Encapsulation of charge-diffuse peralkylated onium cations in the cavity of cucurbit[7]uril†

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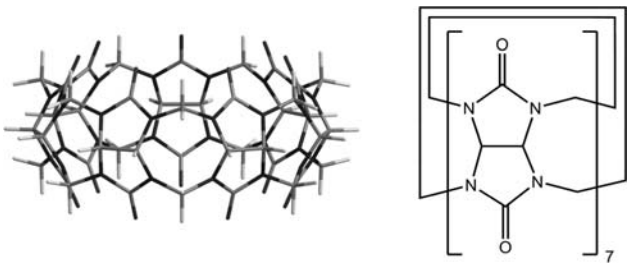
Cucurbit[7]uril binds, with considerable size selectivity, NR_4^+, PR_4^+, and SR_3^+ cations (R = Me, Et, ″Pr, ″Bu), with the smaller guests *inside* its cavity, rather than at the carbonyl-lined portals.

Tetraalkylammonium (NR_4^+), tetraalkylphosphonium (PR_4^+), and trimethylsulfonium (SR_3^+) cations have a number of important uses in chemistry, such as supporting electrolytes in non-aqueous solvents,[1] as phase transfer catalysts,[2] and as the cationic components of ionic liquids.[3] While these species possess a positive charge, the presence of the alkyl groups makes the cation more hydrophobic than with R = H, which give the salts their unique properties. Trimethylammonium groups on biologically important molecules such as acetylcholine and trimethyllysine cations are used as recognition units by proteins, which provide aromatic amino acids such as tryptophan to bind these substrates at the active site, using cation–π interactions.[4] While neutral ''parent'' synthetic macrocyclic hosts such as 18-crown-6,[5] β-cyclodextrin (β-CD),[6] and resorcin[4]arene[7] have weak or negligible interactions with these cations, the stability of host–guest complexes with an NR_4^+ guest can be enhanced by introducing anionic (ion–ion attractions), lipophilic (hydrophobic effects), or electron-rich (cation–π interactions) substituents to the macrocycle units.[8–14] With an estimated 72% of the positive charge of the NMe_4^+ cation residing on the 12 hydrogen atoms,[8] the host–guest complexes are believed to also employ $^+$N–C–H···O hydrogen bonding between the guest alkyl groups and the host oxygen atoms. In this Communication, we report the use of cucurbit[7]uril as a neutral host molecule capable of strong and size selective binding of the charge-diffuse tetraalkylated (NR_4^+, PR_4^+) and trialkylated (SR_3^+) onium cations in aqueous solution.

The cucurbit[*n*]urils (CB[*n*], *n* = 5–8, 10) are a family of cyclic host molecules comprising *n* glycoluril units bridged by 2*n* methylene groups.[15] The portals of the hydrophobic cavity are lined with ureido carbonyl groups, which afford ion–dipole, dipole–dipole, and hydrogen-bonding interactions with the guest. The CB[7] host molecule[16] (Scheme 1) has a cavity volume comparable to those of β-cyclodextrin and *p*-sulfonated calix[4]arene.[17] With cationic guests, the stability constants of



Scheme 1 Cucurbit[7]uril.

the cucurbit[*n*]urils are larger that those of the corresponding cyclodextrins, and can be several orders of magnitude larger when the guest is a dication. The CB[7] host in particular has demonstrated remarkably strong binding ($K_{CB[7]}$ = 10^8–10^{15} dm^3 mol^{-1})[18] towards guests such as cationic substituted ferrocenes[19] and organic (aromatic and adamantyl) cations and dications.[18]

With simple hydrophilic cations, such as protons, alkali metal and alkali earth cations and transition metal ions, the preferred binding location(s) on cucurbiturils are the carbonyl-lined portals, to take advantage of the ion–dipole interactions that may be established.[15] The binding of alkali metal cations on the portal(s) of cucurbit[*n*]urils has been demonstrated to significantly reduce the binding of a variety of guest molecules.[20] With cationic organic or organometallic guests, very strong binding is achieved when the cationic portion(s) of the guest can be positioned near the portals, while the more hydrophobic regions reside within the cucurbituril cavity, such as with the 1-trimethylammonioadamantane cation ($K_{CB[7]}$ = 1.71×10^{12} dm^3 mol^{-1})[18a] in which the NMe_3^+ group is located outside the CB[7] cavity. 1,1′-Bis(trimethylammoniomethyl)ferrocene maximizes these non-covalent interactions and forms an exceedingly stable host–guest complex with CB[7] (3×10^{15} dm^3 mol^{-1}).[19c]

Primary ammonium organic cations (RNH_3^+) and dications ($H_3NRNH_3^{2+}$) form very stable complexes with CB[*n*] in aqueous solution as a result of ion–dipole and hydrogen-bonding attractions[18,21] with the magnitude of $K_{CB[n]}$ depending on the size and shape of the R group. In the course of examining the CB[7] binding of dicationic guests with NMe_3^+ head groups, such as succinylcholine, we observed that the addition of a large excess of CB[7] resulted in the formation of a 2 : 1 host–guest species in which the CB[7] appeared to have abandoned the central portion of the guest in favour of encapsulation of the two NMe_3^+ end groups.[22] This unexpected observation prompted us to investigate the host–guest

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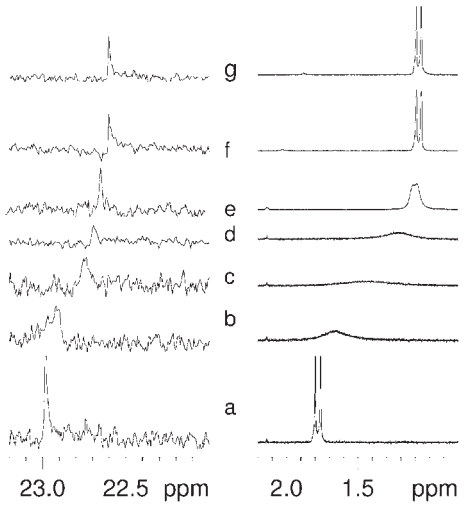

Fig. 1 ^{1}H NMR (right) and ^{31}P{^{1}H}NMR (left) titration of $P(CH_3)_4^+$ with CB[7] in D_2O; (a) no CB[7], (b) 0.21 eq, (c) 0.40 eq (^{1}H), 0.53 eq (^{31}P), (d) 0.67 eq, (e) 0.84 eq, (f) 1.01 eq and (g) 1.26 eq CB[7].

interactions between CB[7] and a series of NR_4^+, PR_4^+, and SR_3^+ guests in aqueous solution using ^{1}H and ^{31}P NMR spectroscopy, and to determine the stability constants by direct chemical shift titrations and competitive binding experiments in D_2O.[23]

Guest protons located within the cavity of cucurbit[*n*]urils are in a shielding environment and shift upfield upon guest inclusion ($\Delta\delta < 0$ ppm), while those located outside of the cavity and near the oxygen atoms of the portal carbonyl groups are deshielded, resulting in a downfield shift ($\Delta\delta > 0$ ppm) with respect to the free guest resonances.[19a] With the NR_4^+, PR_4^+, and SR_3^+ guests, the addition of CB[7] resulted in upfield shifts in all of the alkyl protons, as well as the central P atom in PR_4^+ (Fig. 1).

Depending on the nature of the guest used in this study, the guest exchanges were observed to range from fast (averaged free and bound guest resonances) to intermediate exchange (broadening of guest resonances, Fig. 1) on the NMR timescale. In all cases, a 1 : 1 host–guest stoichiometry was indicated by NMR titrations, with no evidence for 1 : 2 host–guest complexes through the binding of a second guest cation.

The limiting complexation-induced ^{1}H and ^{31}P chemical shift changes ($\Delta\delta_{lim}$) observed upon the formation of the CB[7] host–guest complexes are presented in Table 1.

The magnitudes of the upfield $\Delta\delta_{lim}$ for the alkyl protons suggest that the tetramethyl and tetraethyl onium ions are centered in the CB[7] cavity. As the alkyl group length increases, the methyl groups are required to be located closer to the portals, diminishing the upfield shift. The smaller $\Delta\delta_{lim}$ values for $N^nBu_4^+$, along with the broadness of the resonances at high [CB[7]], suggest that one or more "arms" of the guest may be located outside of the cavity at any given time. Configurations with two "arms" outside for $N^nPr_4^+$ and $N^nBu_4^+$ are supported by energy-minimization calculations.[23]

With stability constants of $<10^4$ dm^3 mol^{-1}, conventional ^{1}H (or ^{31}P) NMR titrations of the guest with CB[7] in D_2O could be carried out, while with larger stability constants, it was necessary to use competitive NMR binding experiments.[23]

Table 1 Complexation-induced chemical shift changes and stability constants for the host–guest complexes formed between CB[7] and the peralkylated onium guests at 25 °C in D_2O[23]

Guest	$\Delta\delta_{lim}$/ppm[a]	$K_{CB[7]}$/dm^3 mol^{-1}
$N(CH_3)_4^{+b}$	−0.72	$(1.2 \pm 0.4) \times 10^{5c}$
$N(CH_2CH_3)_4^{+b}$	−0.87, −0.44	$(1.0 \pm 0.2) \times 10^{6d}$
$N(CH_2CH_2CH_3)_4^{+e}$	−0.70, −0.40, −0.22	$(9.0 \pm 2.4) \times 10^{3c}$
$N(CH_2CH_2CH_2CH_3)_4^{+f}$	−0.28, −0.4, −0.2, −0.2	$(2.8 \pm 0.7) \times 10^{3g}$
$N(CH_3)_3(CH_2Ph)^{+b}$	−0.25(CH$_3$), −0.70(CH$_2$)[h]	$(2.5 \pm 0.6) \times 10^{8di}$
$P(CH_3)_4^{+b}$	−0.71, −0.38[j]	$(2.2 \pm 0.4) \times 10^{6d}$
$P(CH_2CH_3)_4^{+e}$	−0.72, −0.31, −5.77[j]	$(1.3 \pm 0.3) \times 10^{5d}$
$S(CH_3)_3^{+f}$	−0.66	$(3.4 \pm 0.6) \times 10^{4c}$
$S(CH_2CH_3)_3^{+f}$	−0.74, −0.47	$(5.2 \pm 0.9) \times 10^{6d}$
$Si(CH_3)_3CH_2NH_3^{+k}$	−0.72(CH$_3$)	$(8.88 \pm 1.41) \times 10^{8}$

[a] Protons are listed in order from central atom outwards. [b] Br^- salt. [c] From a competitive binding experiment using 1,2-phenylenediamine.[18a d] From a competitive binding experiment using 1,4-phenylenediamine.[18a e] Cl^- salt. [f] I^- salt. [g] From a ^{1}H NMR chemical shift titration. [h] $\Delta\delta_{lim}$ for Ph protons are −1.07(*o*), −0.78(*m*), and −0.47(*p*) ppm. [i] From a competitive binding experiment with 3-trimethylsilylpropionic acid.[18a j] Or central P atom. [k] Ref. 18*a*.

Competition experiments between various pairs of onium cations were found to be consistent with the individually determined $K_{CB[7]}$ values in all cases.[23] These onium cations, therefore, form a useful set of competitor guests for determinations of $K_{CB[7]}$, as they span a range of values, have simple ^{1}H NMR spectra, and are not subject to acid–base equilibria, as found with RNH_3^+ guests.

The stability constants are dependent on the nature of the central atom and the number and length of alkyl substituents on the guest cation (Table 1). The CB[7] has a preference for Et over Me for NR_4^+ and SR_3^+ and the opposite for PR_4^+, with trends of $PMe_4^+ > NMe_4^+ > SMe_3^+$ and $SEt_3^+ > NEt_4^+ > PEt_4^+$ in $K_{CB[7]}$. The trends in the $K_{CB[7]}$ values indicated that the internal cavity dimensions of CB[7] provide for significant size selectivity in the binding of the peralkylated onium cations. Replacement of one of the methyl groups in NMe_3^+ by a benzyl group results in a much higher binding constant (Table 1) as the benzyl group is preferentially encapsulated in the cavity, although the modest upfield shift for the methyl protons suggests that the NMe_3^+ group is also located within the cavity.

The stability constants for the $\{NR_4{\cdot}CB[7]\}^+$ host–guest complexes in aqueous solution (Table 1), with the strong selectivity for NEt_4^+ (Fig. 2), may be compared with trends for polyanionic hosts such as *p*-sulfonated calix[*n*]arenes (*p*-SO_3CA[*n*]), substituted anionic resorcin[*n*]arenes (RA[*n*]), a sulfonated cyclotetrachromotropylene, and two polycarboxylated cyclophanes, which employ electrostatic and cation–π interactions for complexation. These more flexible and "open-bowl" receptors display comparatively little selectivity, with the exception of the unsubstituted tetraanionic RA[4], which exhibits stability constants that are considerably smaller than with CB[7].

This study has shown that while hydrophilic cations, and the cationic portions of a variety of organic and organometallic guests, prefer to bind at the portals of cucurbiturils,[15] the more

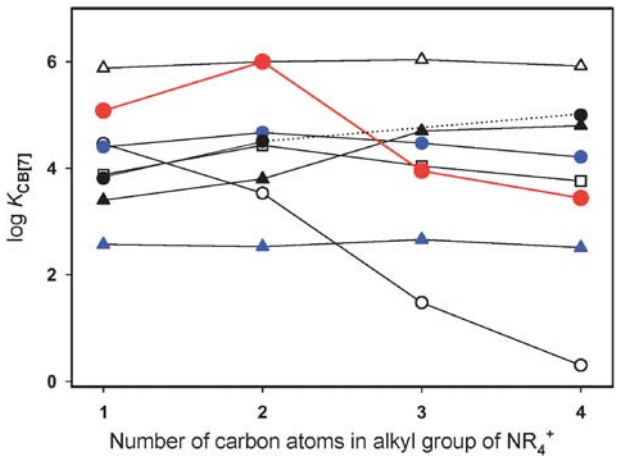

Fig. 2 Plots of log*K* against number of carbon atoms in the alkyl group on the NR_4^+ guest for CB[7] (●), *p*-SO_3CA[4] (●, pH 2, ref. 9*b*), *p*-SO_3CA[4] (▲, pH 2, ref. 9*c*), RA[4] (○, 0.5 mol dm^{-3} NaOD, ref. 10), CNRA[4] (Δ, ref. 11), sulfonated cyclotetrachromotropylene (□, ref. 12), Otto's disulfide-linked pentacarboxylated cyclophane (●, ref. 13) and Lehn's macrotricyclic hexacarboxylated cyclophane (▲, ref. 14).

hydrophobic and charge-diffuse peralkyl onium cations bind primarily within the cavity of CB[7]. The stability constants are dependent on the size and coordination number of the central atom and the size and hydrophobicity of the alkyl group. The latter factor provides an unprecedented degree of size selectivity in binding of NR_4^+ in a neutral host, without the requirement of aromatic subunits and anionic substituents.

Trimethylammonium head groups are important recognition units in acetylcholinesterase, in which cation–π interactions between acetylcholine and aromatic amino acids, such as tryptophan, are utilized. The present study indicates that other $RNMe_3^+$ guests should be strongly bound by CB[7]. We are currently investigating the binding of cholines, such as acetylcholine (Kim and co-workers[24] found that hexa(cyclohexyl)CB[6] binds acetylcholine ($K = 1.3 \times 10^3$ dm^3 mol^{-1}) with the NMe_3^+ group outside of the cavity), and their phosphonium analogs with cucurbit[7]uril in aqueous solution, and studying the subsequent effects on the kinetics of their hydrolysis reactions.[22]

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