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Information transfer in calix[4]arenes: influence of *upper rim* substitution on alkaline metal complexation at the *lower rim*

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ABSTRACT

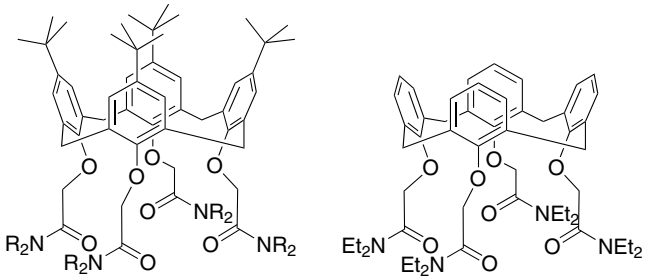
Novel calix[4]arene amides have been synthesized and their interaction with alkaline cations has been evaluated through extracting aqueous solutions of Li-, Na- and K-picrates with solutions of calix[4]arene amides in CH_2Cl_2. Electron-withdrawing groups on the *upper rim* of the calix[4]arene scaffold were found to have a negative effect on the absolute amount of metal ions extracted. The decreased extraction ability is accompanied by a higher selectivity towards sodium cations.

Ion channels play a key role in the transport of ions across cell membranes. The best known result of such transport is the difference in concentration of alkaline metal ions between the inside and the outside of cells: the extracellular concentrations of Na^+ and K^+ are 140 mM and 5 mM, respectively, whereas the intracellular concentrations in humans have about the opposite magnitude (5 mM and 150 mM).[1] Nature has developed very effective strategies to control this concentration difference in order to ensure a proper functioning of cells.

To gain more insight into the mechanism of these natural systems, supramolecular chemists try to develop artificial model systems mimicking the action of ion channels or ion transportation systems. Some of the major challenges are the design of synthetic channels with high metal binding selectivity, the possibility to include these compounds into artificial bilayers and the need to completely span this bilayer (~40 Å).[1] An approach to fulfil these requirements is to include molecules that have proven to bind ions with good selectivity into liposomal bilayers that serve as model compounds for cell membranes.[2] Amongst other good chelators such as crown ethers, some calix[4]arene derivatives are known to bind ions while maintaining their hydrophobicity and thus their ability to be included into bilayers. Therefore, it is not surprising that this class of compounds found some application in the design of artificial transmembrane ion transporters.[1,3]

Previously, it has been shown that *cone*-calix[4]areneamides are able to complex metal ions and therefore, they found applications in various fields.[4–14] Especially, calix[4]arenetetraamides (Scheme 1) show interesting features in the complexation of Li^+, Na^+ and K^+ ions and therefore, they were used as lead structures in artificial transmembrane ion transport systems.[1,15,16]

An easy and fast way to screen the binding abilities of this type of compounds is by performing extraction experiments of metal



1 a R = Et
b R = $(CH_2)_4$
c R = Pr
d R = Bu
e R = Allyl
f R = Propargyl
g R = Benzyl

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Scheme 1.

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salts from an aqueous solution into a solution of the metal binding compound in an organic solvent. The absolute values of the extraction efficiency are of minor importance for application as ion transporters, but the selectivity factors for certain ions are governing the desired properties. The preference of compounds for particular metal ions can be expressed by selectivity factors S. For example, the selectivity for alkaline metal ions by **1** can be given by the ratio of the mole percent extraction Na^+/mol % extraction M^+ (M = Li, K).[17] As shown in Table 1, variation of the N-substituents in **1** leads to significant changes in the selectivity in picrate extraction experiments.

The influence of *upper rim* substitution on the metal complexation at the *lower rim* is demonstrated by the selectivity factors of **2** compared to those of its alkylated derivative **1a**: both selectivity factors show that **2** has a higher selectivity for Na^+ than **1a**. This difference has been attributed to the larger conformational mobility of **2** and to its better solvation which decreases its binding ability towards alkaline cations.[18]

Table 1
Selectivity factors S for picrate extraction of alkali picrates from H_2O into CH_2Cl_2 at 20 °C

	S (Na^+/K^+)[a]	S (Na^+/Li^+)[a]
1a	1.3	1.5
1b	1.6	1.9
1c	1.2	1.3
1d	1.2	1.4
1e	1.4	2.3
1f	6.7	8.8
1g	1.4	2.2
2	1.7	2.5

[a] Values calculated from Refs. 17 and 18.

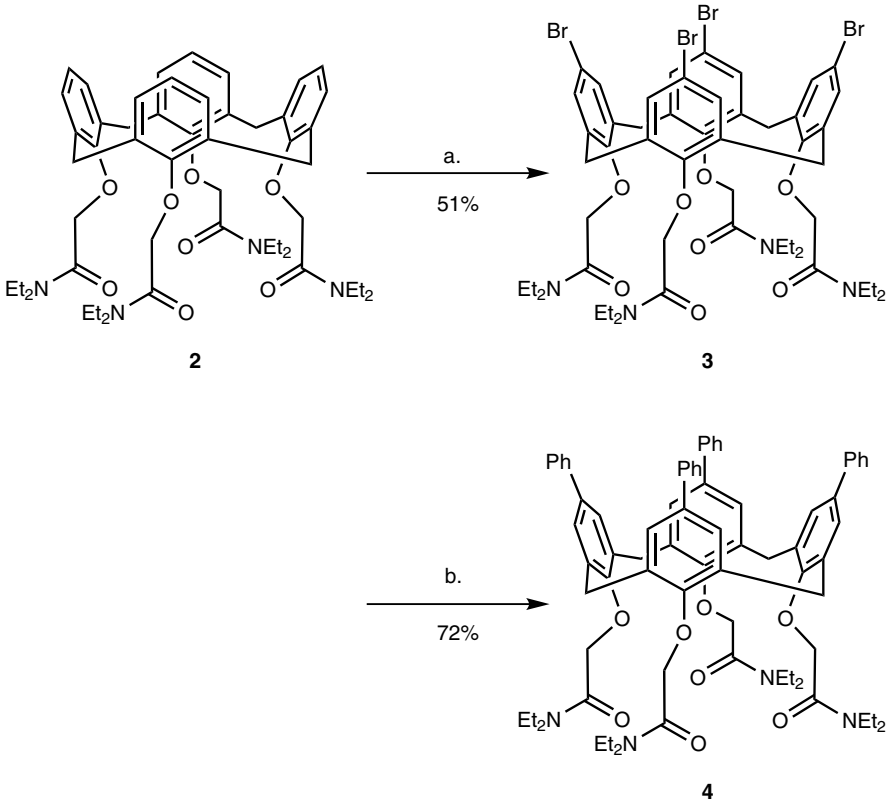
The finding that weaker complexation might lead to enhanced selectivity inspired us to synthesize new calix[4]arenetetraamides bearing different substituents on the *upper rim* of the skeleton. We introduced electron-withdrawing groups (Br, CN) to decrease the electron density at the phenolic oxygen atoms or phenyl rings to mimic steric effects that might occur upon changing the substitution pattern.

Tetrabromo-calix[4]arene **3** was obtained by bromination of **2** using *N*-bromosuccinimide (NBS). The $Pd(PPh_3)_4$-catalyzed Suzuki reaction with phenylboronic acid in a toluene/methanol mixture yielded **4** (Scheme 2).

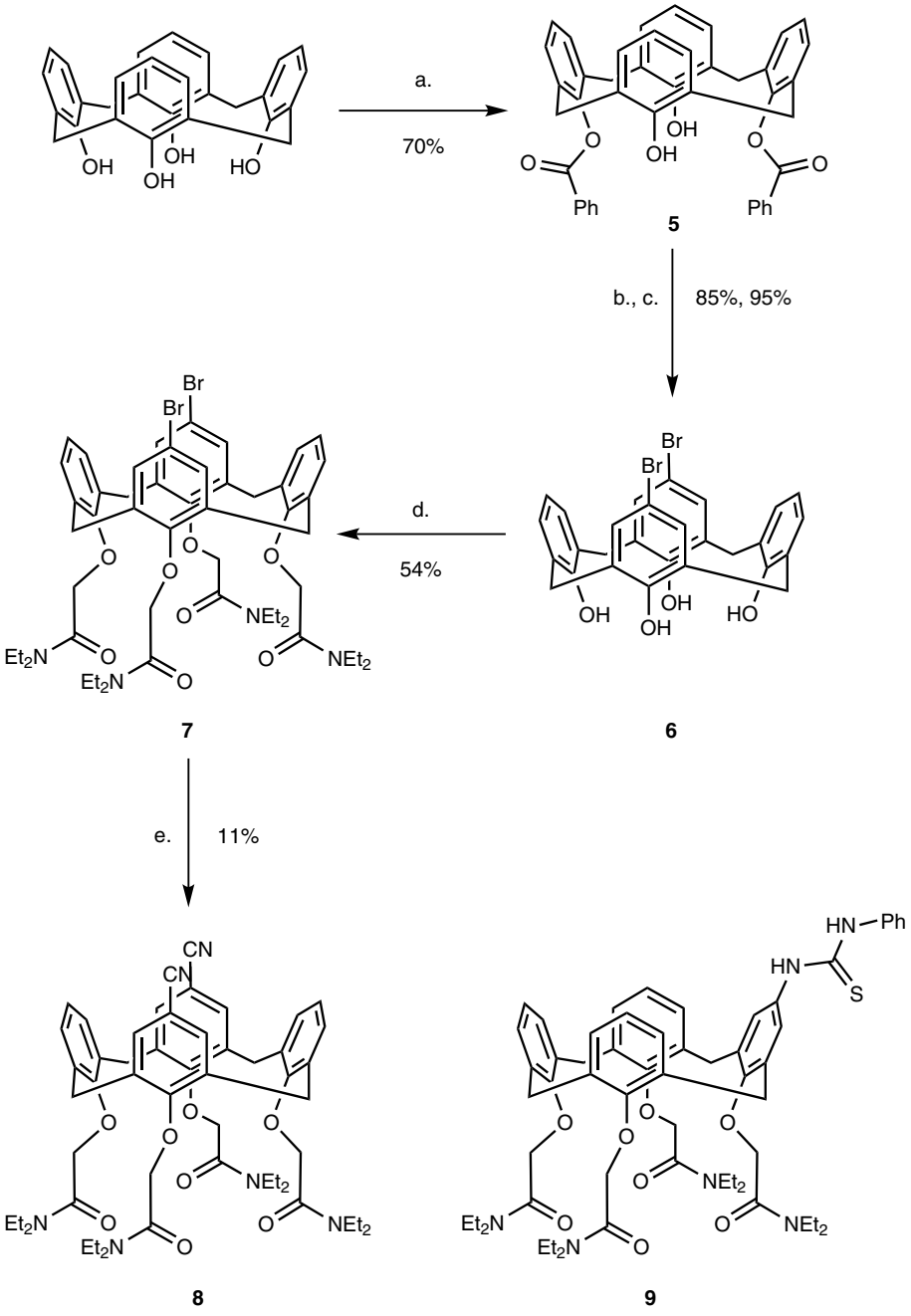
Diprotected calix[4]arene **5** was prepared by bisbenzoylation of tetrahydroxycalix[4]arene in distal position (Scheme 3). During the subsequent bromination to the dibromo derivative **6**, it turned out that the excess of bromine in the reaction mixture could be more easily removed by cyclohexene than with the commonly applied sulfur-based quenching agents. Deprotection in boiling ethanol/water proceeded smoothly, and calixarene **7** was obtained after alkylation with *N*,*N*-diethylbromoacetamide in dmf/thf using a standard protocol.[19]

N,*N*-Diethylbromoacetamide was prepared by a modified literature procedure enabling us to synthesize this compound on a large scale and with high purity.[20] Whereas a previous attempt of another group to synthesize dicyano-calix[4]arene **8** by a palladium-catalyzed reaction was not successful, we could obtain this compound using CuCN in NMP although the yield was rather poor.[19,21] We did not optimize this reaction further, since a sufficient amount of **8** could be achieved by this methodology.

Extraction of metal picrate salts from aqueous into organic solution is a powerful, fast, reliable and well-established method in supramolecular chemistry. From its early days until today, this technique found many applications.[22,23]



Scheme 2. Synthesis of **3** and **4**. Reagents and conditions: (a) NBS, butanone, 5 d, rt; (b) $PhB(OH)_2$, $Pd(PPh_3)_4$, Cs_2CO_3, $PhCH_3$, MeOH, 16 h, 70 °C.



Scheme 3. Synthesis of **7** and **8**. Reagents and conditions: (a) PhCOCl, TEA, MeCN, 3 d, rt; (b) Br_2, $CHCl_3$, 1 d, rt; (c) NaOH, EtOH, H_2O, 3d, 70 °C; (d) $BrCH_2CONEt_2$, NaH, dmf, thf, 4 d, rt; (e) CuCN, NMP, 22 h, 200 °C.

Our main interest lies in the complexation of physiologically relevant alkaline metal ions, so we performed the extraction experiments with lithium, sodium and potassium picrate. The extractions were performed from aqueous solution into dichloromethane at 20 °C (Table 2).[18]

The binding stoichiometry of the complex between the calixarenetetraamide and the metal ions is 1:1, which was exemplarily confirmed by a Job's plot analysis for **2** (data not shown) as well as by literature data.[16,21] The extraction percentages obtained for ligand **2** are consistent with the literature.[18]

To the best of our knowledge, the influence of chemical modifications on one side of the calix[4]arene backbone on the guest binding on its other side is rarely studied. An early example published by Ungaro and co-workers is the complexation of anions by **9** bearing a thiourea unit as a binding motive for anions and the tetraamide pattern also used in the present work.[21] In the presence of Na^+-ions, it binds anions stronger and shows a lower selectivity towards acetate than in the absence of Na^+-ions. The

Table 2
Mole percent extraction (%E)[a] of alkali picrates from H_2O into CH_2Cl_2 at 20 °C

	Li^+	Na^+	K^+	S (Na^+/Li^+)	S_{rel}	S (Na^+/K^+)	S_{rel}
2	38.5	91.4	55.	2.4	1	1.7	1
3	6.3	54.7	8.5	8.7	3.6	6.4	3.8
4	31.	87.7	36.5	2.8	1.2	2.4	1.4
7	17.5	78.1	23.3	4.5	1.9	3.4	2.0
8	5.6	41.8	4.1	7.5	3.1	10.2	6.0

[a] Mean value of at least three independent experiments. Errors of %E generally ⩽2%.

authors attributed this to an electron-withdrawing effect and rigidification of the calixarene backbone upon complexation. Furthermore, changes in the solvation might contribute to the observed increase in binding capability.[18]

The changes in the extraction behavior as shown in Table 2 are a consequence of the same phenomena, which make a quantitative evaluation impossible. Qualitatively, it can be concluded that also in **3**, **4**, **7** and **8** an 'information transfer' occurs between the two different rims of the calixarene backbone.

Comparison of the sodium selectivity of the benchmark ligand **2** with the functionalized ligands **3**, **4**, **7** and **8** shows that electron-withdrawing substituents increase the sodium selectivities roughly by a factor of 2–6. This can be rationalized by the electron-withdrawing effects of the bromo and cyano groups in **3**, **7** and **8**, which decrease the electron density at the phenolic oxygen atoms and therefore, weaken the binding ability of the receptors towards cations. The strong decrease in mainly Li^+- and K^+-binding leads to better Na^+ selectivity in all cases. The selectivity for Na^+ binding is qualitatively correlated with the number of such electron-withdrawing groups, for example, dibromo ligand **7** exhibits only about double the Na^+ selectivity compared to the unsubstituted ligand **2**, whereas tetrabromo-calix[4]arene **3** has about fourfold selectivity. Comparison of ligands **7** and **8** clearly shows that the mesomeric effect of the nitrile groups on the binding abilities of the phenolic oxygen atoms is more effective than the inductive effects caused by bromo substitution and leads to a better sodium selectivity towards both lithium and potassium. Dicyano-calixarene **8** is the only compound studied which shows a higher Na^+/K^+ than Na^+/Li^+ selectivity. This may be explained by additional steric reasons and eventually different solvations. The CN-group has a strong electron-withdrawing effect paralleled by less steric demand compared to the bromo group. Therefore, the ligand sphere located at the *lower rim* is less distorted by the nitrile substituent and the general sodium selectivity resulting from an increasing electron-withdrawing effect can be deployed more effectively.

We explain the small differences between **2** and **4** by mainly steric interactions of the phenyl groups with each other leading to a change in the geometry of the ligand. The repulsion between the phenyl rings seems to lead to a reduced size of the cavity spanned by the amide groups on the *lower rim* of calixarene **4**, since the biggest ion (K^+) experiences a significant decrease in affinity to **4**. Changes in solvation and minor electronic effects cannot be excluded.

In conclusion, we synthesized new calix[4]arene tetraamides and performed extraction experiments of biologically relevant alkaline metal ions in form of their picrate salts. The decreased binding ability towards these cations leads to enhanced Na^+ selectivity over Li^+ and K^+ in extractions. This selectivity is attributed mainly to the more dramatic decrease in Li^+ and K^+ binding compared to Na^+. However, this general trend is fine-tuned by a subtle interplay between electronic and steric effects exerted by the substituents located at the *upper rim,* and whose characteristics are transferred to the binding site at the *lower rim* of the calix[4]arene backbone acting as an electronic and steric 'hinge'. Besides, changes in the flexibility and solubilization of the various compounds can play an additional role in the metal binding. The new, more selective cation receptors or derivatives thereof have potential to be included into liposomes giving access to models for cation transportation across lipid bilayers.

Experimental: The extraction studies were performed according to Ungaro and co-workers.[18] Compound **2** was prepared using a slightly modified literature procedure (see Supplementary data).[24] Tetrahydroxycalix[4]arene is readily available following a known method.[25]

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Supplementary data

Supplementary data (synthetic details as well as characterization of all novel compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.128.

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