COMMUNICATION

OBC
www.rsc.org/obc

Anion recognition by α-arylazo-*N*-confused calix[4]pyrroles†

Rong Gu,[a] Stefaan Depraetere,[a] Jan Kotek,[b,c] Jan Budka,[a,d] Ewa Wagner-Wysiecka,[e] Jan F. Biernat[e] and Wim Dehaen*[a]

[a] *Molecular Design and Synthesis, Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, B-3001, Leuven, Belgium. E-mail: Wim.Dehaen@chem.kuleuven.be; Fax: +32 16 327990; Tel: +32 16 327439*

[b] *Laboratory of Coordination Chemistry, Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, B-3001, Leuven, Belgium*

[c] *Department of Inorganic Chemistry, Charles University, Hlavova 8, 128 40, Prague 2, Czech Republic*

[d] *Department of Organic Chemistry, Institute of Chemical Technology, Technicka 5, 166 28, Prague 6, Czech Republic*

[e] *Department of Chemical Technology, Gdańsk University of Technology, Narutowicza 11/12, Gdańsk, Poland*

Received 27th May 2005, Accepted 24th June 2005

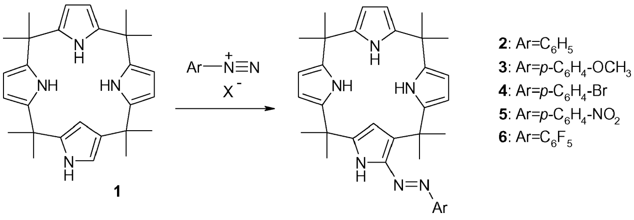
The first example of substitution reaction in the free α-position of *N*-confused calix[4]pyrroles is reported: azo-coupling with various arenediazonium salts. The obtained azocompounds were used for studies of their anion-binding properties by UV-Vis spectroscopy.

Calix[4]pyrroles, a well-known class of macrocyclic compounds discovered by A. Baeyer in 1886,[1] were recently used as a complexation agent in the recognition of anions[2] and neutral substrates.[3] In these complexes, guests are bound to the macrocycles by a system of hydrogen bonds to the pyrrolic nitrogen atoms. However, the stability of the complexes is not high enough for analytical use. To improve its binding ability, the basic calix[4]pyrrole skeleton was functionalized with various groups, especially in the *meso*-position of the macrocycle or the β-positions of the pyrrole units.[4] Furthermore, parent compounds and their complexes are spectroscopically silent to most analytical methods and the complexation can be followed only by NMR detection. Thus, calix[4]pyrroles must be substituted by highly-absorbing, luminescent or electrochemically-active sensing group.[5]

Substitution at the β-position of calix[4]pyrroles is often difficult and separation of the product mixtures is very problematic. On the contrary, substitution at the α-position of the pyrrole ring is easier. In our previous work, we described azo-coupling reactions at the α-position of dipyrroheptane in acceptable yields.[6]

Here we bring the results of expansion of this method for *N*-confused calix[4]pyrroles (compound **1**, Scheme 1), which have a similar skeleton to commonly used calix[4]pyrroles and contain one free α-position. To the best of our knowledge, the present work describes the first example of the α-substitution of *N*-confused calix[4]pyrroles, as the parent compound is not very stable and cannot be easily modified. Furthermore, the new ligands contain a chromophoric azo-group, which can visualize binding of anions in visible part of spectra, and four pyrrolic units, which can co-operate in anion complexation.

Recently, the ligands **3** and **5** were studied as sensors in liquid membrane electrodes for anionic and neutral molecules. Their high binding affinity and selectivity between isomeric nitrophenols was already reported.[7]



Scheme 1 Synthesis of α-arylazo-*N*-confused calix[4]pyrroles.

The starting *N*-confused calix[4]pyrrole **1** was prepared by condensation of acetone and pyrrole as already reported.[8]

Compounds **2**–**6** were prepared by azo-coupling of parent *N*-confused calix[4]pyrrole with an excess of the corresponding benzenediazonium chlorides or tetrafluoroborates in the presence of a base at low temperature (Scheme 1). Chromatographic work-up afforded the products in isolated yields about 50%.‡

^{1}H NMR analysis clearly proved that the substitution took place in the α-position of the pyrrole ring: the α-hydrogen signal of the starting compound (6.40 ppm) disappeared and the signal of the free β-hydrogen of the *N*-confused pyrrole ring was shifted upfield from 5.52 ppm to 4.62–4.80 ppm, depending on the nature of the substituent.

The complexation studies of ligands **1**–**6** were performed using UV-Vis spectroscopy in dichloromethane and acetonitrile as solvents at room temperature. To the solution of investigated derivatives **1**–**6** (concentration about 5×10^{-5} mol dm^{-3}), various volumes of the stock solutions (concentration about 4×10^{-2} mol dm^{-3}) of anionic guests (SCN^-, F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, HSO_4^-, NO_3^-) as the tetrabutylammonium salts were added accordingly to reported method.[9] The addition of thiocyanate, iodide, hydrogensulfate and nitrate did not cause any significant spectral change even when a high excess of anion was employed. Thus, these anions form no (or very weak) complexes with these macrocyclic hosts. On the contrary, additions of lighter halogenides (F^-, Cl^-, Br^-) and dihydrogen phosphate lead to a noticeable spectral change. As an example, the change in absorption spectra upon additions of tetrabutylammonium chloride to the acetonitrile solution of compound **2** is shown in Fig. 1. On addition of chloride, the maximum absorption at *ca.* 400 nm decreases, and a shoulder on the red-side of the absorption band appeared. Crossing of all spectra in one isosbestic point around 430 nm clearly showed the presence of only two light-absorbing species in solution, *i.e.*, the free host and the host–guest complex.

---

† Electronic supplementary information (ESI) available: examples of change in UV-Vis spectra of ligands upon addition of anionic guests and commented OPIUM-input and output files for calculations of stability constants. See http://dx.doi.org/10.1039/b507508d

DOI: 10.1039/b507508d

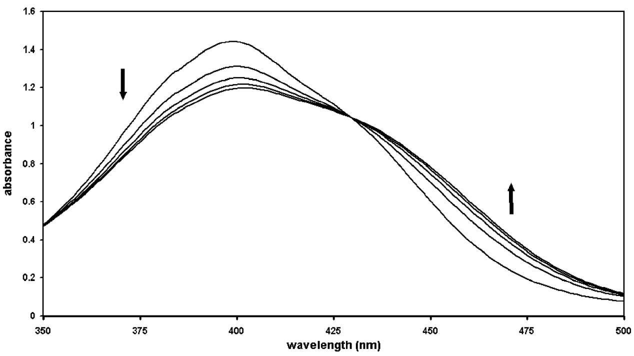


Fig. 1 The absorption spectra of the acetonitrile solution of **2** upon addition of chloride.

The determination of stability constant of the complexes of parent *N*-confused calix[4]pyrrole **1** is rather problematic, as the compound is not absorbing above 250 nm, and there is a very strong and sharp increase in absorption below this wavelength. Furthermore, no reasonable spectral change on addition of anions was found in dichloromethane. Thus, only spectral part close to the absorption edge (range 235–260 nm) can be used for the determination of the stability constants in acetonitrile solutions, and the calculations have big uncertainity because of a high slope of the spectra. Therefore, only one reasonably estimated value determined for chloride complex is given in Table 2.

From the spectral change upon addition of guest anions, the stability constants were determined using the OPIUM program package (refer to the electronic supplementary information).[10] Except for the **1**–Cl^- system (see above), all the calculations were done from a region of *ca.* 100 nm around the isosbestic point from several independent titrations and afforded the same values for each system (within estimated error). The stability constants of complexes formed in dichloromethane are summarized in Table 1, the corresponding stability constants in acetonitrile are compiled in Table 2. Stability constants for corresponding *meso*-dimethyl calix[4]pyrrole in deuterated dichloromethane were reported[2a] and are given for comparison in Table 1.

A special case is made by the fluoride anion, which forms very stable hydrogen bonds and polynuclear aggregates such as HF_2^-. Moreover, hydrofluoric acid is rather weak ($\mathrm{p}K_A = 3.2$[11]). On the reaction of fluoride with the most acidic ligands **5** and **6** with electron-withdrawing pentafluorophenyl or nitrophenyl substituents, it deprotonates the pyrrole aminogroup and forms two separate species L^- and HF_2^- according to the reaction:

$$HL + 2F^- \rightarrow L^- + HF_2^-$$

The spectra of the ligands in the presence of a high excess of fluoride are almost identical with those of the free ligand in the presence of tetrabutylammonium hydroxide (Fig. 2). Accordingly, the spectral change cannot be reasonably fitted by the assumption of a 1 : 1 ligand-to-fluoride stoichiometry, however an employment of a 1 : 2 ratio of reacting components gives very good fits to the experimental data.

Table 1 Stability constants of the host–guest complexes in dichloromethane

	Guest anion complex logβ[a]			
Ligand	NO_3^-	$H_2PO_4^-$	Cl^-	Br^-
Calix[4]pyrrole	—[b]	1.98(2)[c]	2.54(1)[c]	1.00(2)[c]
1	—[d]	—[d]	—[d]	—[d]
2	—[d]	—[d]	—[d]	—[d]
3	—[d]	—[d]	—[d]	—[d]
4	—[d]	—[d]	2.57(2)	—[d]
5	—[d]	3.10(5)	2.81(5)	1.28(4)
6	2.87(2)	4.45(6)	3.10(1)	2.29(5)

[a] β = [complex]/([free ligand] × [free anion]). [b] Not reported. [c] Taken from ref. 2*a* (measured in CD_2Cl_2, determined by ^1H NMR spectroscopy). [d] No spectral change upon addition of anion.

Table 2 Stability constants of the host–guest complexes in acetonitrile. N.m. = not measured

	Guest anion complex logβ[a]			
Ligand	NO_3^-	$H_2PO_4^-$	Cl^-	Br^-
1	—[b]	—[b]	3.01(8)	—[b]
2	—[c]	3.54(1)	3.40(1)	2.20(2)
3	—[c]	N.m.	3.40(1)	2.11(1)
4	—[c]	3.67(1)	3.51(2)	2.01(3)
5	—[c]	3.32(3)	3.48(5)	2.51(1)
6	2.11(2)	3.87(1)	3.23(2)	N.m.

[a] β = [complex]/([free ligand] × [free anion]). [b] Impossible to calculate (see text). [c] No spectral change upon addition of anion.

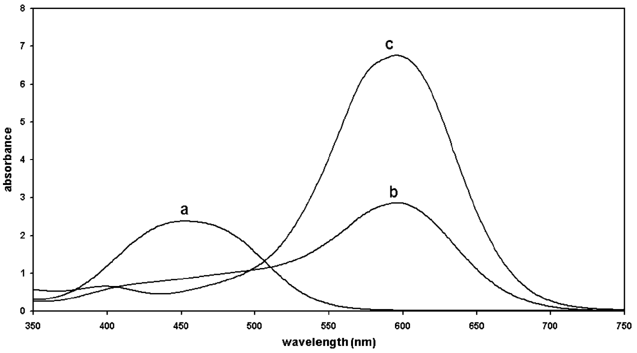


Fig. 2 The absorption spectra of acetonitrile solution of **5** (a) in free form; (b) after addition of 6 eq. NBu_4F; (c) after addition of large excess of NBu_4OH.

In the conclusion, the stabilities of the anion complexes with α-arylazo-*N*-confused calix[4]pyrroles are slightly higher than those of unsubstituted *N*-confused calix[4]pyrrole and calix[4]pyrrole itself (see Tables 1 and 2). Furthermore, the complexation can be easily followed by UV-Vis spectroscopy at low concentrations, as azo-derivatives are highly absorbing and colored compounds. The stability constants of host–guest complexes of α-arylazo-*N*-confused calix[4]pyrroles and anions are not much influenced by side-arm substitution in good donating-solvents such as acetonitrile. For a given anion, the values of the stability constants remain virtually the same (Table 2). On the contrary, in dichloromethane, the binding ability is noticeable increasing with the electron-withdrawing character of the side-arm substituents (Table 1). So, increasing the acidity of the pyrrole hydrogen causes a better interaction of the ligand with anions *via* hydrogen bonding. The most stable adducts are formed with dihydrogen phosphate, as this anion forms hydrogen bonds very readily and is the most basic of the anions used. The anions with low surface charge density such as nitrate or bromide form weak adducts. In the case of very basic fluoride anion and acidic ligands with nitrophenyl and fluorophenyl moieties, deprotonation of pyrrole ring was observed with formation of separate L^- and HF_2^- species.

We like to thank the F.W.O., The University of Leuven, and the Ministerie voor Wetenschapbeleid for continuing financial support. This work has been also funded by bilateral projects BIL03/09 and BIL03/10 between Flanders and the Czech Republic.

Notes and references

‡ Typical synthetic procedure for preparation of α-arylazo-*N*-confused calix[4]pyrroles: a solution of **1** (0.25 g, 0.58 mmol) in anhydrous THF (10 ml) was cooled to −40 °C. Sodium hydrogencarbonate (0.060 g, 0.71 mmol) and benzenediazonium tetrafluoroborate (0.125 g, 0.65 mmol) were added. After stirring at −40 °C for 30 min and

slow heating to room temperature, the solution was diluted by water and extracted by ethyl acetate. Organic extracts were washed twice with H_2O and dried over $MgSO_4$. Volatiles were evaporated and the crude product was purified by column chromatography on silica with petroleum ether : ethyl acetate (10 : 1) as the eluent.

1 A. Beyer, *Ber. Dtsch. Chem. Ges.*, 1886, **19**, 2184.

2 (*a*) P. A. Gale, J. L. Sessler, V. Král and V. M. Lynch, *J. Am. Chem. Soc.*, 1996, **118**, 5140; (*b*) J. L. Sessler and P. A. Gale, in *The Porphyrin Handbook, vol. 6*, ed. K. M. Kadish, K. M. Smith and R. Guilard, Academic Press, San Diego, CA, 2000, pp. 257–278.

3 W. E. Allen, P. A. Gale, C. T. Brown, V. M. Lynch and J. L. Sessler, *J. Am. Chem. Soc.*, 1996, **118**, 12471.

4 J. L. Sessler, P. Anzenbacher, Jr., K. Jursikova, H. Miyaji, J. W. Genge, N. A. Tvermoes, W. E. Allen and J. A. Shriver, *Pure Appl. Chem.*, 1998, **70**, 2401.

5 (*a*) P. A. Gale, P. Anzenbacher, Jr. and J. L. Sessler, *Coord. Chem. Rev.*, 2001, **222**, 57; (*b*) J. L. Sessler, S. Camiolo and P. A. Gale, *Coord. Chem. Rev.*, 2003, **240**, 17.

6 S. Depraetere and W. Dehaen, *Tetrahedron Lett.*, 2003, **44**, 345.

7 M. T. Nechita, S. Lotrean, J. Radecki, H. Radecka, S. Depreatere and W. Dehaen, *Pol. J. Food Nutr. Sci.*, 2003, **12/53**, 81.

8 S. Depraetere, M. Smet and W. Dehaen, *Angew. Chem., Int. Ed.*, 1999, **38**, 3359.

9 P. Anzenbacher, Jr., K. Jursikova, A. Shriver, H. Miyaji, V. M. Lynch, J. L. Sessler and P. A. Gale, *J. Org. Chem.*, 2001, **65**, 7641.

10 M. Kývala and I. Lukeš, *Chemometrics '95, (International Conference), book of abstracts*, p. 63 Pardubice, Czech Republic, 1995; the program package "OPIUM" is available (free of charge) at http://www.natur.cuni.cz/~kyvala/opium.html.

11 N. E. Vanderborh, *Talanta*, 1968, **15**, 1009.