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Synthesis and Characterisation of Two *Azo*benzene Modified 1,3-Calix[4]-*bis*-crowns as Artificial Potentially Allosteric Systems.

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Abstract: *Azo* calix[4]crowns**1-[2,2']** and **1-[4,4']** have been synthetized consisting in *unsymmetrical* 1,3-calix[4]-*bis*-crowns combining one polyether crown-6 and one *azo*benzene modified crown-6, O-attached at each side of a calix[4]arene in the 1,3-alternate conformation. Preliminary complexation of alkalis and ammonium picrates showed the cations to be located in the unmodified crown ether of the 1:1 complexes. Complexation induced changes in the trans/cis ratio of the azobenzene unit of **1-[4,4']** by an allosteric mechanism probably due to conformational changes.

With respect to biological structures that transmit information through molecular motions,[1] supramolecular chemists have developped artificial allosteric systems in which *negative or positive cooperativity* or *noncooperativity*[2] is induced by metal-binding,[3] neutral substrate complexation,[4] conformational changes,[5] and subunit aggregation[6]. A recent example has been given showing evidence of allosteric communication between the metal-binding lower rim and the sugar binding upper rim on a calix[4]crown platform.[7] Positive and negative cooperativities were observed and attributed to a conformational change of the calix unit in the 1,2-alternate conformation.[7]

According to our previous reports on *1,3-alternate* calix[4]-*bis*-crowns[8] and related *azo*benzene modified derivatives,[8-11] we decided to prepare allosteric systems **1** in which an information given at one side of the calix unit could be transmitted to the other, the calix[4]arene unit being used as a relay by the occurrence of conformational changes. Systems **1** consist in *unsymmetrical* 1,3-calix[4]-*bis*-crowns combining one polyether crown-6 and one *azo*benzene modified crown-6, O-attached at each side of a calix[4]arene in the 1,3-alternate conformation. 1,3-Calix[4]-*bis*-crown-6 has been proved to complex potassium, rubidium and cesium cations[12] with good stability constants ranging from 4.1 to 5.4 in methanol and acetonitrile respectively.[13] It is expected that the complexation in the unmodified crown-6 of **1** may be influenced by the trans/cis geometry of the azobenzene unit and *vice versa*. The two systems **1-[2,2']** and **1-[4,4']** were synthetized containing 2,2'- and 4,4'-azobenzene units respectively.

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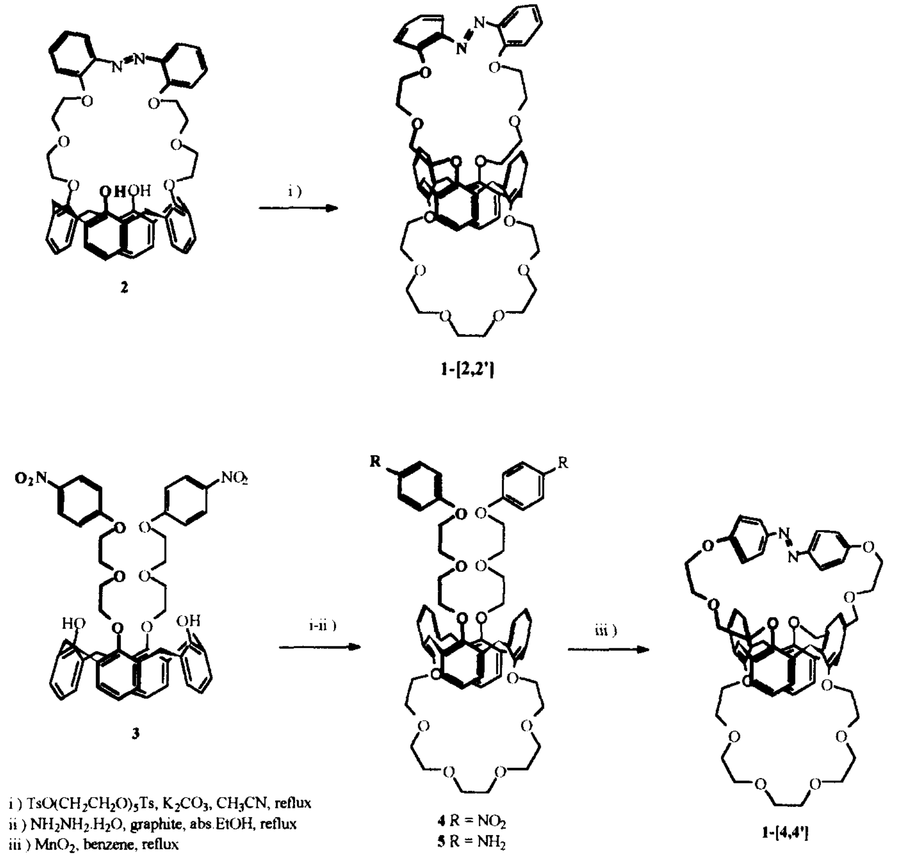

2

1-[2,2']

3

4 R = NO_2
5 R = NH_2

1-[4,4']

i) $TsO(CH_2CH_2O)_5Ts$, K_2CO_3, CH_3CN, reflux
ii) $NH_2NH_2.H_2O$, graphite, abs.EtOH, reflux
iii) MnO_2, benzene, reflux

Scheme 1. Synthetic pathways to **1-[2,2']** and **1-[4,4']**

The synthesis of **1-[2,2']** and **1-[4,4']** is illustrated in Scheme 1. **1-[2,2']** was produced by reaction of the already known[9] calix[4]-(2,2'-azobenzo)-crown-6 **2** in cone conformation with pentaethylene glycol ditosylate in the presence of K_2CO_3 in acetonitrile. The constrained 1,3-alternate conformation was deduced from the ^1H-NMR spectrum of **1-[2,2']** presenting a singlet at 3.69 ppm for the Ar-C*H*$_2$-Ar protons of the calix unit.[14] Similarly dinitro calix[4] **3**[9] was reacted with pentaethylene glycol ditosylate in the presence of K_2CO_3 in acetonitrile to produce dinitro calix[4]crown-6 **4** which was further reduced into diamino calix[4]crown-6 **5** by reacting with $NH_2NH_2.H_2O$ on graphite as described in reference.[16] The cyclization was performed by oxydative coupling with the use of activated MnO_2 in benzene[17] to give **1-[4,4']**. The 1,3-alternate conformation of **1-[4,4']** was confirmed by the presence of a singlet at 3.72 ppm in its ^1H-NMR spectrum.[14] UV-Visible spectra[14] were in agreement of the proposed structures due to their similarity with already published azobenzene calixcrowns containing 2,2'- and 4,4'-azobenzene units.[9-11] Combination of UV-Visible and ^1H-NMR data allowed the determination of trans/cis ratio of 99/1 and 70/30 for **1-[2,2']** and **1-[4,4']** respectively.[14] CPK models indicated that in the cis-form of the 2,2'-azobenzene derivative, a greater number of non-bonded repulsions occurs.

Complexation studies of **1-[2,2']** and **1-[4,4']** with potassium, rubidium, cesium and ammonium picrates were realized by means of ^{1}H-NMR. After a period of 2 days reaction at r.t. between solid picrates and a chloroform solution of the ligands **1** the ratio of metal to ligand in solution, as.estimated by integration of the picrate proton resonance *vs* those of aromatics, was 1:1.

For the 1:1 complexes of **1-[4,4']** we observed changes in the chemical shifts due to complexation in the ^{1}H-NMR spectra for those protons corresponding to the unmodified ether crown-6 chain whereas the protons belonging to the azo modified crown were unchanged. This indicated the cation to be located in the crown-6 unit in agreement with the good stability constants determined for the complexes 1,3-calix[4]-bis-crown-6 with alkali cations[13] and the poor alkali-cation transporting properties of a 4,4'-azobenzene modified calix[4]crown-6 in the 1,3 alternate conformation.[11] At the same time we observed changes in the trans/cis ratio from 70/30 for the free ligand to 80/20, 80/20, 75/25, and 85/15 for K^+, Rb^+, Cs^+, and NH_4^+ complexes of **1-[4,4']** respectively. The largest change was observed for NH_4^+ probably because it formed the strongest complex.

The change in the trans/cis ratio of the benzene unit is probably thermally induced through the conformational change of the calix[4]arene serving as a relay-element.

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14. *General*: Mps, capillaries under N_2, Büchi 500. Chromatography, SiO_2 columns with Kieselgel Merck (Art. 11567). Thin layer chromatography (TLC), SiO_2 Merck plates (Art. 6484). UV-Visible recorded on Cary 13. ^{1}H-NMR in $CDCl_3$, Bruker SY200 (δ in ppm, J in Hz). FAB (+) MS, VG-Analytical ZAB HF. Elemental analyses performed at the Service de Microanalyse of the Institut de Chimie de Strasbourg.

1-[2,2']: Calix[4]-(2,2'-azobenzo)-crown-6 **2** (0.300 g, 0.38 mmol), K_2CO_3 (5.252 g, 38.00 mmol) and CH_3CN (300 mL) were stirred for 24 h at r.t. under N_2. Pentaethylene glycol ditosylate (0.207 g, 0.38 mmol) were added. After refluxing for 10 days, solvents were

evaporated to dryness and the residue was dissolved in CH_2Cl_2. The solution was acidified (1N HCl). The organic solution was dried (Na_2SO_4), filtered and evaporated to dryness. Chromatography (SiO_2, 80:20 CH_2Cl_2:acetone) followed by precipitation in methanol afforded pure **1-[2,2']** (0.136 g, 37 %). Red powder. M.p. 150-151 °C. TLC (SiO_2, 70:30 CH_2Cl_2:acetone): Rf's = 0.43. UV-Visible (acetonitrile, $c = 10^{-4}$ M) $\lambda_{trans} = 354$ nm, $\varepsilon_{trans} = 7.96 \times 10^3$ $mol.^{-1}l.cm^{-1}$. Trans/cis ratio was calculated 99/1. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.71 (d, $J = 8.0$, 2 Ar*H* azobenzene), 7.40 (t, $J = 8.0$, 2 Ar*H* azobenzene), 7.17-7.06 (m, 6 Ar*H*), 7.00 (d, $J = 7.5$, 4 Ar*H* calix), 6.90-6.80 (m, 4 Ar*H*), 6.66 (t, $J = 7.5$, 2 Ar*H* calix), 4.30 (t, $J = 6.0$, 2 N=NArOCH_2), 4.07-3.73 (m, 6 CH_2), 3.69 (s, 4 ArCH_2Ar), 3.59-3.56 (m, 4 CH_2), 3.43 (m, 2 CH_2), 3.28 (t, $J = 6.0$, 2 CH_2), 3.08 (t, $J = 6.0$, 2 CH_2). FAB (+) MS: *m/z* 981.3 (M^+). *Anal. Calcd.* for $C_{58}H_{64}N_2O_{12}$: C, 71.00; H, 6.57. *Found.* C, 71.27; H, 6.72.

4: Same as for **1-[2,2']**. **3** (3.000 g, 3.55 mmol), K_2CO_3 (4.900 g, 35.50 mmol), pentaethylene glycol ditosylate (1.944 g, 3.55 mmol) and CH_3CN (150 mL) were refluxed for 13 days under N_2. Chromatography (SiO_2, 85:15 CH_2Cl_2:acetone) followed by precipitation in methanol afforded pure **4** (2.04 g, 55 %). White powder. M. p. 118-119 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) 8.19 (d, $J = 9.0$, 4 Ar*H* nitrobenzene), 7.11 (d, $J = 7.0$, 4 Ar*H* calix), 7.09 (d, $J = 7.5$ Hz, 4 Ar*H* calix), 6.98 (d, $J = 9.0$, 4 Ar*H* nitrobenzène), 6.84 (t, $J = 7.5$ Hz, 2 Ar*H* calix), 6.74 (t, $J = 7.5$, 2 Ar*H* calix), 4.19 (t, $J = 4.5$, 2 ArOCH_2), 3.76-3.40 (m, 20 CH_2 and ArCH_2Ar). *Anal. Calcd.* for $C_{58}H_{64}N_2O_{16}$: C, 66.65; H, 6.17. *Found.* C, 66.58; H, 6.07.

5: **4** (1.70 g, 1.62 mmol), graphite (8.00 g) and absolute EtOH(150 mL) were stirred at r.t for 2 h under N_2. $NH_2NH_2.H_2O$ (8.00 g, 159.80mmol) dissolved in absolute EtOH (20 mL) was added dropwise and the reaction mixture was refluxed for 13 days. After cooling to r.t., the solution was filtered over celite and washed with CH_2Cl_2. The solvents were evaporated to dryness to afford **5** (1.483 g, 92 %). Transparent oil. **5** was used without purification. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.10 (d, $J = 7.5$, 8 Ar*H*), 6.88-6.72 (m, 8 Ar*H*), 6.63 (d, $J = 9.0$, 4 Ar*H* aminobenzene), 4.03 (t, $J = 5.0$, 2 ArOCH_2), 3.77-3.41 (m, 40 CH_2, ArCH_2Ar and ArNH_2 exchangeable with D_2O), 3.34 (t, $J = 6.0$, 2 CH_2). *Anal. Calcd.* for $C_{58}H_{68}N_2O_{12}$: C, 70.71; H, 6.96. *Found.* C, 70.86; H, 7.22.

1-[4,4']: In a 500 mL round-bottomed flask equipped with a Dean-Stark, **5** (1.400 g, 1.42 mmol), activated MnO_2 (8.00 g, 92.01 mmol) and benzene (250 mL) were stirred vigorously at reflux for 1 day. After filtration through celite, washing with CH_2Cl_2 and drying ($MgSO_4$) the solvents were evaporated to dryness. Chromatography (SiO_2, 85:15 CH_2Cl_2:acetone) followed by precipitation in methanol afforded pure of **1-[4,4']** (0.414 g, 30 %). Orange powder. M. p. 216-217.°C. TLC (SiO_2, 90:10 CH_2Cl_2:acetone): Rf's = 0.40 (more intense) and 0.20 attributed to trans (the less polar) and csi (the more polar) isomers respectively. UV-Visible (acetonitrile, $c = 5\ 10^{-5}$ M) $\lambda_{trans} = 361$ nm, $\varepsilon_{trans} = 28.09 \times 10^3$ $mol.^{-1}l.cm^{-1}$, $\varepsilon_{cis} = 3.80 \times 10^3$ $mol.^{-1}l.cm^{-1}$.[15] ^{1}H-NMR (200 MHz, $CDCl_3$) 8.06 (d, AB system, $J = 9.0$, 4 Ar*H* azobenzene, trans isomer), 7.29 (d, AB system, $J = 9.0$, 4 Ar*H* azobenzene, trans isomer), 7.14 (d, AB system, $J = 8.0$, 2 Ar*H* azobenzene, cis isomer), 7.09 (d, AB system, $J = 8.0$, 2 Ar*H* azobenzene, *cis* isomer), 7.02 (d, $J = 7.5$, 4 Ar*H* calix, trans isomer), 6.84-6.73-m, 6 Ar*H*, cis isomer), 6.65 (t, $J = 7.5$, 2 Ar*H* calix, trans isomer), 6.55 (d, $J = 7.5$, 4 Ar*H* calix, trans isomer),), 6.39 (t, $J = 7.5$, 2 Ar*H* calix, cis isomer), 6.32 (t, $J = 7.5$, 2 Ar*H* calix, *trans* isomer), 4.48 (t, $J = 4.0$, 2 N=NArOCH_2, trans isomer), 4.22 (t, $J = 6.0$, 2 N=NArOCH_2, cis isomer), the remaining part of the spectrum belongs to both isomers: 3.83-3.76 (m, 10 CH_2), 3.72 (s, 4 ArCH_2Ar), 3.69-3.60 (m, 2 CH_2), 3.38 (m, 4 ArOCH_2). The ratio between trans/cis isomers was calculated 70:30 from the triplets at 4.30 and 4.22 ppm. FAB (+) MS *m/z* 981.3 (M^+). *Calcd.* for $C_{58}H_{64}N_2O_{12}$: C, 71.00; H, 6.57 *Found.* C, 71.26; H, 6.73.

15. $\varepsilon_{trans}/\varepsilon_{cis}$ was chosen equal to 7.4 with comparison to related compounds see: Shinkai, S.; Nakaji, T.; Ogawa, T.; Shigematsu, K.; Manabe, O. *J. Amer. Chem. Soc.* **1981**, *103*, 111-115.

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