4H, ArH), 5.76 (br s, 2H, NH), 3.84 (s, 8H, $ArCH_2Ar$), 3.45 (t, $J = 5.1$ Hz, 4H, NCH_2), 3.30 (t, $J = 7.8$ Hz, 4H, OCH_2), 3.18 (t, $J = 5.1$ Hz, 4H, OCH_2), 1.27 (s, 18H, $C(CH_3)_3$), 1.16 (s, 18H, $C(CH_3)_3$), 1.00–1.08 (m, 4H, CH_2), 0.68 (t, $J = 7.5$ Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.1 (C=O), 154.9 (ArC), 154.5 (ArC), 145.5 (ArC), 144.6 (ArC), 144.4 (ArC), 142.0 (ArC), 133.7 (ArC), 132.7 (ArC), 126.5 (ArC), 125.9 (ArC), 125.2 (ArC), 117.8 (ArC), 72.1 (NCH_2), 70.5 (OCH_2), 41.2 (OCH_2), 39.2 ($ArCH_2Ar$), 33.9 ($(CH_3)_3C$), 33.9 ($(CH_3)_3C$), 31.5 ($(CH_3)_3C$), 31.3 ($(CH_3)_3C$), 21.8 (CH_2), 9.8 (CH_3); FAB-MS *m/z* 1147$(M+1)^+$. Elemental Anal. Calcd for $C_{68}H_{86}N_6O_{10}$: C, 71.20; H, 7.50; N, 7.33. Found: C, 71.01; H, 7.24; N, 6.98.
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