Molecular recognition of alkyl- and arylalkyl-amines in dichloromethane and chloroform by calix[4]-crown ethers

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The calix[4]-crown-6 ether **2** exhibited pronounced molecular recognition properties toward alkylamines. $-\Delta G°$ values obtained for the solvent extraction of alkylamines into dichloromethane by compound **2** ranged up to 9.7 kcal mol^{-1}. This binding strength generally decreased with the increasing size of the alkyl chain of the ammonium guests. ^1H NMR titrations of compound **2** with alkyl- or arylalkyl-ammonium guests in $CDCl_3$ revealed that the primary binding site is the central part of the crown moiety. Host **2** exhibited a much larger discrimination than the dibenzo-18-crown-6 ether, favouring linear over other isomeric amines. Transport selectivity between butyl- and *tert*-butyl-ammonium guests was found to be greater than a 70-fold excess, as assessed by the competitive transport through chloroform liquid membrane.

Calixarenes have attracted much research interest as versatile building blocks for the design of new biomimetic systems.[1] Over the last few decades, many intriguing host molecules have been synthesized utilizing calixarenes as a structural platform for the molecular recognition of many interesting guest molecules. Numerous attempts have been made to modify and endow unique binding characteristics to the crown ethers.[2] Of these, incorporation of a subcyclic unit and intraannular functionalization[3] of the crown ether backbone are widely used approaches.

Recently, Ungaro and Reinhoudt have synthesized calix[4]-crown ethers and related derivatives that have a versatile calix[4]arene moiety as a subcyclic unit of the crown ether, and characterized their ion-binding properties toward alkali and alkaline earth metal cations.[4,5] Several different host compounds based on the calix–crown framework, including selective chromoionophores for potassium ions[6] and double-calix–crowns,[7] have been prepared and their ionophoric properties were investigated. Along with these efforts, calix[4]-crown-5 was investigated as a biomimetic nucleophilic catalyst with transacylase activity.[8] However, few studies have been performed concerning molecular recognition of biologically important guests, such as biogenic amines.[9,10] We report here the molecular recognition properties of calix–crowns toward alkyl- and arylalkyl-amines, as a first step for the design of selective receptors for the biologically important amine guests. A preliminary report concerning molecular recognition toward butyalmines has already been published.[11]

Results and discussion

Extraction of alkyl and arylalkylammonium guests

The molecular recognition properties of calix–crowns were determined by the standard solvent extraction technique of alkylammonium picrate into dichloromethane at 25 °C.[12] The stoichiometry of the host–guest complex was determined using the Job's method[13] and found to be a 1:1 ratio using UV and ^1H NMR titration experiments. The employed guests are picrate salts of alkylamines ranging from ammonia to butylamines and arylalkylamines. Arylalkylamines were employed to give an insight into the binding properties for biogenic amines and related guests. For the purpose of comparison, an extraction experiment for dibenzo-18-crown-6 (**DB18C6**) was also performed.

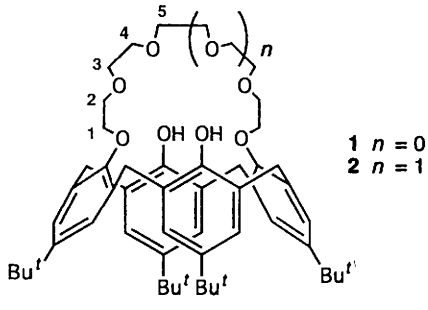
From the extraction experiments, the extraction constants K_{ex} were calculated according to the reported method.[14] Association constants K_a were obtained from the K_{ex} and the distribution constant K_d as shown in the following equation.[15]

$$K_a = K_{ex}/K_d$$

$$\Delta G = -RT \ln K_a$$

From the K_a value, the free energy of complexation was obtained and summarized in Table 1.

The calix[4]-crown-6 host **2** exhibited significant extraction efficiency and obvious discrimination between the various alkyl- and arylalkyl-ammonium picrates. The free energy of complexation $-\Delta G°$ for the extraction of alkylamines ranged from 6.7 to 9.7 kcal mol^{-1}, which is comparable to the value of *ca.* 9 obtained for **DB18C6**. The fact that the calix–crowns,



1 $n = 0$
2 $n = 1$

which are devoid of the lower crown ether structural part, exhibited such affinity for the alkylamines is interesting, although the hosts **2** and **DB18C6** have the same number of oxygen atoms in the binding site. Quite contrary to expectation,[5] however, the calix[4]-crown-5 host **1** exhibited poor extraction efficiency toward most alkylamines except for the ammonium guest. Examination of Corey–Pauling–Koltun molecular model suggests that the ammonium cation seems to interact efficiently with the host **1** by four hydrogen bonds; two with the ether oxygens of crown ether moiety and the remaining two with the phenol oxygens. The poor binding property of the host **1** for the alkylamines might be due to the rather narrow binding site and mismatching hydrogen bonds of calix[4]-crown-5 for the accommodation of the ammonium moiety of the guests.

The binding strength of host **2** decreases in the following sequence, R = :H > Me > Et ≈ Pr > Bu, for straight-chain

Table 1 Free energies of association ($-\Delta G°$, kcal mol^{-1}) for the solvent extraction of alkylammonium picrates[a]

Ligands	Alkylammonium picrates											
	R = H	Me	Et	Pr	Pr^i	Bu	Bu^i	Bu^s	Bu^t	Bn	1-PhEt	2-PhEt
1	9.48	7.87	7.18	7.43	7.16	6.64	6.47	6.27	*b*	6.28	5.71	5.50
2	9.74	8.99	9.09	8.42	8.06	7.96	7.71	7.49	6.96	7.91	6.74	7.29
DB18C6	9.29	8.73	8.11	8.39	8.40	8.11	7.95	8.03	8.19	8.17	7.81	7.33

[a] At 25 °C, H_2O:CH_2Cl_2 = 3.0 cm^3:3.0 cm^3, [Ligand] = 3.5 × 10^{-3} mol dm^{-3}, [$RNH_3^+Pic^-$] = 7.0 × 10^{-5} mol dm^{-3}. [b] Too low to be determined precisely by solvent extraction experiments. Bn = benzyl, PhEt = phenylethyl.

Table 2 ^{1}H NMR induced shifts ($\Delta\delta$) of calix–crown-6 upon complexation with alkyl- and arylalkyl-ammonium picrates[a]

Protons of host	$\Delta\delta$ of complexed host[b]					
	Bu	Bu^t	Bn	DFBn	NapMe	NapEt
Bu^t	0.09	−0.02	−0.07	−0.05	*c*	−0.02
Bu^t	0.02	0.01	0.02	0.01	0.02	0.01
CH_2(eq)	0.08	0.02	0.07	0.04	0.03	0.02
1-H	0.05	0.02	−0.02	*c*	*c*	*c*
2-H	−0.04	−0.02	−0.19	−0.09	−0.09	−0.07
3-H	−0.05	−0.01	−0.19	−0.05	−0.09	−0.03
4-H	−0.10	−0.03	−0.17	−0.10	−0.02	−0.07
5-H	−0.14	−0.04	−0.18	−0.11	−0.01	−0.08
CH_2(ax)	−0.24	−0.06	−0.20	−0.14	−0.02	−0.06
ArH	−0.18	−0.03	−0.08	−0.06	*c*	−0.02
OH	−0.33	−0.10	−0.23	−0.13	−0.03	−0.03
ArH	0.05	0.01	0.05	0.02	0.03	0.01

[a] [**2**] = [$RNH_3^+Pic^-$] = 5.0 × 10^{-3} mol dm^{-3} in $CDCl_3$ at 25 °C. [b] $\Delta\delta = \delta_{complexed} - \delta_{free}$. [c] Less than 0.01 ppm. Bn = benzyl, DFBn = difluorobenzyl, NapMe = naphthylmethyl, NapEt = naphthylethyl.

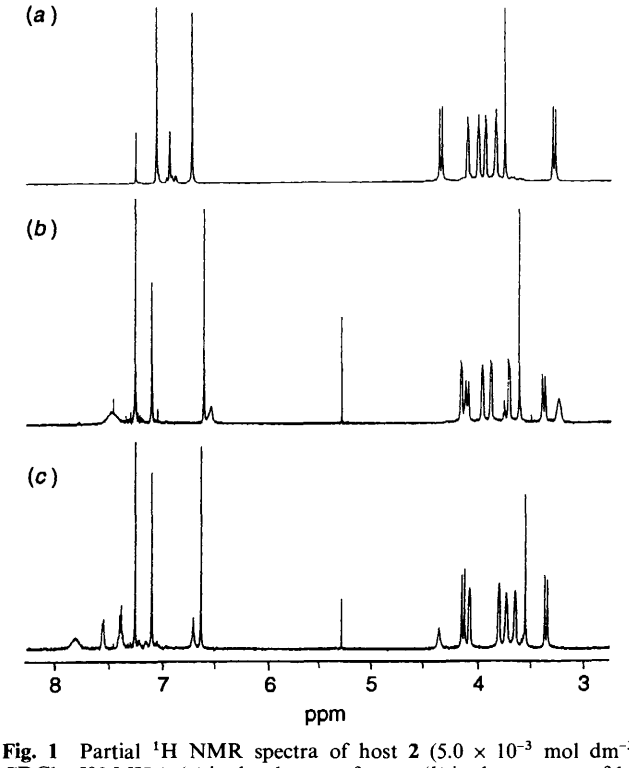


Fig. 1 Partial ^{1}H NMR spectra of host **2** (5.0 × 10^{-3} mol dm^{-3}, $CDCl_3$, 500 MHz): (*a*) in the absence of guest, (*b*) in the presence of 1.0 equiv. of butylammonium picrate, and (*c*) in the presence of 1.0 equiv. of benzylammonium picrate

alkyl amines. This trend closely follows the extraction behaviour of **DB18C6**. However, one particular thing to note is that the selectivity within structural isomers is more prominent compared with **DB18C6**. The selectivity pattern found for the isomers of butylamine is Bu > Bu^i > Bu^s > Bu^t, and for the propylamine is Pr > Pr^i, clearly exhibiting preference toward linear isomers. Selectivity between butyl- and *tert*-butyl-ammonium guests, estimated by the $\Delta\Delta G°$, is about 1 kcal mol^{-1} for host **2** compared with the almost negligible selectivity of **DB18C6**. That is attributable to the three dimensional nature of host **2** compared to the two dimensional coronand type structure of **DB18C6**.[16] The molecular recognition ability of the calix–crown might originate from, in addition to the primary interaction between the alkylammonium guest and the crown moiety, the lateral interaction between the alkyl moiety of ammonium guests and the bulky *p-tert*-butyl substituted benzene rings of the calixarene backbone.

Another interesting fact is the moderate discrimination between benzyl (Bn), 1-PhEt and 2-PhEt ammonium guests. The binding strength decreases in the following sequence: 2-PhEt > Bn > 1-PhEt. 1-PhEt with an extra α-methyl substituent should exhibit a larger steric interaction and result in a reduced binding efficiency, compared with either the 2-PhEt or the benzylammonium guests.

The idea of utilizing the calixarene backbone as a recognition handle for the molecular recognition of amines is well visualized by the extraction experiments. All the results obtained clearly indicate that the calix[4]crown-6 fusing the structural functions of calix[4]arene moiety and crown framework, is particularly superior to the discrimination of linear isomeric amines compared with **DB18C6**.

NMR measurements

To elucidate the solution structure of the present host–guest complex, ^{1}H NMR titrations of the host **2** with alkyl- and arylalkyl-ammonium picrates were performed in $CDCl_3$ at 25 °C. Upon interaction with the guest, the resonances of the host changed significantly (Table 2). Particularly, the resonances of the inner part of the crown moiety (especially the protons 4-H and 5-H) moved significantly upfield as shown in Fig. 1 for the case of the butylammonium guest, while the protons adjacent to the phenolic ether (proton 1-H) were relatively unchanged. This indicates that the guest interact

more strongly with the inner part ether oxygens of the crown ether moiety. Another thing to note is the shift behaviour of the bridging methylene protons. In the case of the butylammonium guest, for example, higher field resonance (δ 3.29), which is ascribable to the equatorial protons of the host,[17] shifted to a downfield position (δ 3.37, $\Delta\delta = 0.084$). The lower field one (δ 4.36), which is ascribable to the axial protons, moved to a higher field position (δ 4.12, $\Delta\delta = -0.24$). The aromatic protons were also affected, although the shift is less pronounced. The higher field one (δ 6.73) owing to the aromatic protons of the intact phenol moiety shifted upfield ($\Delta\delta = -0.18$) compared to the downfield shift ($\Delta\delta = 0.049$) of the lower field one (δ 7.07) containing the crown ether moiety. Furthermore, the Bu^t protons also moved towards the opposite direction upon complexation ($\Delta\delta = -0.09$ and 0.02, respectively). Other employed guests, such as *tert*-butyl-, benzyl-, difluorobenzyl-(DFBn), naphthylmethyl- (NapMe) and naphthylethyl-ammonium (NapEt) picrates also exhibit similar behaviour but the changes are somewhat less pronounced. One interesting thing to note is the changes in chemical shifts of the bridging methylene protons. As mentioned above, upon complexation the differences in chemical shifts are generally decreased (0.74–1.01 ppm) compared with the value of the free host (1.06 ppm). That might be due to the endo-rotation of the phenolic OH groups to the complexing calix–crown, forming somewhat flattened calixarene framework upon complex formation. The differences in chemical shifts of bridging methylene protons are known to decrease significantly with a fairly minor increase in the flatness of the calix[4]arene backbone.[18] All these observations strongly indicate that the central part of crown periphery is the primary binding site and the conformation of the calixarene moiety changes into a somewhat flattened cone form upon complexation with alkyl- and arylalkyl-ammonium guests.

The solution structures of the free and complexed host were also assessed from the ^{13}C NMR measurements. ^{13}C NMR chemical shift of the bridging methylene carbons of free host at 33.8 ppm indicates that the free calix–crown host preferentially adopts the cone conformation in chloroform solution.[19] Upon complexation with 1.05 equivalents of ethylammonium picrate, there is no significant change in this bridging carbon signal, which might indicate that the complexed host mainly adopts the somewhat flattened, cone shaped conformation, rather similar to the free host in solution. In this cone conformation, the underivatized phenol rings protrude outward relative to the mean plane of crown moiety, thus forcing the guest to interact with the phenyl and *p-tert*-butyl moiety, resulting in a lateral discrimination toward alkylammonium guests upon complex formation.

Transport experiments

To have more insight into the molecular recognition properties of the calix–crown ligands, we have performed competitive transport experiments of butylamines and arylalkylamines through a chloroform liquid membrane. After constant stirring of the organic membrane layer for 24 h, the receiving phase was removed and the amounts of transported amine guests were determined by both an ion selective electrode technique and ^1H NMR spectroscopy.

The transport efficiency of host **2** for the varying structures of butylamine decreases in the following order; Bu > Bu^i > Bu^s ≫ Bu^t, which is in good correlation with the results of the extraction experiments. The discrimination characteristic between Bu, Bu^s and Bu^i guests is moderate (Table 3). However, the discrimination between Bu and Bu^t guests is remarkable. In fact, the estimation of transported *tert*-butylamine was difficult due to the almost unresolved weak signal even with 500 MHz ^1H NMR spectrum. Furthermore, the resonance of Bu^t guest was incidentally overlapped with the C-3 methylene resonance of butylammonium guest. The selectivity obtained from the integration, although subject to error, is greater than 70-fold. The periphery of host **2** seems to be insufficient for accommodating *tert*-butyl guests with α-methyl substituents in competition with the other less sterically demanding butylammonium guests.

Table 3 Competitive transport of butylammonium perchlorates[a]

	Transport rates × 10^5 mol h^{-1}			
Carriers	Bu	Bu^i	Bu^s	Bu^t
2	17.2	9.01	4.17	0.24
DB18C6	10.4	6.25	5.42	3.83

[a] Source phase: 0.5 mmol each of butylammonium perchlorates in D_2O (5.0 cm^3). Membrane phase: 0.05 mmol carrier in $CDCl_3$ (15 cm^3).

In the case of the arylalkylamines, the transport efficiency was greater than that of butylamines, mainly due to the larger lipophilicity of the former. The transport efficiency decreased in the following order: 2-PhEt > Bn > 1-PhEt. However, the transport selectivity is not so significant; they are not larger than 2.0. For example, the selectivity ratio for the transport of 2-PhEt and benzylammonium guest by host **2** is 1.9 and 1.5, respectively, with reference to 1-PhEt. The larger lipophilicity of the employed arylalkylamines seems to be unfavourable for the precise discrimination by transport process in the present system.

Experimental

General

^1H and ^{13}C NMR spectra were obtained using a Bruker AMX 500 spectrometer. UV spectra were obtained using a Jasco V-550 spectrophotometer. Perchlorate ion concentration was determined by an Orion 901 Ionalyzer, using a perchlorate ion selective electrode (Orion 938100). The calix[4]-crown ethers **1** and **2** were prepared by the reaction of *p-tert*-butylcalix[4]arene with the appropriate oligoethylene glycol ditosylate in refluxing benzene, according to the reported procedure of Ungaro and co-workers.[5] Alkylammonium picrates were prepared by the neutralization reaction of the appropriate amine with picric acid in methanol and purified by recrystallization from methanol.[20] **DB18C6** was purchased from Aldrich and used without further purification.

^1H NMR titrations

^1H NMR titrations were performed in $CDCl_3$ using TMS as an internal standard. An aliquot of $CDCl_3$ solution of host (5.0×10^{-3} mol dm^{-3}) was treated with a suitable guest and the resulting changes in the ^1H NMR spectra were monitored after each addition of the guests (up to two equivalents).

Extraction experiments

Stock solutions (7.0×10^{-5} mol dm^{-3}) of alkyl- and arylalkylammonium picrate salts were prepared in deionized water. In centrifuge tubes equipped with a Teflon-lined screw cap, the aqueous stock solution of picrate guest (3.0 cm^3) and the calix-crown host solutions (3.0 cm^3, 3.5×10^{-3} mol dm^{-3} in dichloromethane) were placed and equilibrated for an hour in a thermostat at 25 °C. After 1 h, the whole mixture was extracted with a Vortex–Genie for 1 min. The procedure was repeated twice to ensure thermal equilibration and complete extraction. The resulting mixture was centrifuged to hasten the phase separation and the extraction efficiency was determined by measuring the absorbance of picrate salt in aqueous phase using a UV spectrophotometer.[12]

Transport experiments

Competitive transport experiments across the liquid membrane were performed at 25 °C using a U-tube (1.8 cm, i.d.) apparatus.[21] Deuteriated solvents were employed for the sake of convenience in ^{1}H NMR measurements. The source phase was either a mixture of four butylammonium perchlorates or a mixture of 1-phenylethyl- (1-PhEt), 2-PhEt and benzyl-ammonium perchlorates (each 0.50 mmol) in 5.0 cm^3 of D_2O and the receiving phase was 5.0 cm^3 of D_2O. Membrane phase was 3.0×10^{-3} mol dm^{-3} solution of carrier in 15 cm^3 of $CDCl_3$. The membrane phase was magnetically stirred at a constant speed of 200 rpm (with a tachometer). The total transport rate was obtained by measuring the concentration of co-transported perchlorate ion in receiving aqueous phase by an ion selective electrode technique. The individual transport rates of constituent guests were determined by the integration of characteristic resonances in the ^{1}H NMR spectrum (500 MHz) of the receiving phase.

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