Encapsulation of N_2, O_2, Methanol, or Acetonitrile by Decamethylcucurbit[5]uril$(NH_4^+)_2$ Complexes in the Gas Phase: Influence of the Guest on "Lid" Tightness

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Cucurbiturils, named after the Latin for "pumpkin," are pumpkin-shaped, cyclic glycoluril polymers. They are known to form inclusion complexes in condensed media, selectively binding guests of the proper size to fit within their cavities, with cations forming "lids" complexed to the rims to close the container.[1] Cucurbiturils are of current interest as encapsulating agents, as catalysts, and as "wheel" components of rotaxanes. Most reports to date have dealt with the 6-mer cucurbituril,[2] but recently synthetic procedures for the higher homologues have been developed.[3] Only a few reports of the methylated 5-mer (Figure 1), decamethylcucurbit[5]uril ($C_{40}H_{50}N_{20}O_{10}$, hereafter referred to as mc5), have appeared.[4,5] In solution, mc5 has been reported[5] to be a highly selective host for Pb^{2+}. Herein we describe the observation of guest@mc5$(NH_4^+)_2$ complexes (Figure 2) (where guest = N_2, O_2, methanol, or acetonitrile) via electrospray ionization Fourier transform mass spectrometry. Further, we show the complex can be opened in the gas phase by use of an ionophore, removing a "lid" cation and releasing the guest, and that the rate of this reaction depends on the size of the guest molecule, which likely influences how strongly the "lid" is attached.

All experiments were performed using a Fourier transform ion cyclotron resonance mass spectrometer (model APEX 47e; Bruker Daltonics; Billerica, MA) and a microelectrospray ionization source modified[6] from an Analytica (Analytica of Branford; Branford, MA) design. The instrument was controlled using a MIDAS[7] data system (National High Magnetic Field Ion Cyclotron Resonance Facility; Tallahassee, FL). Samples of mc5, obtained from IBC Advanced Technologies (American Fork, UT) about 1 mM in neat water, 50:50 methanol:water, 50:50 acetonitrile:water, or 50:50 ethanol:water, along with 2 mM ammonium acetate (Mallinckrodt; Paris, KY), were electrosprayed. A few samples were sprayed from 50:50 methanol-d_1:D_2O (99 and 99.9 atom %, respectively; both from Cambridge Isotope Laboratories; Andover, MA). The complex ions were also allowed to react with 18-crown-6 (Sigma; St. Louis, MO) introduced into the trapping region of the instrument via a direct-exposure probe, with partial pressures typically about 2×10^{-7} mbar. Isolation of reactant ions in the trap was performed using stored waveform inverse Fourier transform (SWIFT) techniques.[8] Reactant and product ion populations were measured as a function of reaction time to determine rate constants. Rate constants were determined both by isolating particular reactant ions, thus studying their reactions individually, and by studying a group of reactant ions concurrently.

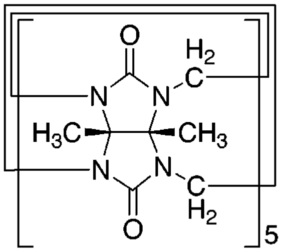

Figure 1. Structure of decamethylcucurbit[5]uril, mc5.

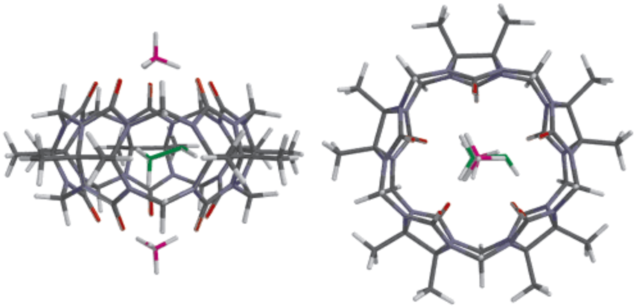

Figure 2. Side and top views (from HF/3-21G* calculations) of MeOH@decamethylcucurbit[5]uril$(NH_4^+)_2$. Ammonium ions (purple) hydrogen bond to carbonyl oxygens (red) on the upper and lower rims, closing the "container"; the methanol guest (green) is trapped inside.

Molecular models were built using *Macromodel*, ver. 7.1 (Schrodinger, Inc.: Portland, OR) and minimized using the MMFF94s force field included with *Macromodel*. Limited (1000 starting structures) Monte Carlo conformational searches were also carried out using this force field; these tended to find the same minimum-energy structure tens to hundreds of times. These minimum-energy structures were used as the starting point for full geometry optimizations at the semiempirical AM1 level (*MacSpartan Pro*, ver. 1.0.2; Wavefunction, Inc.: Irvine, CA) and at the ab initio HF/3-21G* level (*Gaussian 98*, ver. A.7; Gaussian, Inc.: Pittsburgh, PA).

Electrospray of mc5 along with ammonium acetate results in mass spectra composed of peaks corresponding to mc5 with one NH_4^+ attached, mc5 with two NH_4^+ attached, and the latter with a guest molecule included. The complexity of the resulting mass spectrum depends on the spray solvents employed. We have observed no water inclusion complexes, even when spraying from neat water. Spraying from methanol:water solutions results almost exclusively in observation of doubly charged, doubly NH_4^+-capped complexes with methanol included, whereas spraying from acetonitrile:water (Figure 3) yields peaks corresponding to "empty" doubly charged, doubly capped mc5 as well as guest-included complexes of N_2, O_2 (from air), or acetonitrile. The identity of the methanol guest was verified by spraying from 50:50 methanol-d_1:D_2O, which resulted in a shift of +0.5 *m/z* for the doubly charged complex ion (allowing for deuteration of the caps). We observed no ethanol guests when spraying from ethanol:water solutions but observed abundant "empty" doubly ammoniated complexes and doubly ammoniated complexes containing N_2 or O_2. The molecular formulas of the latter two complexes

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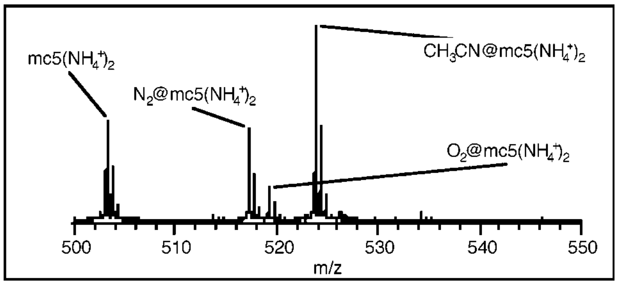

Figure 3. Mass spectrum resulting from electrospray of mc5/ammonium acetate from 50:50 acetonitrile:H_2O.

Table 1. Relative Rate Constants for NH_4^+ Removal from Mc5 Complexes by 18-Crown-6[a,b]

complex	prompt[c]	delayed[d]
$N_2@mc_5(NH_4)_2^{2+}$	1.9 ± 0.7	1.1 ± 0.1
$O_2@mc_5(NH_4)_2^{2+}$	2.2 ± 0.4	1.1 ± 0.1
methanol@$mc5(NH_4)_2^{2+}$	1.9 ± 0.1	1.3 ± 0.1
acetonitrile@$mc5(NH_4)_2^{2+}$	4.3 ± 2.1	1.3 ± 0.1

[a] All rates relative to that for $mc5(NH_4^+)_2 = 1.0$. [b] Reported errors are standard deviations for three or more measurements. [c] Obtained by fitting data with reaction times ≤1 s. [d] Obtained by fitting data with reaction times ≥1 s.

were verified by high-resolution measurements with poly(ethylene glycol) as an internal mass calibrant; all agreed with the predicted masses to within 5 ppm or better.

At the background pressure of the instrument (7×10^{-10} mbar) and ambient temperature, the various complexes exhibited less than 10% loss of guest over periods of up to 240 s in the trap, suggesting that they are true inclusion complexes with high intrinsic stabilities. However, in the presence of the ionophore 18-crown-6, NH_4^+ is abstracted by the crown, and the guest is lost from the $mc5(NH_4^+)$ product. Guest loss is rapid; double resonance ejection of the singly capped, guest-containing proposed (but not directly observed) intermediate, guest@$mc5(NH_4^+)$, results in no attenuation of the $mc5(NH_4^+)$ product, suggesting guest loss occurs more quickly than the time required to eject guest@$mc5(NH_4^+)$, about 65 μs in these experiments.

Fitting intensities as a function of time to exponentials allows determination of the rate constants for removal of NH_4^+. Some of the data [chiefly those for decay of the "empty" $mc5(NH_4^+)_2$] are not well described by a single exponential, but exhibit an induction period of roughly 1 s. The reason for the induction period is unclear, but may have to do with a slow isomerization of $mc5(NH_4^+)_2$ to a more reactive form as it enters the gas phase. "Prompt" and "delayed" rate constants (relative to that for the "empty" $mc5(NH_4^+)_2$ complex) for the various species are given in Table 1. The absolute efficiencies for "prompt" and "delayed" NH_4^+ abstraction from $mc5(NH_4^+)_2$ by 18-crown-6 are 14 ± 8 and 36 ± 13%, respectively. Interestingly, we observe that the rate of NH_4^+ removal is dependent on the presence and nature of the trapped guest.

Surprisingly, both "prompt" and "delayed" reaction rates for the guest@$mc5(NH_4^+)_2$ complexes are all faster than the corresponding rates for the "empty" $mc5(NH_4^+)_2$. The differences are greatest in the "prompt" rates, largely because the prompt rate for "empty" $mc5(NH_4^+)_2$ is slow. Further, the rate enhancement is least for the smaller guests (N_2 and O_2) and largest for the bulkiest guests (methanol and acetonitrile).

Table 2. Computed Bond Strengths for the Second Ammonium Ion[a]

	$D(NH_4^+$-guest@$mc5(NH_4^+))$		
	level of theory		
guest	MMFF	AM1	HF/3-21G*
none	−294.8	−155.8	−285.5
N_2	−292.5	−154.9	−280.6
methanol	−262.9	−147.9	−262.6
acetonitrile	−182.8	−123.1	−209.5

[a] kJ mol^{-1}

Some insight into this interesting kinetic behavior comes from computational study of these systems. Binding energies calculated at three levels of theory for the second ammonium ion, $D(NH_4^+$-guest@$mc5(NH_4^+))$, are given in Table 2. Although the size of the cucurbituril complex makes the use of high-level ab initio theory difficult (and probably makes the absolute binding energies inaccurate[9]), all of these lower-level approaches exhibit similar trends. Molecular mechanics, semiempirical, and Hartree−Fock calculations all indicate that inclusion of N_2 within the mc5-$(NH_4^+)_2$ container has little effect on how strongly the NH_4^+ lid is bound. However, inclusion of methanol or acetonitrile results in significant weakening of the bond, by about 22 or 75 kJ mol^{-1}, respectively (according to HF/3-21G* theory). Apparently, these guests are large enough that they interfere with optimum binding of the second capping NH_4^+; no hydrogen bonding between the guests and the caps is evident.

These preliminary results suggest cucurbiturils will be an interesting area for further gas-phase studies of host−guest systems. The binding cavity of mc5 is roughly comparable in size to that of α-cyclodextrin, but mc5 is much more rigid and has smaller portals than the cyclic polysaccharide, making size effects much more easily observed than for the cyclodextrin,[10−12] and facilitating computational studies. The ability of mc5 to include small molecules such as N_2, O_2, methanol, and acetonitrile suggests this host might be useful in gas purification or separation schemes.

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(9) 18-Crown-6 binds methylammonium with an enthalpy of 170 ± 17 kJ mol^{-1} (Meot-Ner, M. *J. Am. Chem. Soc.* **1983**, *105*, 4912−4915). The fact that 18-crown-6 removes NH_4^+ from $mc5(NH_4^+)_2$ indicates $D(NH_4^+$-mc5-$(NH_4^+))$ should be less than that value.

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