Preparation of new azobenzene crown ether *p-tert*-butylcalix[4]arenes and their roles as switchable ionophores for Na$^+$ and K$^+$ ions

Bongkot Pipoosananakaton,[a] Mongkol Sukwattanasinitt,[a] Nongnuj Jaiboon,[a] Narongsak Chaichit[b] and Thawatchai Tuntulani[a,*]

[a]*Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand*
[b]*Department of Physics, Faculty of Science, Thammasat University at Rangsit, Pathumthani 12121, Thailand*

Abstract

New azobenzene crown ether *p-tert*-butylcalix[4]arenes (**6** and **7**) have been synthesized by reductive coupling reactions between two nitrobenzene groups. Their isomerization and switchable binding properties towards Na$^+$ and K$^+$ were studied by ^{1}H NMR spectroscopy. The results showed that Na$^+$ preferred to bind the *cis* form of **6** while K$^+$ preferred to bind the *trans* isomer. © 2000 Published by Elsevier Science Ltd.

*Keywords:* azobenzene; calixarene; isomerization; switchable ionophore.

Azobenzenes make up an interesting class of compounds that exhibit photoresponsive properties. They have been incorporated into a number of supramolecular frameworks to produce ionophores for transports and photo-switchable receptors.[1] We are interested in constructing a switchable molecular system which can selectively bind Na$^+$ or K$^+$ mimicking the biological Na$^+$/K$^+$ pump.[2] According to a report by Swager and co-workers, it was found that bithiophene calix[4]arenes containing six ethereal oxygen donors were able to bind Na$^+$ and K$^+$ to different extents.[3] In the same manner, we anticipated that an azobenzene crown calix[4]arene would also form complexes with both Na$^+$ and K$^+$, and the binding abilities could then be switchable. We therefore synthesized two azobenzene crown ether calix[4]arenes (**6** and **7**) and studied their isomerization properties.

---

* Corresponding author.

One way to synthesize compounds **6** and **7** would be to attach two ethoxy nitrobenzene groups into the calix[4]arene framework. Reductive coupling of nitrobenzene groups would then be carried out to afford the azobenzene crown ether calix[4]arenes. This synthetic approach is depicted in Scheme 1. Nitrobenzene calix[4]arenes, **4** and **5**, were synthesized by nucleophilic substitution reactions of 2-(2-bromoethoxy)nitrobenzene, **3**,[4] with *p-tert*-butylcalix[4]arene, **1**,[5] and dimethoxy *p-tert*-butylcalix[4]arene, **2**,[6] respectively. In a typical reaction, **1** (6.48 g, 10.00 mmol) and potassium carbonate (1.45 g, 10.49 mmol) were mixed in acetonitrile (230 mL) and refluxed for 3 hours. Compound **3** (4.92 g, 20.00 mmol) was then added slowly into the reaction mixture which was then refluxed further for 4 days. Upon separation and crystallization, sugar-like crystals of **4** were obtained (6.50 g, 66%).[7] A similar reaction between **2** and **3** produced **5** in 20% yield.[8] It should be noted that the yield of **5** was significantly lower than that of **4** due to the steric congestion of the methoxy group which may decelerate the reaction rate. While the ^{1}H NMR spectrum of **4** was quite simple, the ^{1}H NMR spectrum of **5** showed complicated broad signals signifying the existence of conformational isomerism of the calix[4]arene framework similar to the tetramethoxy calix[4]arene due to the lack of intramolecular hydrogen bonding.[9] Subsequently, reductive coupling reactions of **4** and **5** were carried out. A mixture of **4** (0.70 g, 0.71 mmol) in isopropanol (8 mL), sodium hydroxide (0.28 g, 7.00 mmol) in H_2O (4 mL) and zinc (0.20 g, 3.06 mmol) was stirred and refluxed under nitrogen for 48 hours. After standard workup and purification on a silica gel column using 15% ethyl acetate/hexane as eluant, **6** was able to crystallize from hot methanol to give orange crystals (0.05 g, 8%).[10] A similar coupling reaction of **5** afforded **7** as orange crystals in 12% yield.[11] The ^{1}H NMR spectrum of **7** was quite well resolved, compared to that of **5**. This implies that the calix[4]arene compartment of **7** becomes more rigid and stays in a cone conformation upon the formation of the azobenzene crown ether ring.
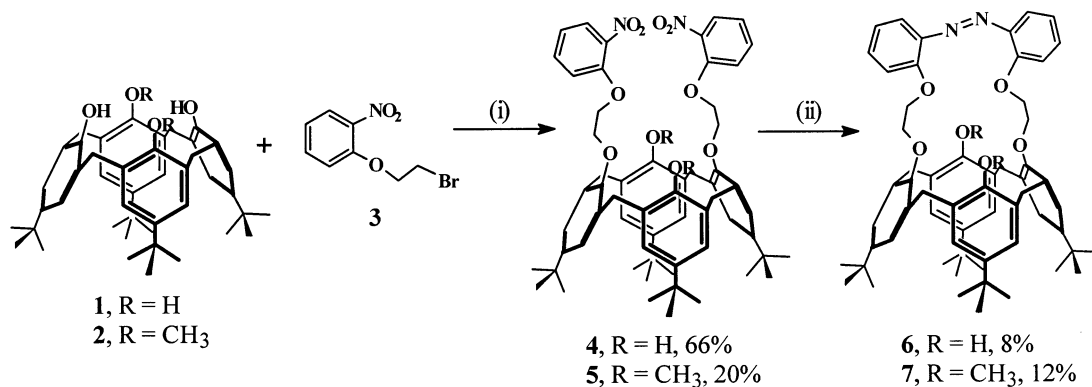
Scheme 1. Reagents and conditions: (i) when R = H: K_2CO_3, CH_3CN, reflux, 4 days; when R = CH$_3$: K_2CO_3, KOH (3 pellets), CH_3CN, reflux, 4 days; (ii) ^{i}PrOH, NaOH/H_2O, Zn, reflux, 2 days

We were able to obtain crystals of both **6** and **7**. However, only crystals of **6** were suitable for single crystal X-ray analysis. The X-ray structure[12] of **6** in Fig. 1 shows that the azobenzene unit is in the *trans* form and a molecule of ethyl acetate has been included into the calix[4]arene unit pointing the $-CH_2CH_3$ moiety into the upper rim cavity. The N=N distance is 1.179 (6) Å. The

relative torsion angle of C(48)–N(2)–N(1)–C(54) is 178.35° suggesting that the azobenzene unit is almost flat. The ethereal and hydroxy oxygen atoms are preorganized for binding cations. Recently, Thuéry and co-workers have reported the crystal structure of 2,2′-azobenzene-substituted calix[4]arene-crown-6 which possessed longer glycolic units and the azobenzene unit in a *trans* form.[13]
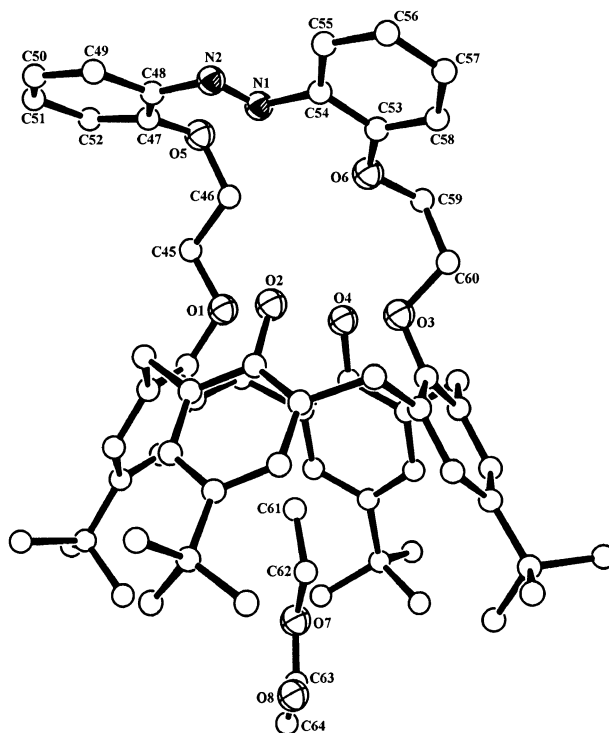

Figure 1. Crystal structure of **6**. Hydrogen atoms were omitted for clarity

Nakamura and colleagues have demonstrated the use of UV spectrophotometry to study photoisomerization of azobenzocrown ethers.[14] Unfortunately, both *trans* and *cis* plus *trans* forms of our compounds gave almost the same UV spectra. We, therefore, studied photoisomerization of **6** and **7** using ^{1}H NMR spectroscopy. Typically, an NMR tube containing **6** or **7** (3.28 mmol) in CDCl$_3$ (0.7 mL) was placed in a photo-reactor (quartz) and irradiated with a 180 W mercury low-pressure lamp for at least 4 hours. The isomerization process was followed by ^{1}H NMR using a Bruker 400 MHz NMR spectrometer. The ^{1}H NMR spectra of **6** and **7** before and after irradiation are depicted in Fig. 2. The following signals belonging to the *cis* isomer of **6** appear distinctively in the spectrum after irradiation: *t*-Bu (1.21 and 1.19 ppm), ArC*H*$_2$Ar (3.31 and 4.35), ROAr*H* (6.97), HOAr*H* (7.06) and ArO*H* (8.41). The ratio of *cis* and *trans* can then be estimated from the integral area of the signals to be 36:64. Interestingly, we found that upon

standing in the dark at room temperature for several days, compound **6** in CDCl$_3$ also underwent *trans* to *cis* isomerization. This result correlates with the observation of Vicens and colleagues in which azobenzene calixcrowns containing one glycolic unit were stable as the *cis* isomers.[15] However, thus far, we cannot isolate the *cis* isomer of **6**.
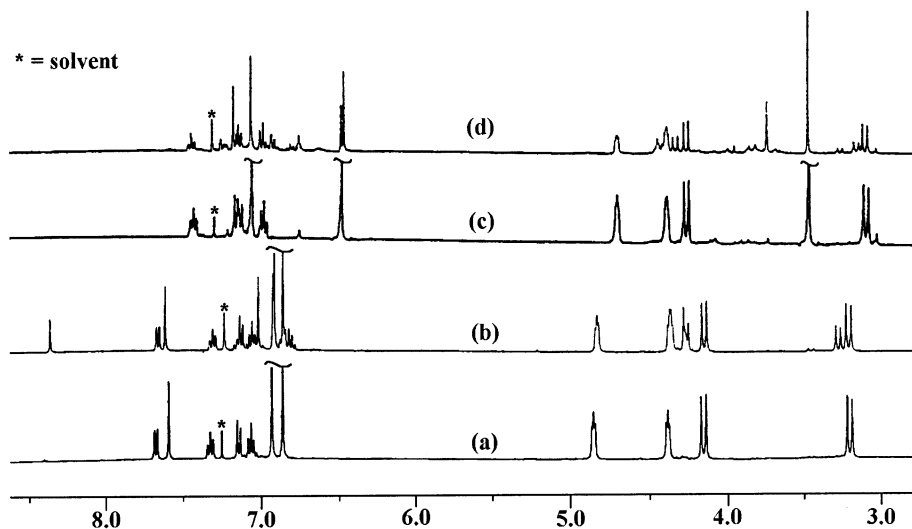

Figure 2. ^{1}H NMR spectra of **6** (a) before, (b) after irradiation and **7** (c) before and (d) after irradiation

The ^{1}H NMR spectrum of **7** also changed dramatically after irradiation and upon standing in the dark for several hours. However, we cannot conclusively say that the *cis–trans* isomerization has occurred since we do not have a crystal structure of **7** to substantiate the isomer of the azobenzene moiety before irradiation. However, a ^{1}H NMR spectrum of **7** in Fig. 2(d) shows complicated signals of aromatic, methylene bridge and ^{t}Bu protons which may result from various conformations of the calix[4]arene unit. We suspect that **7** may just undergo conformational change rather than the *cis–trans* isomerization.

Owing to the complicated conformational behavior of **7**, only the switchable binding property of **6** towards Na$^+$ and K$^+$ was investigated. The picrate salts of Na$^+$ and K$^+$ ions were employed in complexation studies. The metal salts were added into the ligand in CDCl$_3$ before and after UV irradiation.[16] ^{1}H NMR spectra (Fig. 3) of complexes of **6** after addition of sodium and potassium picrates possessed two doublet signals at 3.26 and 4.20 ppm ($J \sim 13$ Hz) indicating that **6** maintained the cone conformation of calix[4]arene after complexation with the metal ions. The spectrum in Fig. 3(a) shows a singlet signal due to picrate protons at 8.64 ppm. The broad peak of the glycolic protons of the *trans* isomer at 4.44 ppm separates from those of the *cis* isomer at 4.40 ppm and multiplet signals appear around 6.82–6.93 ppm. Furthermore, the doublet peaks of the methylene bridge protons of the *trans* form at 3.26 ppm and the *cis* form at 3.32 ppm shift slightly from those of the free ligand. It was found from the integration that the amount of the *cis* isomer increased from 36 to 47%. Addition of potassium picrate into **6** results in an appearance of a singlet signal due to the picrate protons at 8.92 ppm (Fig. 3(b)). The intensity of the signals corresponding to the *cis* isomer decreases dramatically. The integration showed that the percentage of *cis* isomer decreased from 36 to 10%, and on the other hand, the amount of the *trans* isomer increased to 90%. However, upon standing under the room light, the amount of the *cis* form gradually increased to 25% after standing for 19 days,

and reached 42% in 30 days. We do not have a definite explanation for the increasing concentration of the *cis* isomer. However, it is possible that K$^+$ firstly formed a complex with the *trans* form of **6** and increased the percentage of the *trans* form. Later, the thermal *trans* to *cis* isomerization took place and increased the amount of the *cis* form. The result also implies that the stability of the *trans*-**6**·K complex is not very strong.
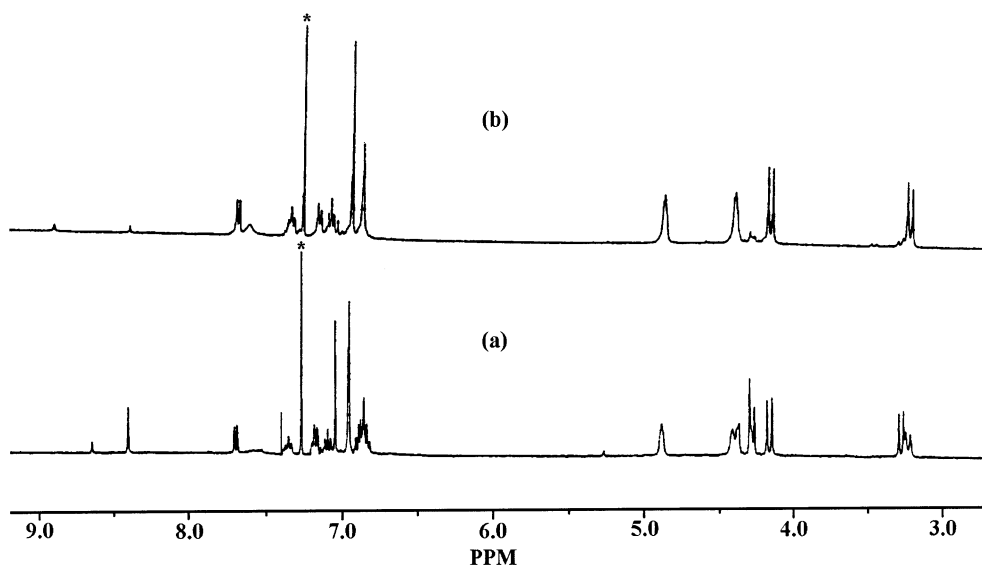

Figure 3. Partial ^{1}H NMR (400 MHz, CDCl$_3$) of **6** in the presence of (a) Na$^+$ (b) K$^+$. * Denotes signals of the solvent

We have demonstrated that **6** can possibly be used as a switchable ionophore for Na$^+$ and K$^+$ ions in which the *cis* form of **6** is suitable for binding Na$^+$ while the *trans* form is appropriate for K$^+$. We are currently investigating conformational behaviors of compound **7** upon binding alkali metal ions and developing **6** and **7** to be switchable sensors for Na$^+$ and K$^+$ ions. The results will then be reported in due course.

Acknowledgements

References

1. Balzani, V.; Scandola, F. *Supramolecular Photochemistry*; Ellis Horwood: New York, 1991; pp. 199–215 and references cited therein.
2. Kaim, W.; Schwederski, B. *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life*; John Wiley & Sons: New York, 1994; pp. 281–284.
3. Marcella, M. J.; Newland, R. J.; Carroll, P. J.; Swager, T. M. *J. Am. Chem. Soc.* **1995**, *117*, 9842.

4. Compound **3** was prepared from the reaction between o-nitrophenol and 1,2-dibromoethane in the same manner as 2-(2′-bromoethoxy)benzaldehyde in: Seangprasertkij, R.; Asfari, Z.; Arnaud, F.; Weiss, J.; Vicens, J. *J. Incl. Phenom*. **1992**, *14*, 141. For **3**: δ_H (200 MHz; CDCl$_3$) 3.65 (2 H, t, *J* 6.0, -OC*H*$_2$C*H*$_2$Br), 4.40 (2 H, t, *J* 6.0, -OC*H*$_2$CH$_2$Br), 7.02–7.10 (2 H, m, aromatic), 7.52 (1 H, t, *J* 8.0, aromatic), 7.81 (1 H, d, *J* 8.0, aromatic); anal. calc. for C$_8$H$_8$BrNO$_3$: C, 39.05; H, 3.28; N, 5.69. Found C, 39.07; H, 3.21; N, 5.65. Mp: 164–165°C.

5. Gutsche, C. D.; Iqbal, M. *Org. Synth*. **1989**, *68*, 234.

6. Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.

7. For **4**: δ_H (200 MHz; CDCl$_3$) 0.94 and 1.28 (18 H each, s, *t*-Bu protons), 3.28 (4 H, d, *J* 13.0, ArC*H*$_2$Ar), 4.26–4.33 (8 H, m, ArC*H*$_2$Ar and -OC*H*$_2$C*H*$_2$O-), 4.45–4.47 (4 H, m, -OC*H*$_2$C*H*$_2$O-), 5.19 (2 H, s, *H*OAr), 6.75 (4 H, s, HOAr*H*), 6.95 (2 H, t, *J* 8.0, nitrobenzene), 7.03 (4 H, s, ROAr*H*), 7.24 (2 H, d, *J* 8.0, nitrobenzene), 7.46 (2 H, t, *J* 7.0, nitrobenzene), 7.7 (2 H, d, *J* 8.0, nitrobenzene); anal. calc. for C$_{60}$H$_{70}$N$_2$O$_{10}$: C, 73.60; H, 7.21; N, 2.86. Found C, 73.62; H, 7.27; N, 2.73. Mp: 205–207°C.

8. For **5**: δ_H (200 MHz; CDCl$_3$) 0.84 and 1.05 (9 H each, br s, CH$_3$OAr*t-Bu*), 1.28 (18 H, br s, ROAr*t-Bu*), 3.00–3.40 (4 H, br, ArC*H*$_2$Ar), 3.47 (6 H, s, -OC*H*$_3$), 3.60–4.60 (12 H, br, ArC*H*$_2$Ar and -OC*H*$_2$C*H*$_2$O-), 6.40–6.69 (4 H, br, CH$_3$OAr*H*), 6.92–7.30 (8 H, br, nitrobenzene and ROAr*H*), 7.51 (2 H, t, *J* 7.0, nitrobenzene), 7.81 (2 H, d, *J* 8.0, nitrobenzene); anal. calc. for C$_{62}$H$_{74}$N$_2$O$_{10}$: C, 73.93; H, 7.40; N, 2.78. Found C, 73.92; H, 7.46; N, 2.76. Mp: 189–191°C.

9. van Hoorn, W. P.; Briels, W. J.; van Duynhoven, J. P. M.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Org. Chem*. **1998**, *63*, 1299; Fisher, S.; Grootenhuis, P. D. J.; Groenen, L. C.; van Hoorn, W. P.; van Veggel, F. C. J. M.; Reinhoudt, D. N.; Karplus, M. *J. Am. Chem. Soc*. **1995**, *117*, 1611; Shinkai, S.; Iwamoto, K.; Araki, K.; Matsuda, T. *Chem. Lett*. **1990**, 1263.

10. For **6** (*trans* form): δ_H (400 MHz; CDCl$_3$) 1.03 and 1.20 (18 H each, s, *t*-Bu protons), 3.20 and 4.15 (4 H each, d, J_{AB} 13.0, ArC*H*$_2$Ar), 4.38 and 4.84 (4 H each, br t, -OC*H*$_2$C*H*$_2$O-), 6.86 (4 H, s, ROAr*H*), 6.92 (4 H, s, HOAr*H*), 7.08 (2 H, t, *J* 6.0, azobenzene), 7.16 (2 H, d, *J* 8.0, azobenzene), 7.34 (2 H, t, *J* 6.0, azobenzene), 7.61 (2 H, s, *H*OAr), 7.70 (2 H, d, *J* 8.0, azobenzene); anal. calc. for C$_{60}$H$_{70}$N$_2$O$_6$·C$_4$H$_8$O: C, 76.62; H, 7.84; N, 2.79. Found C, 77.21; H, 7.51; N, 2.72. Mp: 195–197°C (decomp.). UV/vis [λ (nm), ε (dm^3 mol^{-1} cm^{-1})]: 344, 19233; 446, 3167.

11. For **7**: δ_H (400 MHz; CDCl$_3$) 0.82 and 1.28 (18 H each, s, *t*-Bu protons), 3.10 and 4.23 (4 H each, d, J_{AB} 12.0, ArC*H*$_2$Ar), 3.44 (6 H, s, -OC*H*$_3$), 4.34 and 4.63 (8 H, m, -OC*H*$_2$C*H*$_2$O-), 6.42 (4 H, s, CH$_3$OAr*H*), 6.94 (2 H, m, azobenzene), 7.01 (4 H, s, ROAr*H*), 7.08 (4 H, m, azobenzene), 7.41 (2 H, m, azobenzene); anal. calc. for C$_{62}$H$_{74}$N$_2$O$_6$: C, 78.95; H, 7.91; N, 2.97. Found C, 79.06; H, 7.91; N, 2.97. Mp: 228–230°C. UV/vis [λ (nm), ε (dm^3 mol^{-1} cm^{-1})]: 334, 19385; 440, 7714.

12. Crystallographic data (excluding structure factors) for **6**·C$_4$H$_8$O$_2$ have been deposited with the Cambridge Crystallographic Data Center (CCDC 137509). Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

13. Thuéry, P.; Nierlich, M.; Saadioui, M.; Asfari, Z.; Vicens, J. *Acta Crystallogr*., *Sect. C* **1999**, *55*, 443.

14. Tahara, R.; Morozumi, T.; Nakamura, H. *J. Phys. Chem. B* **1997**, *101*, 7736.

15. Saadioui, M.; Asfari, Z.; Vicens, J.; Reynier, N.; Dozol, J. F. *J. Incl. Phenom*. **1997**, *28*, 223; Saadioui, M.; Asfari, Z.; Vicens, J. *Tetrahedron Lett*. **1997**, *38*, 1187; Saadioui, M.; Asfari, Z.; Thuéry, P.; Nierlich, M.; Vicens, J. *Tetrahedron Lett*. **1997**, *38*, 5643.

16. The results obtained when metal picrates were added before and after irradiation of **6** are essentially the same.

.