Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

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Burcu Kendi[a]; Hayriye Nevin Naziroglu[b]; Mustafa Yilmaz[a]; Abdulkadir Sirit[a]
[a] Department of Chemistry, Selçuk University, Konya, Turkey [b] Department of Chemistry, Karamanoglu Mehmetbey University, Karaman, Turkey

Online publication date: 28 January 2010

To cite this Article Kendi, Burcu , Naziroglu, Hayriye Nevin , Yilmaz, Mustafa and Sirit, Abdulkadir(2010) 'Synthesis and Anion Binding Properties of Diamide Derivatives of *p-tert*-Butylcalix[4]arene', Journal of Macromolecular Science, Part A, 47: 3, 225 — 229
To link to this Article: DOI: 10.1080/10601320903526923
URL: http://dx.doi.org/10.1080/10601320903526923

Journal of Macromolecular Science®, Part A: Pure and Applied Chemistry (2010) **47**, 225–229

ISSN: 1060-1325 print / 1520-5738 online
DOI: 10.1080/10601320903526923

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Synthesis and Anion Binding Properties of Diamide Derivatives of *p-tert*-Butylcalix[4]arene

BURCU KENDI[1], HAYRIYE NEVIN NAZIROGLU[2], MUSTAFA YILMAZ[1]* and ABDULKADIR SIRIT[1]

[1]*Department of Chemistry, Selçuk University, 42099, Konya, Turkey*
[2]*Department of Chemistry, Karamanoglu Mehmetbey University, 70100, Karaman, Turkey*

Received and Accepted September 2009

Two novel calix[4]arene based anion receptors containing positively charged binding sites in combination with amide groups have been synthesized. Anion binding properties of these receptors towards $H_2PO_4^-$ and HSO_4^- ions were studied by ^{1}H-NMR spectroscopy and the results reflected that receptor 5 selectively recognize $H_2PO_4^-$ in preference to HSO_4^- ions. The molar ratio and the association constants of the complexes were determined by using Job plots and a nonlinear least-squares fitting method, respectively.

Keywords: Anion recognition, amide, calix[4]arene, tetrabutylammonium salt

1 Introduction

The rational design and synthesis of artificial receptors for anion recognition is receiving considerable attention due to the fundamental roles of anions in a wide range of chemical and biological processes (1–7). Types of noncovalent interactions for anion binding are electrostatic interactions, hydrogen bonding, hydrophobicity, coordination to a metal ion, and combinations of these interactions working together (8). Anion binding is usually accomplished by neutral receptors through hydrogen bonding (9–14). But a single hydrogen-bonding interaction of non-activated amide or alcohol with anion is weak (15–17), and strong binding can only be achieved by multiple interactions.

In the literature, many synthetic receptors bearing pyrrole (18), guanidinium (19–21), Lewis acid (22–24), amide (25–27), and urea/thiourea (28–30) groups have been reported for anions. Among them, amide groups are one of the most popular hydrogen bond donors used for the selective recognition of anions and are often incorporated into macrocyclic structures.

Calixarenes, cyclic oligomers of phenolic units linked through the ortho positions, are a fascinating class of macrocycles, because of their skeleton simplicity associated with versatile recognition properties towards ions and neutral molecules (31–37). The capability of being modified at both the lower and upper rims have made this class of synthetic ionophores increasingly attractive for the chemists involved in supramolecular chemistry. Therefore, a variety of macrocyclic compounds containing calix[4]arene backbone have been designed and synthesized for use as selective anion complexing ligands (38–41).

We have previously reported the synthesis of calix[4]arene based receptors as novel extractants (42, 43), sorbents (44, 45), membrane transport carriers for anions (46), chiral hosts (47) and catalysts (48). Herein we report the synthesis and binding properties of calix[4]arene based anion receptors containing positively charged or neutral binding sites in combination with amide groups which have often been claimed to act as binding sites in the complexation of dichromate anions.

2 Experimental

2.1 Instrumentation

Melting points were determined on a Electrothermal 9100 apparatus in a sealed capillary. NMR spectra were recorded on a Varian 400 MHz spectrometer in deuterated solvent. Chemical shifts (δ) are given in ppm from $CDCl_3$:DMSO-d_6 (1:1) at 7.24 ppm. Coupling constants J are given in Hz. IR spectra were obtained on a Perkin-Elmer 1605 FTIR spectrometer as KBr pellets. UV-Visible spectra were obtained on a Shimadzu 160 A UV-Visible recording spectrophotometer. Elemental analysis data were performed on a Leco CHNS-932 analyzer. A Crison MicropH 2002 digital pH meter was used for the pH measurements.

*Address correspondence to: M. Yilmaz, Faculty of Science, Department of Chemistry, Selcuk University, Konya, 42075, Turkey. Tel.: + 90 332 2232774; Fax: +90 332 2410520; E-mail: myilmaz42@yahoo.com

2.2 Reagents

All starting materials and reagents used were of standard analytical grade from Fluka, Merck and Aldrich, and used without further purification. Commercial grade solvents such as chloroform, methanol, acetone, ethyl acetate, and hexane were distilled, and then stored over 4Å molecular sieves. Acetonitrile was dried from calcium hydride and stored under N_2 over 4 Å molecular sieves. Tetrabutylammonium salts of dihydrogen phosphate and hydrogen sulphate were stored in a desiccator under vacuum containing self-indicating silica. The drying agent employed was anhydrous $MgSO_4$. Thin layer chromatography (TLC) was performed using Merck prepared plates (silica gel 60 F254 on aluminum). Column chromatography separations were performed on Merck Silica Gel 60 (230–400 Mesh). All aqueous solutions were prepared with deionized water that had been passed through a Millipore milli-Q Plus water purification system.

2.3 Synthesis

Compound **2**–**4** were synthesized according to previously described methods (49–51). Compound 3 and 4 (0.18 mmol) and 37% aqueous HCl (6.5 mmol) in dichloromethane (15 mL) were stirred at room temperature for 6 h. The reaction mixture was dried by adding $MgSO_4$. After filtration and removal of the solvent, the residue was precipitated with methanol to give **5** and **6**.

2.3.1. *Compound 5*

White solid; Yield: 70%; ^{1}H-NMR (DMSO-d_6): 9.08 (bs, 2H, NH), 8.80 (t, J = 5.4 Hz, 2H, NH), 8.42 (s, 2H, OH), 7.18 (s, 4H, ArH), 7.15 (s, 4H, ArH), 4.54 (s, 4H, OCH_2CO), 4.17 (d, 4H, J = 12.7 Hz, ArCH_2Ar), 3.84 (b, 8H, OCH_2CH_2N), 3.60–2.80 (m, 20H, NHCH_2CH_2CH_2N + ArCH_2Ar+NCH_2CH_2O + NHCH_2CH_2CH_2N), 1.92 (b, 4H, NHCH_2CH_2CH_2N), 1.17 (s, 18H, C(CH_3)$_3$), 1.10 (s, 18H, C(CH_3)$_3$). ^{13}C-NMR (DMSO-d_6): 166.78, 148.12, 148.01, 147.85, 143.55, 132.46, 126.54, 125.73, 125.01, 99.32, 74.25, 73.93, 73.62, 72.83, 58.27, 55.58, 31.23, 30.97; Anal. cald for $C_{62}H_{90}N_4O_8Cl_2$ (1090.33): C, 68.30; H, 8.32; N, 5.14. Found: C, 68.47; H, 8.50; N, 5.42.

2.3.2. *Compound 6*

White solid; Yield: 74%;^{1}H-NMR (DMSO-d_6): 9.27 (bs, 2H, NH), 8.72 (t, J = 5.3 Hz, 2H, NH), 8.28 (s, 2H, OH), 7.14 (s, 4H, ArH), 7.05 (s, 4H, ArH), 4.42 (s, 4H, OCH_2CO), 4.12 (d, 4H, J = 12.8, ArCH_2-Ar), 3.52-2.73 (m, 8H, NHCH_2CH_2N + ArCH_2Ar), 2.38 (t, J = 6.6 Hz, 4H, NHCH_2CH_2N), 2.31-2.35 (m, 8H, NCH_2), 1.18-1.26 (m, 12H, NCH_2CH_2CH_2), 1.09 (s, 18H, C(CH_3)$_3$), 1.02 (s, 18H, C(CH_3)$_3$). ^{13}C-NMR (DMSO-d_6): 166.12, 148.64, 148.13, 147.65, 143.55, 132.56, 127.87, 126.54, 124.96, 74.43, 58.21, 55.14, 37.02, 34.43, 34.02, 32.54, 31.06, 30.51, 25.49, 24.04, 22,95; Anal. cald for $C_{62}H_{90}N_4O_6Cl_2$ (1058.33): C, 70.36; H, 8.57; N, 5.29. Found: C, 70.57; H, 8.65; N, 5.42.

2.4 ^{1}H-NMR Titrations

In a typical anion titration experiment, aliquots of TBA anion salts (tetrabutylammonium dihydrogen phosphate and hydrogen sulfate) (0.5 M, 1.0×10^{-4} moles in 0.5 mL) and a receptor (0.01 M, 7.0×10^{-6} moles in 0.5 mL) in deuterated solvent ($CDCl_3$:DMSO-d_6 1:1) were prepared. To this solution 0, 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4, 1.6, 1.8, 2, 3, 4, 5, 7 and 10 equivalents of tetrabutylammonium salts were added in the NMR tube and the spectra were recorded. The chemical shift of a specific proton on the receptor was followed and plotted against the equivalents guest added. ^{1}H-NMR spectra and titration were recorded on a 400 MHz spectrometer. The resulting titration data was analyzed by the computer program EQNMR (52) to yield stability constants for the anion/receptor binding processes.

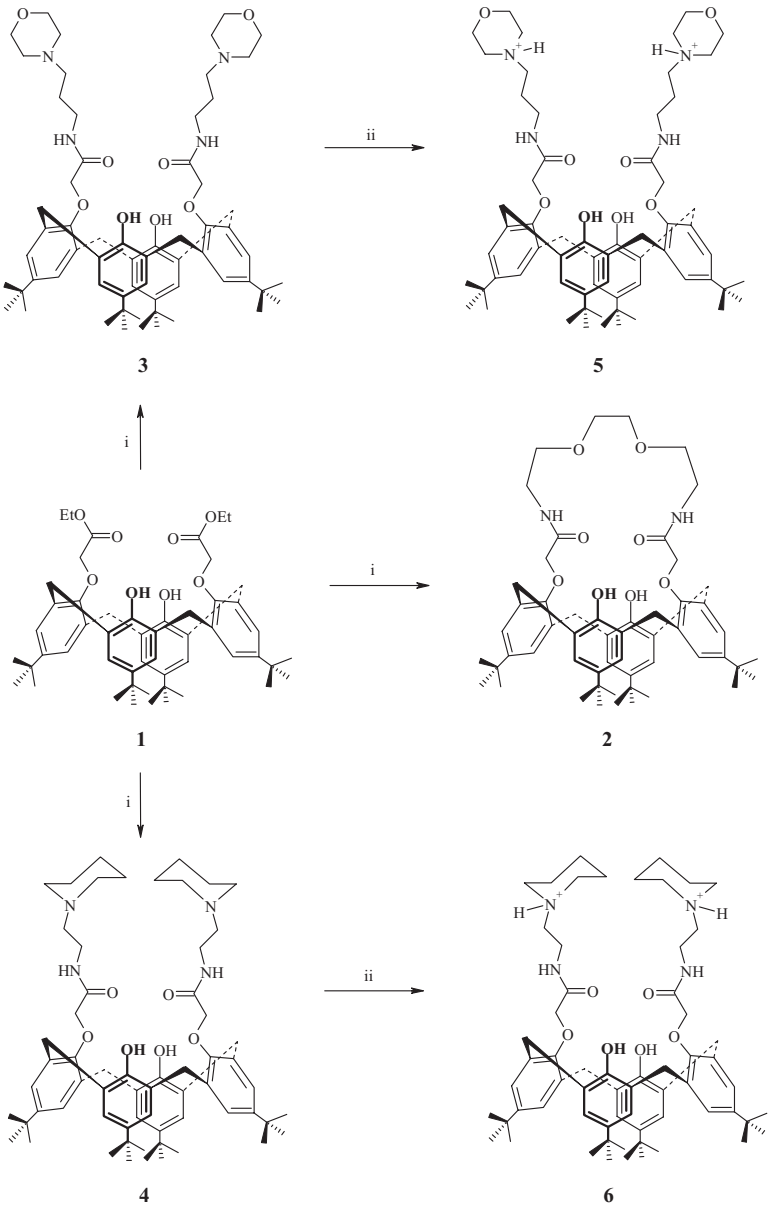
3 Results and Discussion

3.1 Synthesis

Calixarenes containing hydrogen bonding donor and acceptor groups at the lower rim has affected their host-guest properties and has given rise to new possibilities for anions complexation. The introduction of amide groups and positively charged nitrogen binding sites into the calix[4]arene platform could serve as receptors for anions such as HSO_4^- and $H_2PO_4^-$. Calixarene derivatives **2**–**4** were prepared by amidation of the ethyl ester functions by the appropriate primary amine as already described previously. The protonation of the basic nitrogen atom of **3** and**4** was carried out by reaction with 37% aqueous HCl in chloroform to give **5** and **6** in 70% and 74% yield, respectively (Scheme 1). The conformation of **5** and **6** was deduced to be cone from the ^{1}H-NMR spectra presenting characteristic AB systems for the ArCH_2Ar methylene protons of the calix macroring. The downfield shifts from 2.25 to 2.31–2.37 ppm and from 2.18 to 2.80–2.85 ppm of the NCH_2 signals for **3** and **4** respectively due to the protonation of the tertiary nitrogen atom and the appearance of new N-H signals at δ 9.08 and δ 9.27 confirmed the formation of quaternary ammonium salt **5** and **6**.

3.2 Complexation Studies

The complexation ability of host molecules **2**–**6** towards HSO_4^- and $H_2PO_4^-$ anions were studied by standard ^{1}H-NMR titration experiments (Table 1) in deuterated solvent. The addition of tetrabutylammonium dihydrogen phosphate and hydrogen sulfate result in the complexation-induced shift of NH or OH signals. All titration experiments were performed with variable



Sch. 1. Reaction conditions: (i) primary amine, Toluene/MeOH (1:1), reflux; (ii) HCl, CH_2Cl_2.

Table 1. Complexation constants *K* of receptors towards selected anions (^{1}H-NMR, $CDCl_3$:DMSO-d_6, 25°C, 400 MHz)

	HSO_4^-		$H_2PO_4^-$	
Ligand	*NH proton* K_{ass}	*Phenolic OH proton* K_{ass}	*NH proton* K_{ass}	*Phenolic OH proton* K_{ass}
2	105 ± 16	[a]	78 ± 3	437 ± 44
3	76 ± 5	[a]	98 ± 13	[a]
4	85 ± 5	198 ± 20	92 ± 12	231 ± 33
5	79 ± 1	[a]	1224 ± 182	328 ± 4
6	225 ± 24	[a]	347 ± 27	[a]

[a]Very weak binding, a stability constant value could not be calculated in this solvent.

concentration of host molecules (8.3–10 mM) and increasing concentrations of the anion (83.3–2.0 mM) added.

As can be seen from Figure 1, the NH signal of **5** at δ 8.80 was greatly downfield shift upon the addition of $H_2PO_4^-$ and the downfield shift of a singlet of phenolic protons at δ 8.42 were noticed, whereas relatively weak complexation was observed with HSO_4^- . Similarly, compound **6** has a considerably higher affinity for $H_2PO_4^-$ than the parent calix[4]arene derivative **4** whilst binding HSO_4^- with moderately higher affinities. These results suggest that receptors **5** and **6** achieve the anion binding through the electrostatic attraction of the anion by the positive charge in combination with hydrogen bonding interactions between the receptor and anions.

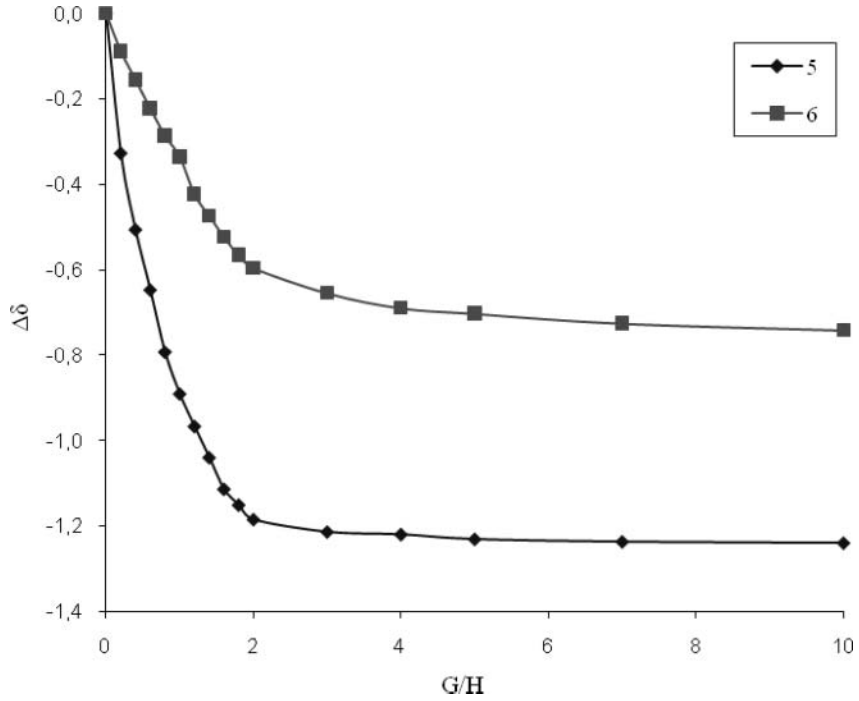


Fig. 1. ^{1}H-NMR titration curves for **5** and **6** upon addition of $H_2PO_4^-$ anions in 1:1 $CDCl_3$: DMSO-d_6.

Ligand **2**, bearing two amide groups and a crown unit in its framework, showed relatively strong complexation ability towards HSO_4^- and $H_2PO_4^-$ ions when compared with other neutral receptors **3** and **4**. The chemical shift for the NH and phenolic OH proton resonances upon addition of HSO_4^- and $H_2PO_4^-$ to a solution of **2** in deuterated solvent indicated that both the NH and OH protons participate in the formation of co-operative hydrogen bonds with the anionic oxygens, as previously reported in the literature (53).

The stoichiometry of the host–guest complexes was determined according to Jobs method of continuous variations. The total concentration of the hosts and the guest was kept constant (10 mM) in deuterated solvent, whilst the molar fraction of the guest [G]/([H]+[G]) was continuously varied. In all cases studied, maxima were observed when the molar ratio of the receptors and guests was 1:1 (X = 0.5), which indicated that hosts and the guests formed 1:1 instantaneous complexes as illustrated in Figure **2** for the complexation of **5** with $H_2PO_4^-$. The association constants of the receptors for anionic species, K_{ass}, which were shown in Table 1, were determined by non-linear fitting analyses of the titration curves according to 1:1 host–guest complexation equation.

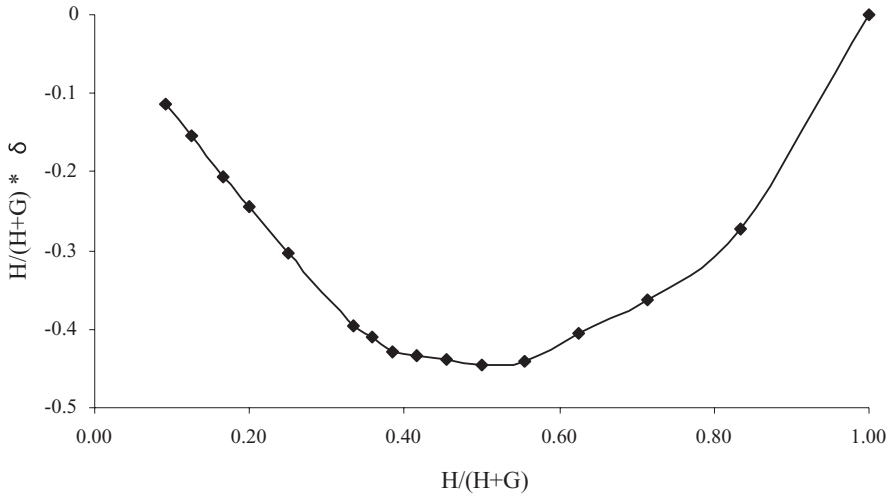


Fig. 2. Job's plot of the titration of $H_2PO_4^-$ with receptor **5**.

4 Conclusions

In conclusion, we have synthesized a series of novel calix[4]arene based receptors containing amide moiety and positively charged nitrogen binding sites 5 and 6. Anion binding properties of the new receptors were studied by ^{1}H-NMR spectroscopy. The stoichiometric ratio of the host–guest complexes was determined as 1:1 instantaneous complexes according to Job's method of continuous variations. Receptor 5 selectively recognizes $H_2PO_4^-$ in preference to HSO_4^- ions. The enhanced selectivity of 5 for $H_2PO_4^-$ anions could be due to electrostatic attraction of the anion by the positive charge and hydrogen bonding interactions between the receptor NH and OH protons.

Acknowledgement

We thank the Research Foundation of Selcuk University, Konya-Turkey (BAP 09201094) for financial support of this work.

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