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Water-soluble calix[*n*]arenes as receptor molecules for non-polar substrates and inverse phase transfer catalysts

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Abstract—Water-soluble calix[*n*]arenes are powerful receptors for non-polar substrates in aqueous solution. The inclusion of the guests is studied by ^{1}H NMR titration experiments and molecular modeling studies combined with ab initio NMR shift calculations. The complexation is mainly enthalpically driven. The tested water-soluble calix[*n*]arenes are promising candidates for carrier molecules for the transport of non-polar substrates through bulk water as well as inverse phase transfer catalysts as proven for the Suzuki coupling of iodobenzene with phenyl boronic acid. In all cases the efficiency of the tested macrocycles is higher than that for β-cyclodextrin. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Organic reactions in aqueous solution[1,2] such as hydroformylation or carbonylation are of technical interest.[3] Water as a reaction medium is not only environmentally acceptable but also interesting from a mechanistic point of view. The hydrophobic effect, known as a principal driving force in biochemistry, can significantly enhance the rate of organic reactions in water.[1,2] However, the use of water as a solvent in organic synthesis is limited because of the low solubility of most organic substrates in aqueous media. One approach to overcome this problem is the use of counter or inverse phase transfer catalysis (iPTC). The organic substrate is transported by the catalyst from the organic into the aqueous phase in which the transformation occurs. Usually, cyclodextrins are used for this purpose.[4] Recently, calix[*n*]arenes[5,6] bearing polar substituents which render the macrocycle water-soluble, are studied as host molecules for amino acids,[7] ammonium salts,[8,9] fullerenes,[10,11] testosterone,[12] and small organic guests such as acetonitrile or ethanol[13,14] in aqueous solution. Driving forces for the complex formation are CH/π-,[15–18] electrostatic,[9,14,19] and aromatic interaction[20] as well as hydrophobic effects.[21]

Especially sulfonated calix[*n*]arenes are already tested as thermally and chemically very stable alternatives to cyclodextrins which can be used to inhibit[22] or enhance organic transformation in water, e.g. ester hydrolysis,[23] Aldol condensation,[24,25] nucleophilic substitution reactions,[26,27] and hydroformylation.[28,29]

Because of the great synthetic importance we choose the even in pure water as solvent highly efficient and reproducible Suzuki coupling reaction of aromatic halides[30,31] with boronic acids as a model to test calixarenes as inverse phase transfer catalysts.

2. Results and discussion

2.1. Complexation of aromatic guest by water-soluble calixarenes in aqueous solution

2.1.1. ^{1}H NMR titration experiments. First step in an inverse phase transfer catalysis process is the complex formation between substrate and catalyst. Therefore, association constants of various aromatic compounds with calixarenes **1–3** were determined in aqueous buffered solutions containing less than 1% of methanol by standard ^{1}H NMR

Table 1. Association constants for the complexation of aromatic guests with water soluble calixarenes

Guest	K_{ass} (L mol^{-1})			
	1[a]	**2**[a]	**3**[b]	**6**[a]
Ph–B(OH)$_2$ (**7**)	20.6	8.4	101.7	88.2
Ph–I (**8**)	59.6	55.7	402.0	>1000
Ph–Ph (**9**)	43.5	41.2	472.7	[c]
Ph–CH$_3$ (**10**)	24.9			140[33]
4-Cl–C$_6$H$_4$–CN (**11**)	40.0			152.5
Ph–CHO (**12**)	79.2			85.3
Ph–CH=CH–CHO (**13**)	77.8			38.4

[a] Aqueous buffered solution at pD=7.4.
[b] pD=1.4.
[c] Precipitation of the host–guest complex during titration experiment.

Keywords: calixarenes; solvent and solvent effects; Suzuki reactions; molecular modeling.

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Table 2. Complex induced shift for the complexation of **1** with aromatic guests in aqueous solution

	$\Delta\delta_H$[a] (ppm)						
	7	**8**	**9**	**10**	**11**	**12**	**13**
H_{para}	0.18	1.40	–[b]	0.56	– (=Cl)	2.42	2.38
H_{meta}	1.55	1.02	0.62	0.56	1.08	2.21	1.71
H_{ortho}	3.69	0.73	0.31	0.69	0.36	1.07	0.89
H_R	–	–	–	0.69	–	0.37	0.19

[a] $\Delta\delta$ denotes an up-field shift of the chemical shift of the observed proton.
[b] Signal hidden under host absorptions.

titration experiments (Tables 1–3).[8,32] The methanol is used for the addition of the guest molecule from stock solutions.

In all cases, an up-field shift of the aromatic guest protons could be observed during the titration experiments (Tables 2 and 3) indicating an inclusion of the aromatic moiety into the hydrophobic pocket of the water-soluble calix[*n*]arenes. Usually, the five aromatic protons are pointing inside and the functional group of the guest molecule is pointing outside the cavity due to hydrophobic and π/π-interaction. In contrast, when toluene is offered for the host–guest complexation, the methyl group of the guest molecule is located inside the cavity as proven by the highest complex induced shift of the CH_3-protons ($\Delta\delta$=0.69 ppm). By this orientation additional CH/π interactions already known for the inclusion of toluene in *p-tert*-butylcalix[4]arene[34] are possible. However, this additional interaction does not increase the binding strength significantly as indicated by similar association constants for toluene and boronic acid **7**. Presumably, the favorable CH/π interaction is compensated by a less effective π/π interaction compared to guests **7**–**9**. When 4-chlorobenzonitrile (**11**) is used as a guest, the chlorine substituent is placed inside the hydrophobic cavity. The arrangement of the chlorine atom near the aromatic bowl formed by the calixarene skeleton seems to be energetically more favorable than complexation via the nitrile functionality.

In general, the sulfonated calix[*n*]arenes **1** and **2** exhibit similar association constants compared to β-cyclodextrin except for iodobenzene as guest, which shows an about 20 times higher affinity to cyclodextrin than to the calixarenes. Tetra amino methyl substituted calix[4]arene **3** is a better receptor for aromatic guests as the sulfonated calixarenes **1** and **2**. Under the acidic conditions using for the titration experiment, the binding strength is presumably increased by additional cation/π-interaction[8] of the protonated amino methyl groups at the upper rim towards the aromatic moiety of the included guest. Thus, calixarenes bearing cationic groups at the upper rim seem to be ideal candidates for receptor molecules for neutral aromatic guests in aqueous solution.

Table 3. Complex induced shift for the complexation of **3** with aromatic guests in aqueous solution

	$\Delta\delta_H$[a] (ppm)		
	7	**8**	**9**
H_{para}	1.66	1.66	–[b]
H_{meta}	1.49	1.49	1.92
H_{ortho}	0.51	0.51	1.87

[a] $\Delta\delta$ denotes an up-field shift of the chemical shift of the observed proton.
[b] Signal hidden under host absorptions.

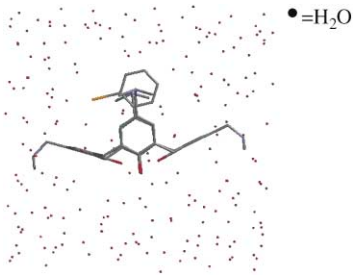


Figure 1. Calculated host–guest geometries for calixarene $[\mathbf{3}+4H]^{4+}$ with iodobenzene (MM+force field calculation).

In case of the complexation of iodobenzene (**8**) by calixarene **3**, temperature-dependent ^{1}H NMR measurements show that this inclusion is due to enthalpic reasons (ΔH=−(34.9±8.3) kJ mol^{-1}; ΔS=−(66.5±15.9) J K^{-1} mol^{-1}, T=300–335 K). This finding parallels similar data obtained for the inclusion of non-polar guest molecules into water-soluble cyclophanes which show strong enthalpically driven complexation in water as well.[35]

2.1.2. Molecular modeling. From complex induced shifts a qualitative picture of the geometry of the host–guest complex can be deduced. This interpretation can be supported by molecular modeling studies. Therefore, structures of hosts **3** with iodobenzene as a guest are modeled using the MM+ force field in a box of water molecules followed by molecular dynamics calculations to test the stability of the complexes following a published procedure.[8] Because the NMR titration experiment was performed at a pD=1.4 fully protonation of calix[4]arene **3** was assumed for the calculations. When the functional group of the iodobenzene guest is located in the cavity fast de-complexation occurs during the molecular dynamics simulation.

The obtained geometry for the $[\mathbf{3}+4H]^{4+}$-iodobenzene complex is shown in Fig. 1. The guest molecule is held by two bifurcated aromatic rings of the C_2 symmetrical calix[4]arene in a pincer-like arrangement. The substituent of the guest molecule lies roughly parallel to a plane formed by the four methylene bridges of the calixarene skeleton.

In a second computational approach we wanted to correlate experimental complex induced shifts obtained from the NMR titration experiments by extrapolating to 100% complexation to theoretically derived values to support any structural model.[36] Various starting geometries of host and guest describing a complexation of the guest molecule with the functional group pointing inside or outside the cavity, respectively, as well as an arrangement in which the calixarene host is covered by the guest were subjected to geometry optimizations using the Merck94 force field. The minima obtained were used as input structures for GIAO-DFT ^{1}H NMR chemical shift calculations of the guest molecule in the complex compared to the free guest itself. Thus, theoretically derived complex induced shifts

Table 4. Calculated (B3LYP/3-21G//MMFF) complex induced shift for the complexation of **1** with iodobenzene (**8**) in aqueous solution

	$\Delta\delta_H$[a] (ppm)			
Geometry	(**1**·**8**)A	(**1**·**8**)B	(**1**·**8**)C	Experimental
E_{rel}[b] (kcal mol^{-1})	1.88	0.00	1.38	–
H_{para}	0.77	2.04	0.27	1.40
H_{meta}	−0.31	1.64	0.86	1.02
H_{ortho}	0.89	0.74	0.94	0.73

[a] $\Delta\delta$ denotes an up-field shift of the chemical shift of the observed proton.
[b] Potential energy obtained from the force field (MMFF) optimization.

Table 5. Calculated (B3LYP/3-21G//MMFF) complex induced shift for the complexation of **3** with iodobenzene (**8**) in aqueous solution

	$\Delta\delta_H$[a] (ppm)				
Geometry	(**3**·**8**)A	(**3**·**8**)B	(**3**·**8**)C	(**3**·**8**)D	Experimental
E_{rel}[b] (kcal mol^{-1})	0.57	3.52	0.00	2.47	–
H_{para}	−0.44	3.28	1.44	−0.74	1.88
H_{meta}	0.04	2.54	2.98	−0.60	1.49
H_{ortho}	1.44	0.60	2.86	−0.41	1.51

[a] $\Delta\delta$ denotes an up-field shift of the chemical shift of the observed proton.
[b] Potential energy obtained from the force field (MMFF) optimization.

can be compared to experimentally observed values (Tables 4 and 5).

Up to now, only a qualitative correlation between experiment and theory can be drawn. This is probably due to neglected medium effect and neglected motion of the guest in the complex. However, most model geometries can be ruled out when comparing the complex induced shift pattern for the aromatic guest protons even in cases when the energetic difference between the structures is small. For both host molecules **1** and **3** a geometry (geometries (**1**·**8**)B and (**3**·**8**)C in Fig. 2, respectively) can be identified in which the experimentally observed complex induced shift pattern is similar to the calculated pattern supporting the structural models shown in Fig. 2. Furthermore, the host–guest-structure of $[\mathbf{3}+4H]^{4+}$-iodobenzene obtained by this methodology is very similar to the structure shown in Fig. 1.

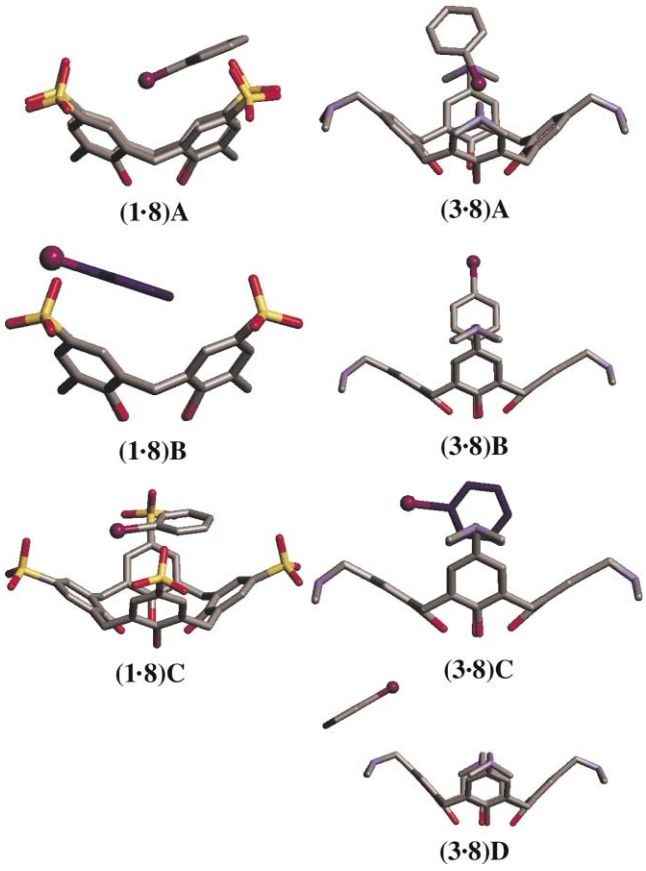


Figure 2. Calculated host–guest geometries for calixarene $\mathbf{1}^{4-}$ (left) and $[\mathbf{3}+4H]^{4+}$ (right) with iodobenzene; for computational details see text.

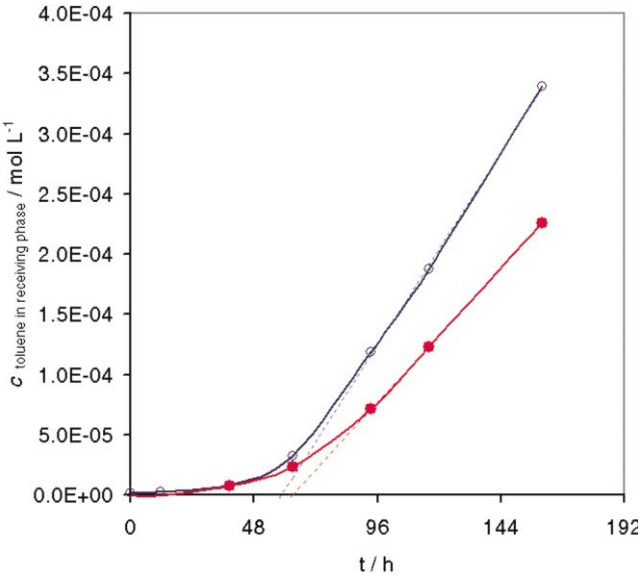


Figure 3. Transport of toluene through bulk water (pH=1) using tetra amino methyl calix[4]arene **3** (○) as artificial carrier and without any carrier (●).

2.2. Inverse phase transfer catalysis

Beside complexation the ability to cross the boundary between aqueous and organic phase is important for an efficient phase transfer catalyst. Therefore, water/chloroform partitioning coefficients log *P* were determined by UV spectroscopy for the macrocycles **1**–**5**. As expected, the highly charged macrocycles **1**–**3** show a high affinity towards the aqueous phase (log *P*=2.2 for **1**, 1.5 (**2**), 1.5 (**3**), −0.3 (**4**), −0.8 (**5**)), whereas mono- and di-aminomethyl substituted calix[4]arenes exhibit less hydrophilicity. The observed phase transfer of the macrocycles can be utilized to transport lipophilic substances along a concentration gradient through an aqueous solution. Therefore, standard U-type cell transportation experiments were carried out using calixarenes **1** and **3** as artificial carriers.[37] Pure toluene was used as the source phase. The aqueous phase containing the carrier molecule is magnetically stirred and the concentration of toluene transported through the bulk water to the receiving phase (*n*-hexane) is determined by UV spectroscopy. After an initial time of about 50 h a linear increase of toluene in the receiving phase is observable and from the slope of the linear part of a plot of the concentration of toluene in the receiving phase vs time the rate of transport of the guest across the aqueous phase is determined (Fig. 3 and Table 6).

Table 6. Relative rates of transport of toluene through the aqueous phase mediated by calixarenes **1** and **3** at room temperature

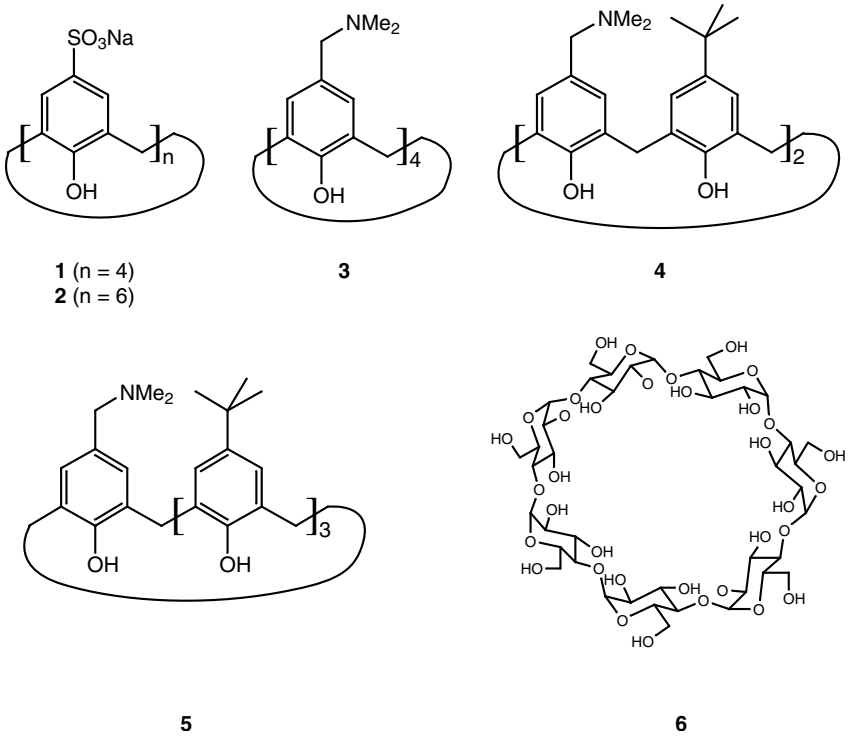
Carrier	pH	Rate of transport (10^6×mol L^{-1} h^{-1})	Relative rate of transport (10^6×mol L^{-1} h^{-1})
None	7	2.24	≡1
1	7	2.18	0.98
None	1	23.3	≡1
3	1	33.3	1.43

Surprisingly, sulfonated calixarene **1** does not increase the transport rate compared to the rate without any carrier, but addition of calix[4]arene **3** accelerates the transport of toluene through the aqueous phase by a factor of 1.4. Presumably, the association constant of calix[4]arene **1** with toluene is too small and the partitioning between organic and aqueous phase is not efficient enough to make it a good carrier. Both properties are more favorable in case of cationic calix[4]arene **3**.

To evaluate water-soluble calix[4,6]arenes **1**–**5** (Scheme 1) prepared by literature procedures[38–41] as inverse phase transfer catalyst we chose the Suzuki coupling of boronic acid **7** and iodobenzene (**8**) yielding biphenyl (**9**) in aqueous solution as the test reaction (Scheme 2). The ^{1}H NMR spectra of the calixarenes **1**–**3** at different concentrations showed no changes in the chemical shifts of host protons. Thus, micelle formation of these host molecules could be excluded in the concentration range used for the ^{1}H NMR titration experiments. The addition of macrocycles **1**–**6** to the reaction medium has only minor influence on the macroscopic polarity of the solvent as indicated by measuring the E_T-values[42] of the solvent prior and after addition of compounds **1**–**6** ($\Delta E_T < 1$).

First kinetic measurements of the Suzuki coupling (Scheme 2) in aqueous solution with added macrocycles **1**–**6** showed enzyme-like product inhibition indicating participation of the calix[*n*]arenes in the reaction. In every case yields >98% of biphenyl could be obtained.

Therefore, the following protocol was used to test the influence of water-soluble macrocycles **1**–**6** on the test reaction: All kinetic runs of the aryl–aryl coupling reactions were stopped at small levels of conversion (<10–15%) to exclude product inhibition effects, and the yields were determined by gas chromatography. Only parallel runs performed under identical conditions were compared and correlated to the yield obtained in a reaction without addition of any macrocycle (Table 7, entry 1). Thus, any additional influence of reaction conditions such as stirring rate or catalyst activity could be excluded. Besides iodobenzene itself, no additional organic solvent was used to



1 (n = 4)
2 (n = 6)

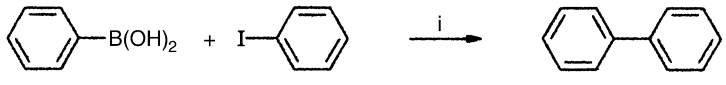
3

4

5

6

Scheme 1. Tested water-soluble calix[*n*]arenes.



7 **8** **9**

Scheme 2. Suzuki coupling reaction catalyzed by water-soluble calix[*n*]arenes; i H_2O, 3 equiv. base, 10% $PdCl_2$, P(*m*-C_6H_4–$SO_3Na)_3$.

Table 7. Relative yields of the Suzuki coupling of **7** and **8** in aqueous solution

Entry	Macrocycle (added equiv.)	Relative yield		
		No base	$HNPr_2$	Cs_2CO_3
1	–		≡1.0	3.4
2	**1** (10 mol%)		2.4	
3	**2** (10 mol%)		2.9	
4	**2** (25 mol%)		2.6	
5	**3** (10 mol%)	1.1	5.8	8.1
6	**3** (25 mol%)		7.5	
7	**4** (10 mol%)	0.1	2.2	5.5
8	**5** (10 mol%)	0.1	3.6	12.7
9	**6** (10 mol%)		2.1	3.4

avoid competition of such a solvent with the starting materials as potential guest molecules for the inclusion in the water-soluble hosts. The results of this approach are summarized in Table 7. As expected,[43] Cs_2CO_3 is a superior base compared to diisopropylamine, the initial yields being in general 2–3 times higher. Sulfonated calix[*n*]arenes **1** and **2** as well as β-cyclodextrin (**6**) show small effects on the effectiveness of the coupling reaction. Further addition of water-soluble macrocycle led to minor changes only (Table 7, entries 4 and 6). Amino substituted calix[4]arenes **3**–**5** are promising candidates for efficient phase transfer catalysis. The initial yields could be determined to be 4–8 times higher compared to the reaction in the absence of any macrocycle.

Surprisingly, the macrocyclic system with the lowest solubility in water, the mono-substituted calix[4]arene **5**, showed the highest effect on the initial reaction rate (Table 7, entry 8). In this case the yield was increased by a factor of 3.7 and 12.7, respectively, compared to the standard system (entry 1). The observed increase of initial yields seems to be determined by a balance of binding ability of the host molecule and phase-transfer properties as given by the water/chloroform partitioning coefficient $\log P$ of the used macrocycles. Furthermore, all tested calixarenes are superior to β-cyclodextrin.

3. Conclusion

In conclusion, water-soluble calixarenes are efficient receptor and carrier molecules for aromatic substrates in aqueous solution. This complex formation can be utilized to render substrates water-soluble and enhance aryl–aryl coupling reactions in water as a solvent by increasing the concentration of substrate in the reaction medium. The determination of partitioning coefficient, relative rates of transportation of non-polar substrates through bulk water and association constants between host and guests by ^{1}H NMR titration experiments is important for screening water-soluble macrocycles for their use as inverse phase transfer catalysts. Amino substituted calixarenes **3**–**5** are promising candidates for this purpose and are currently under investigation as inverse phase transfer catalysts of other organic transformations in water such as cycloaddition reaction or reductions.

4. Experimental

4.1. General method for Suzuki coupling of iodobenzene and phenyl boronic acid

To a suspension of iodobenzene (0.389 mmol, 79.36 mg), phenyl boronic acid (0.398 mmol, 47.43 mg) and base (0.972 mmol, 2.5 equiv., HN^iPr_2 or Cs_2CO_3) in water (4 mL) 10% or 25% of macrocycle were added as a solution in water (0.5 mL). Finally 2.5 mol% $PdCl_2$ and 5 mol% TPPTS were added from a stock solution in water (0.5 mL). The reaction mixture was stirred at rt and was stopped by dilution and freezing in liquid nitrogen after 30 min, respectively, with conversions less than 10–15%. The yields of biphenyl were determined by GC. All reactions were performed parallel to a reaction without added macrocycle at the same stirring rate and the yields obtained were referenced to this standard reaction.

4.2. ^{1}H NMR titration experiments

All experiments were performed in aqueous buffer solutions containing 0.83% methanol-d_4. ^{1}H NMR titrations with calix[*n*]arenes as host molecules were carried out as follows (400 MHz, T=293±2 K): The guest concentration was kept constant at $1.3–1.4\times10^{-3}$ mol L^{-1}. The guest solutions were added as a stock solution in methanol-d_4 (5 μL). The calixarene host concentration was varied from a ratio guest–host from about 0.8 to 15. Each experiment consisted of 15 points. In all cases the aromatic signals of the guest were followed, and association constants (K_a) were calculated using a non-linear curve fit of the observed chemical shifts.

4.3. Distribution coefficient

Distribution coefficient were determined by sonicating mixture of a 10^{-3}–10^{-4} mol L^{-1} solution of the corresponding compound in CH_2Cl_2 (2 mL) and water (2 mL) for 60 min. After phase separation, the remaining concentrations of the tested compound in the organic layer was determined using UV spectroscopy and compared to the initial concentration.

4.4. Transport experiments

Transport experiment were performed in a standard U-tube cell (d=2.0 cm) at rt using pure toluene (4 mL) as source and *n*-hexane (6 mL) as receiving phase. The aqueous phase (50 mL) consisted of aqueous buffer containing 10^{-2} mol L^{-1} of calixarene **1** or **3**. The concentration of toluene transported through the aqueous to the *n*-hexane phase was determined by UV-spectroscopy and transport rates (mol L^{-1} h^{-1}) were determined from the slope of the linear part of the transport curves (c(toluene in receiving phase) vs time).

4.5. Molecular modeling studies

Calculations of $[\mathbf{3}+4H]^{4+}$-iodobenzene were performed using the Hyperchem 5.0 program package.[44] Atomic charges used in the molecular mechanics optimization were calculated using PM3. In the first step, host, guest and finally the host–guest complex were optimized in the

gas phase. Then, a water box of 20×20×20 Å containing 215 water molecules was put around the structure obtained in the gas phase and minimization was performed by conjugate gradient method (Polak–Ribiere) until reaching a final RMS gradient of 0.05 kcal $Å^{-1}$ mol^{-1} in roughly 500 iterations. The optimization process was followed by a short molecular dynamics simulation over a trajectory of 5 ps at 300 K to test the stability of the obtained structures. Geometry optimizations for the combined molecular mechanics–NMR calculations were performed using the PC-Spartan Pro[45] program package. Various structures for host–guest complexes were optimized using the Merck94 force field under standard convergence criteria followed by frequency calculation to ensure minima structures. For calix[4]arene **1** a tetra anionic and for calix[4]arene **3** a tetra cationic species was assumed. These structures were used as input geometries for single-point GIAO/DFT NMR calculations (B3LYP/3-21G basis set) using Gaussian98.[46]

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