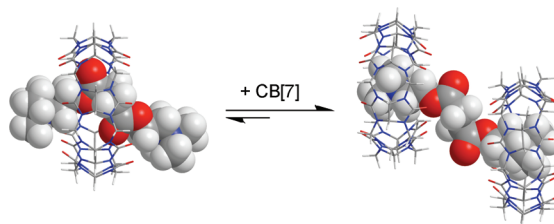# Host−Guest Complexes and Pseudorotaxanes of Cucurbit[7]uril with Acetylcholinesterase Inhibitors

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Received August 27, 2009

Pseudorotaxanes may be assembled in aqueous solution using dicationic acetylcholinesterase inhibitors, such as succinylcholine, BW284c51, and α,ω-bis(trialkylammonium)alkane dications (or their phosphonium analogues), as bolaform axles and cucurbit[7]uril (CB[7]) as the wheel. With the exceptions of the shorter $[(CH_3)_3N(CH_2)_nN(CH_3)_3]^{2+}$ ($n = 6, 8$) dications, the addition of a second CB[7] results in the translocation of the first CB[7], such that the hydrophobic $-NR_3^+$ and $-PR_3^+$ end groups (R = Me or Et) are located in the cavities of the wheels, while the central portion of the axles extend through the CB[7] portals into the bulk solvent. In the case of the $[Quin(CH_2)_{10}Quin]^{2+}$ (Quin = quinuclidinium) dication, the CB[7] host(s) resides only on the quinuclidinium end group(s). The 1:1 host−guest stability constants range from 8×10^6 to 3×10^{10} M^{-1} and are dependent on both the nature of the end group as well as the length and hydrophobicity of the central linker. The magnitude of the stability constants for the 2:1 complexes closely follow the trend observed previously for CB[7] binding with the NR_4^+ and PR_4^+ cations.

Introduction

One of the most efficient enzymes for catalyzing the hydrolysis of its physiological substrate is the serine hydrolase acetylcholinesterase,[1] which exhibits a k_{cat}/K_m ratio of $> 5 \times 10^9$ M^{-1} min^{-1} with the brain neurotransmitter acetylcholine (ACh). The substrate approach to the active site, which is located at the bottom of a deep and narrow "gorge", is limited only by diffusion control. This remarkable efficiency is attributed to the close proximity of (a) a Trp indole ring which participates in cation−π binding with the trimethylammonium group, (b) a Glu-His-Ser catalytic triad

for serine nucleophilic attack on the ester and for proton transfers, and (c) an "acyl pocket" containing Phe residues for recognition of the acetyl group.[1,2] The enzyme also has a peripheral binding site near the mouth of the active site "gorge" in which Trp and anionic Asp residues are located.[2]

There has been a growing interest in the roles of acetylcholinesterase (AChE) and the related butyrylcholinesterase (BuChE) in neurodegenerative diseases such as Alzheimer's disease (AD).[3] It has been known for a quarter of a century that a deficiency in acetylcholine (and, discovered more recently, an increase in levels of BuChE) is linked to the pathogenesis of AD,[3] and the standard therapy for mild to moderate AD is one of several AChE inhibitors, including rivastigmine, donepezil, tacrine, or galantamine. For moderate to severe AD, the *N*-methyl-D-aspartate receptor

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CHART 1.   Cucurbit[7]uril
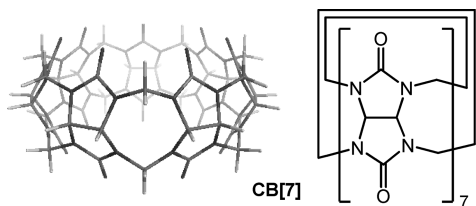
antagonist memantine (1,3-dimethyladamantamine) is used alone or in combination with one of the AChE inhibitors. The AChE inhibitors and memantine have been shown to slow the progression of the disease through acetylcholine regulation, as well as by providing anti-inflammatory benefits and increased antioxidant production.[4,5]

The inhibition of AChE can be accomplished irreversibly (organophosphates form a strong covalent bond with the serine residue in the catalytic triad), pseudoirreversibly (using carbamates, as the carbamylated serine is slowly hydrolyzed to regenerate the active enzyme), or reversibly (transient noncovalent binding through electrostatic interactions with the active and/or peripheral sites), depending on the nature of the interaction of the inhibitor with the enzyme site.[6] The reversible inhibitors may be classified as (a) active-site inhibitors directed toward the catalytic anionic subsite at the bottom of the gorge, (b) peripheral anionic site inhibitors which bind at the entrance to the gorge, or (c) elongated gorge-spanning inhibitors which bridge the two sites.[6] The extended bis(quaternary ammonium) dications, such as 1,10-bis(trimethylammonium)decane (decamethonium), succinylcholine (suxamethonium), and BW284c51 (1,5-bis(4-allyldimethylammoniumphenyl)pentan-3-one), are potent reversible "gorge-spanning" inhibitors that interact with both the active and peripheral sites, which are located 12−15 Å apart. Crystal structures of *Torpedo californica* acetylcholinesterase (*Tc*AChE) with the BW284c51[7] and decamethonium[8] inhibitors indicate that they occupy similar peripheral binding sites. Succinylcholine has been used as a potent nicotinic acetylcholine receptor (nAcR) blocker and depolarizing neuromuscular relaxant for over 50 years, although it is not without multiple side effects.[9]

We have recently observed that cholines, including acetylcholine, and their trialkylphosphonium analogues form stable 1:1 host−guest complexes with cucurbit[7]uril in aqueous solution.[10] The cucurbit[*n*]urils (CB[*n*], *n* = 5−8, 10) are a family of macrocyclic host molecules comprising *n* glycoluril units bridged by 2*n* methylene groups (Chart 1).[11] Their hydrophobic cavities and constrictive polar portals, lined with *n* ureido carbonyl groups, allow for the formation of exceedingly stable host−guest complexes in aqueous solution, particularly cucurbit[7]uril with cationic organic and organometallic guests. With the 1,1′-bis(trimethylammoniomethyl)ferrocene guest, for example, a host−guest stability constant of $K_{CB[7]} = 3 \times 10^{15}$ M^{-1} with CB[7] (Chart 1) has been determined from serial competitive binding studies.[12] The inclusion of a variety of cationic guests has been shown to significantly affect their chemical properties such as pK_a values,[13] chemical and photolytic stabilities,[14] and UV−vis absorption and emission spectra.[15] Nau and co-workers have devised enzyme assays based on fluorescent indicator displacement CB[7] detection of enzymatic substrates or products.[16] Mohanty and co-workers have found that the fluorescent dye thioflavin T, used extensively to probe the presence of amyloid fibrils, forms 1:1 and 2:1 host−guest complexes with cucurbit[7]uril, with binding constants of ∼10^5 and ∼10^3 M^{-1}, respectively.[17] Interestingly, this cationic benzothiazonium dye molecule also binds to the peripheral site of *Tc*AChE and can be used to probe substrate interactions at the catalytic site in the gorge.[18]

The vast majority of host−guest complexes of CB[7] with cationic guests, such as methylviologen,[19] assemble such that the cationic portion of the guest is located outside of the cavity, adjacent to the oxygens of the portal carbonyls, with the remaining hydrophobic portion of the guest positioned inside the cavity. We have shown that for the

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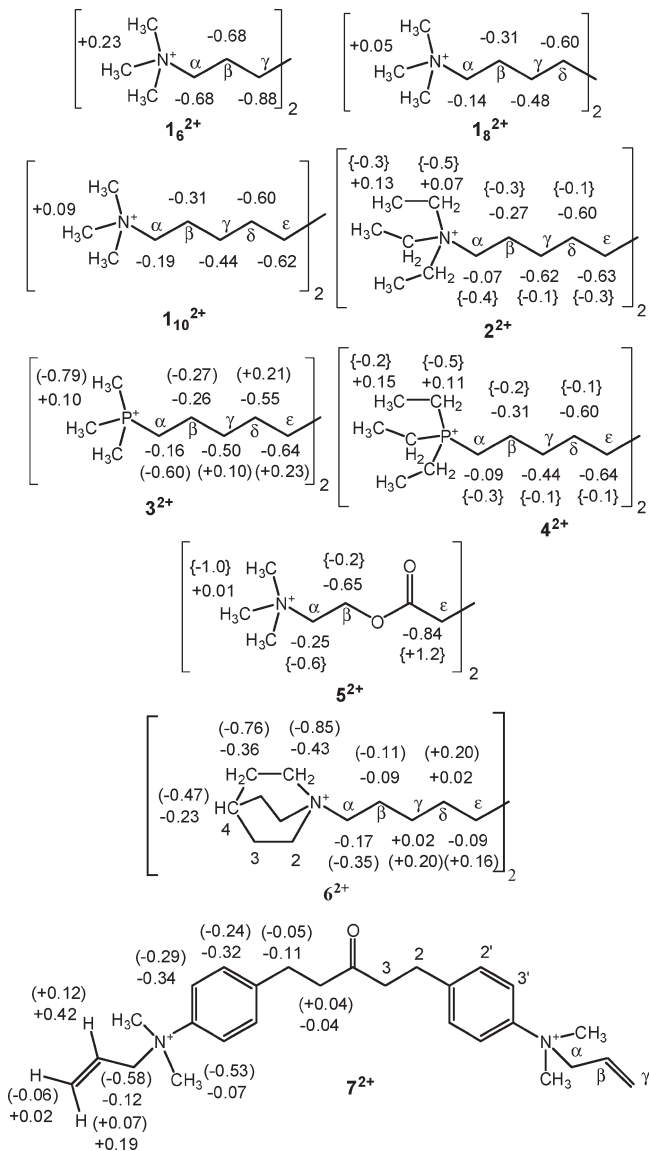
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CHART 2. Structures of the Dicationic Guests Used in This Study, along with the Proton Labeling and the Complexation-Induced Chemical Shifts ($\Delta\delta_{lim}$) upon the Formation of 1:1 and 2:1 Host−guest Complexes with CB[7][a]

^{a} The directly measured values of $\Delta\delta_{lim}$ for the 2:1 host−guest complexes are given in round braces, while the extrapolated values of $\Delta\delta_{lim}$ are given in curly braces.

[CH$_3$bpy(CH$_2$)$_6$bpyCH$_3$]$^{4+}$ guest, the first CB[7] resides over the hexamethylene chain, forming a [2]pseudorotaxane.[20] The subsequent addition of a second equivalent of CB[7] results in the original CB[7] being translocated such that both CB[7] hosts include the methylviologen end groups. Similar behavior has recently been observed with a series of substituted bis(pyridinium)alkane dications.[21] While it may be expected that the cationic end groups would prefer to be located near the oxygens of the polar portal-lining carbonyl groups, as observed in the case of ammonium-terminated guests (RNH$_3$$^+$),[11] the presence of the methyl or other alkyl

substituents make these groups more hydrophobic. We have recently reported that the NMe$_4$$^+$, NEt$_4$$^+$, PMe$_4$$^+$, and PEt$_4$$^+$ cations are encapsulated within the cavity of CB[7], with $K_{CB[7]} = (1.2 \pm 0.4) \times 10^5$, $(1.0 \pm 0.2) \times 10^6$, $(2.2 \pm 0.4) \times 10^6$, and $(1.3 \pm 0.3) \times 10^5 \, M^{-1}$, respectively.[22] Similar trends in the binding constants were determined with choline and its analogues with NEt$_3$$^+$, PMe$_3$$^+$, and PEt$_3$$^+$ head groups.[10]

In extending these studies, we sought to assemble [2]pseudorotaxanes of CB[7] with threads which possess both cationic end groups as well as neutral polar central regions, such as the acetylcholinesterase inhibitor succinyl-choline, with the expectation that the NMe$_3$$^+$ end group would position itself outside the cavity near the carbonyl oxygens on the portal, while the remainder of the guest would be located in the hydrophobic cavity, possibly employing quadrupole−dipole interactions between the guest carbonyl groups and the CB[7] cavity.[23] This study involves the use of a series of "bolaform"[24] guests with two cationic end groups, such as succinylcholine chloride, decametho-nium bromide, and BW284c51, which are potent acetylcho-linesterase inhibitors and depolarizing muscle relaxants. We had previously employed the decamethonium dication (and related dications with other polymethylene chain lengths) as the axle in the formation of [2]pseudorotaxanes with α-cyclodextrin[25] and found the replacement of the N centers with P resulted in a million-fold decrease in the rate constant for the formation of the [2]pseudorotaxane.

In the present study, we investigated the assembly of host−guest complexes and [2]pseudorotaxanes of cucurbit-[7]uril with a series of threads based on the decamethonium ($1_{10}$$^{2+}$) or succinylcholine ($5$$^{2+}$) structures containing NMe$_3$$^+$, NEt$_3$$^+$, quinuclidinium, PMe$_3$$^+$,[26] and PEt$_3$$^+$ end groups (Chart 2), characterized in solution by ^{1}H and ^{31}P NMR spectroscopy, as well as ESI mass spectrometry. The relative binding constants for the 1:1 and 2:1 host−guest and [2]pseudorotaxane complexes are rationalized in terms of the nature of the cationic end groups and the central linkers.

Results and Discussion

Host−Guest Complex Formation. The formation of host−guest complexes between cucurbit[7]uril and the dicatio-nic guests in Chart 2 has been established by using ^{1}H and ^{31}P NMR spectroscopy and ESI mass spectrometry. In addition to providing information about the stoichiometry of the host−guest complexes, the NMR spectra also provide an indication of the location(s) of the host molecule(s) with respect to the guest, through the direction of the complexa-tion-induced chemical shift change ($\Delta\delta_{lim} = \delta_{bound} - \delta_{free}$) of the guest nuclei.[11,25] The guest proton (and phosphorus)

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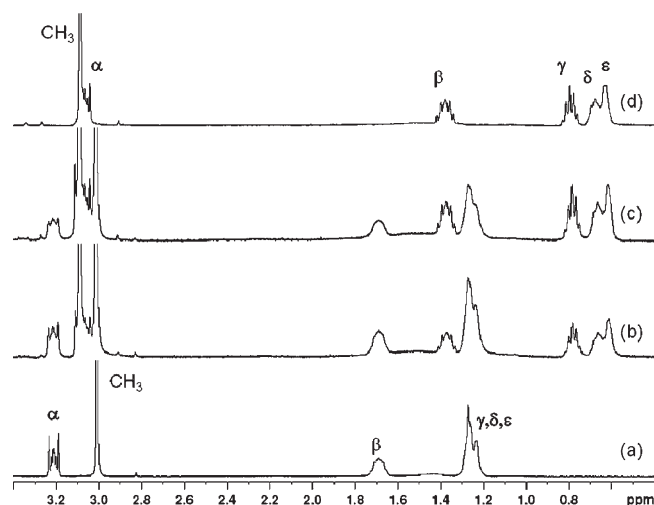
FIGURE 1. ^{1}H NMR spectra (400 MHz) of 1,10-bis(trimethyl-ammonium)decane (1_{10}^{2+}, 1.31 mM) in the presence of (a) 0.0, (b) 0.46, (c) 0.62, and (d) 1.57 equiv of CB[7] in D_2O.

FIGURE 2. ^{1}H NMR spectra (400 MHz) of the [$(CH_3)_3P(CH_2)_{10}$-$P(CH_3)_3$]$^{2+}$ dication (3^{2+}, 1.22 mM) upon the addition of (a) 0.00, (b) 0.43, (c) 0.98, (d) 1.48, and (e) 3.08 equiv of CB[7] in D_2O.

resonances which exhibit upfield chemical shifts ($\Delta\delta < 0$ ppm) signify the location of these nuclei within the host cavity, while downfield shifts ($\Delta\delta > 0$ ppm) are associated with positions outside of the cavity near the carbonyl-lined portals. The addition of 1 equiv of CB[7] to solutions of the dicationic guests (with the exception of guest 6^{2+}) in aqueous solution resulted in the formation of [2]pseudorotaxanes, with the host residing primarily over the central linker. Figure 1 shows the changes in the proton resonances of the 1,10-bis(trimethylammonium)decane dication (1_{10}^{2+}) in the presence of increasing equivalents of CB[7]. The limiting chemical shift changes for the guests in this study are given in Chart 2. The $\Delta\delta_{lim}$ values for the guest proton resonances indicate that the NR_3^+ or PR_3^+ end groups (small downfield shifts in the methyl resonances) are located outside the host, near the portal oxygens. The values observed for {1_8·CB[7]}$^{2+}$ are in good agreement with those reported previously by Bali et al.[27] Exchange between the free and complexed forms of the guests is slow on the ^{1}H NMR time scale, with distinct resonances for the protons of the free and bound guests being observed. As the central chains of the guests are generally longer than the axial length of the CB[7] cavity itself, the host likely moves back and forth between the ion−dipole interactions with the cationic quaternary ammonium or phosphonium moieties at either end of the [2]pseudorotaxane axle.

With the shorter 1_6^{2+} and 1_8^{2+} guests, the addition of excess CB[7] (beyond 1 equiv) has no noticeable effect on the ^{1}H NMR spectrum of the [2]pseudorotaxane, while only small changes are seen with the 1_{10}^{2+} guest. With guests 2^{2+}, 3^{2+}, 4^{2+}, 5^{2+}, and 7^{2+}, however, adding excess CB[7] to the [2]pseudorotaxane results in varying changes to the positions of the guest proton resonances. Figure 2 illustrates these changes for the [2]pseudorotaxane containing the 3^{2+} axle. The guest proton resonances exhibit intermediate to fast exchange behavior (peaks represent the average chemical shifts of the bound and free guests), and the magnitude and direction of the chemical shift changes (Figure 2) suggest the
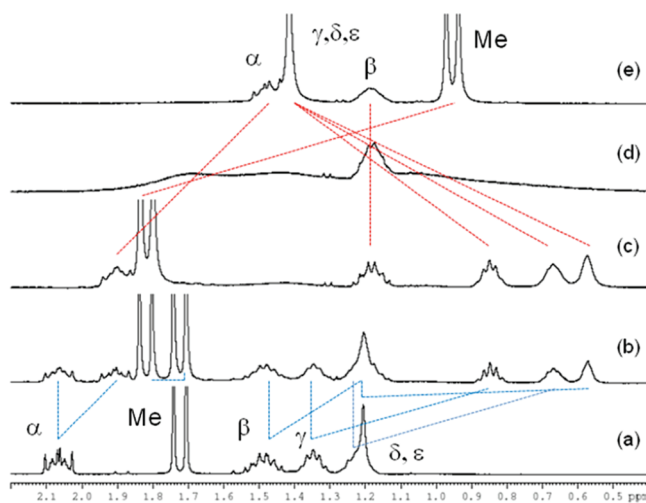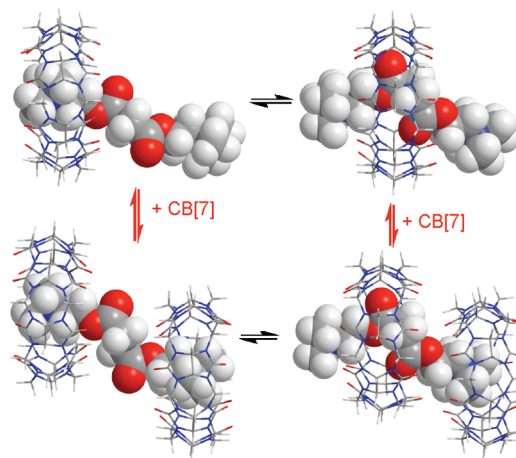
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SCHEME 1. Formation of the [2]Pseudorotaxane and 2:1 Host−guest Complex with CB[7] and Succinylcholine after Initial Formation of the 1:1 Complex (Upper Left)

conversion of the [2]pseudorotaxane to either a dumbbell-shaped 2:1 host−guest complex, with the cationic NR_3^+ or PR_3^+ end groups residing in the two CB[7] cavities (Scheme 1), or a [2]semirotaxane, with the second CB[7] encapsulating one end of the guest. With choline, acetylcholine, and their phosphonium analogues, we have also observed upfield shifts for the methyl resonances of the quaternary center upon host−guest complex formation with CB[7], indicating that the cationic center resides within the host cavity.

In the cases of the PMe_3^+- or PEt_3^+-capped guests, the ^{31}P NMR spectra were also consistent with the initial formation of a [2]pseudorotaxane followed by its conversion to the 2:1 host−guest complex, as shown in Figure 3 for guest 3^{2+}. The initial [2]pseudorotaxane formation resulted in a small up-field shift of −0.06 ppm (3^{2+}) and −0.1 ppm (4^{2+}), followed by much larger upfield shifts of −0.65 ppm (3^{2+}) and ∼ −3 ppm (4^{2+}), when the trialkylphosphonium groups were placed in the CB[7] cavities in the 2:1 complex. These latter quantities may be compared with the $\Delta\delta_{lim}$ values of −0.38 and −5.77 ppm

FIGURE 3. ^{31}P NMR spectra (162 MHz) of the $[(CH_3)_3$-$P(CH_2)_{10}P(CH_3)_3]^{2+}$ dication (3^{2+}, 1.22 mM) upon the addition of (a) 0.00, (b) 0.23, (c) 0.55, (d) 0.84, (e) 1.16, (f) 1.33, (g) 1.78, (h) 3.98, and (i) 4.98 equiv of CB[7] in D_2O.

FIGURE 4. ^1H NMR spectra (400 MHz) of the BW284c51 dication (7^{2+}, 1.03 mM) with (a) 0.0, (b) 0.26, (c) 0.49, (d) 0.72, (e) 0.93, (f) 1.12, (g) 1.31, (h) 1.56, (i) 1.80, (j) 2.08, and (k) 3.24 equiv of CB[7] in D_2O.

observed previously for the PMe_4^+ and PEt_4^+ guests, respectively, with CB[7].

With guest 6^{2+}, the replacement of the trialkylammonium end groups with quinuclidinium groups results in very strong binding to the end groups at the expense of the central decamethylene linker. The quinuclidinium protons as well as the α and β protons of the decamethylene chain experience upfield shifts, while the protons in the central portion (γ, δ, and ε) shift downfield. The two binding processes exhibit slow exchange behavior with the $\Delta\delta_{lim}$ values for the 1:1 host–guest complex being approximately one-half of those for the 2:1 complex (Chart 2). The limiting chemical shift changes for the 2:1 host–guest complex with 6^{2+} are almost identical to those observed for the 1:1 complex with the *N*-methylquinuclidinium cation ($\Delta\delta_{lim} = -0.84, -0.69, -0.48,$ and -0.42 ppm for the H2, H3, H4, and CH_3 protons, respectively), confirming the locations of the two CB[7] hosts in the $\{6\cdot2CB[7]\}^{2+}$ dumbbell.

In a similar fashion, the BW285c51 dication (7^{2+}) exhibits sequential 1:1 and 2:1 host–guest species with CB[7] (Figure 4). The complexation-induced chemical shifts (Chart 2) for the $\{7\cdot CB[7]\}^{2+}$ and $\{7\cdot2CB[7]\}^{2+}$ species suggest that first CB[7] host molecule is primarily situated over one of the aromatic rings in the central portion of the guest, with the largest upfield chemical shift changes measured for the H2′ and H3′ protons. The allyl $H\gamma$ proton resonances move downfield initially as this group is situated outside of the cavity near a portal. The addition of a second CB[7] host serves to localize the two host molecules more over the cationic end units, with significant upfield shifts in the allyl $H\alpha$ and the methyl protons on the carbons adjacent to the quaternary nitrogens.

The high-resolution electrospray ionization mass spectra of aqueous solution of the dicationic guests in the presence of
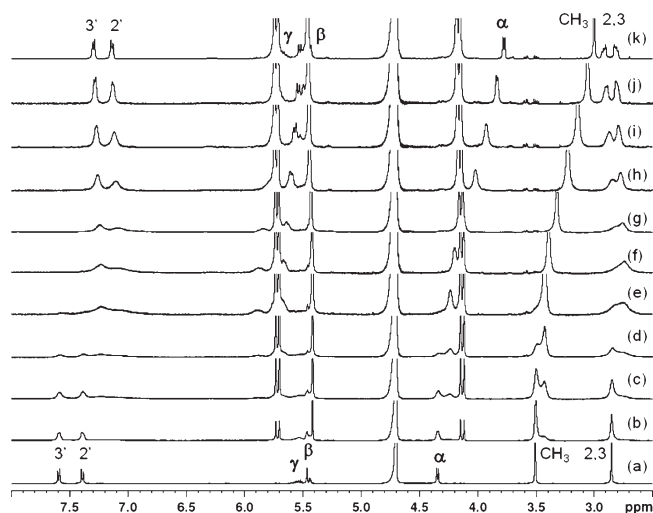
a 3-fold excess of the CB[7] (Table 1) are consistent with the relative 1:1 and 2:1 host–guest binding strengths. With guests in which the 2:1 binding constant is significant (3^{2+}, 6^{2+}, and 7^{2+}), a peak consistent with $\{M\cdot2CB[7]-2X\}^{2+}$ ($X = Br^-$ or Cl^-) species is observed (in addition to the expected $\{M\cdot CB[7]-2X\}^{2+}$), whereas with guests having smaller 2:1 binding constants, no $\{M\cdot2CB[7]-2X\}^{2+}$ species is observed.

Host–Guest Stability Constants. The stability constants for the 1:1 host–guest complexes and [2]pseudorotaxanes were too large for conventional ^1H NMR chemical shift titrations and were thus determined (Table 2) from competitive ^1H NMR binding studies (at pD = 4.75 (0.050 M NaOAc-d_3/0.025 M DCl)[28] using tetraethylphosphonium chloride ($K_{CB[7]} = (1.3 \pm 0.3)\times10^5$ M^{-1}),[22] tetramethylphosphonium bromide (($2.2 \pm 0.4)\times10^6$ M^{-1}),[22] 3-trimethylsilylpropionic acid (($1.82 \pm 0.22)\times10^7$ M^{-1}),[28] benzyltrimethylammonium bromide (($2.5 \pm 0.6) \times 10^8$ M^{-1}),[22] or *p*-xylylenediammonium (($1.84 \pm 0.34) \times 10^9$ M^{-1})[28] as the competitor guests.

The stability constants for the 1_n^{2+} guests show a dependence on the alkyl chain length, with the value maximizing at $n = 8$. With the NH_3^+ end groups, this maximum is observed at $n = 5$ or 6 for CB[6] or cyclohexanoCB[6].[29] With the more hydrophilic NH_3^+ end groups, compared with NR_3^+, the ion–dipole interactions with the carbonyl oxygens on the portals are important and the penta- or hexamethylene chain length clearly maximizes these interactions with the diammonium guests in the smaller CB[6] cavity. With the NR_3^+ end groups and the larger (but not longer) CB[7] host, it appears that more folding of the longer polymethylene chains within the cavity is afforded by weaker repulsions between the two end groups. The binding constant of 2.6×10^8 M^{-1} for 1_{10}^{2+} with cucurbit[7]uril may be compared with values of 1360 M^{-1} and 1580 M^{-1} reported for α-cyclodextrin (value for

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TABLE 1. High-Resolution ESI Mass Spectral Data for the 1:1 ($\{M \cdot CB[7] - 2X\}^{2+}$) and 2:1 ($\{M \cdot 2CB[7] - 2X\}^{2+}$) Host−guest Complexes (X = Br⁻ for all except 5^{2+}, where X = Cl⁻) with CB[7] (Calculated Values Given in Parentheses)

guest	$\{M \cdot CB[7] - 2X\}^{2+}$ m/z	$\{M \cdot 2CB[7] - 2X\}^{2+}$ m/z
$1_6{}^{2+}$	682.2919 (682.2917 for $[C_{54}H_{72}N_{30}O_{14}]^{2+}$)	not observed
$1_8{}^{2+}$	696.3078 (696.3073 for $[C_{56}H_{76}N_{30}O_{14}]^{2+}$)	not observed
$1_{10}{}^{2+}$	710.3229 (710.3230 for $[C_{58}H_{80}N_{30}O_{14}]^{2+}$)	1291.4930 (1291.4947 for $[C_{100}H_{122}N_{58}O_{28}]^{2+}$)
2^{2+}	752.3723 (752.3699 for $[C_{64}H_{92}N_{30}O_{14}]^{2+}$)	not observed
3^{2+}	727.2933 (727.2936 for $[C_{58}H_{80}N_{28}O_{14}P_2]^{2+}$)	1308.5332 (1308.4654 for $[C_{100}H_{122}N_{56}O_{28}P_2]^{2+}$)
4^{2+}	769.3407 (769.3406 for $[C_{64}H_{92}N_{28}O_{14}P_2]^{2+}$)	1350.5174 (1350.5124 for $[C_{106}H_{134}N_{56}O_{28}P_2]^{2+}$)
5^{2+}	726.2820 (726.2814 for $[C_{56}H_{72}N_{30}O_{18}]^{2+}$)	not observed
6^{2+}	762.3630 (762.3543 for $[C_{66}H_{88}N_{30}O_{14}]^{2+}$)	1343.5748 (1343.5260 for $[C_{108}H_{130}N_{58}O_{28}]^{2+}$)
7^{2+}	784.3204 (784.3204 for $[C_{69}H_{80}N_{30}O_{15}]^{2+}$)	1365.4987 (1365.4922 for $[C_{111}H_{122}N_{58}O_{29}]^{2+}$)

TABLE 2. Stability Constants for the [2]Pseudorotaxanes ($K_{CB[7]}$) and 2:1 Host−guest Complexes ($K_{2CB[7]}$) of Cucurbit[7]uril in Aqueous Solution at 298 K

guest	$K_{CB[7]}$, M⁻¹	$K_{2CB[7]}$, M⁻¹
$1_6{}^{2+}$	$(3.9 \pm 0.9) \times 10^{9a}$	[b]
$1_8{}^{2+}$	$(2.8 \pm 0.8) \times 10^{10a}$	[b]
$1_{10}{}^{2+}$	$(2.6 \pm 1.3) \times 10^{8c}$	< 10
2^{2+}	$(1.4 \pm 0.3) \times 10^{7c}$	250 ± 30
3^{2+}	$(9.0 \pm 1.5) \times 10^{7c}$	$(6.5 \pm 0.5) \times 10^3$
4^{2+}	$(6.8 \pm 1.0) \times 10^{7c}$	$(1.1 \pm 0.2) \times 10^2$
5^{2+}	$(8.6 \pm 1.6) \times 10^{6c}$	42 ± 5
	$(9.6 \pm 2.0) \times 10^{6d}$	
	$(1.1 \pm 0.3) \times 10^{7e}$	
6^{2+}	$(1.9 \pm 0.6) \times 10^{10a}$	$(5.6 \pm 3.2) \times 10^{8a}$
	$(8.7 \pm 2.5) \times 10^{9f}$	$(6.1 \pm 2.1) \times 10^{8f}$
7^{2+}	$(1.3 \pm 0.2) \times 10^{8c}$	$(3.5 \pm 0.5) \times 10^4$

[a] Determined using *p*-xylenediammonium as the competitor guest. [b] Not observed. [c] Determined using 3-(trimethylsilyl)propionic acid as the competitor guest. [d] Determined using $PMe_4{}^+$ as the competitor guest. [e] Determined using $PEt_4{}^+$ as the competitor guest. [f] Determined using NMe_3Bz^+ as the competitor guest.

$1_8{}^{2+}$ is only 44 M⁻¹[25] and 9.0×10^5 M⁻¹ for an anionic resorcin[4]arene.[30] With the α-CD host, a [2]pseudorotaxane is formed with the hydrophobic decamethylene chain inside the host cavity, while for the resorcin[4]arene, only complexation of the $N(CH_3)_3{}^+$ head groups is observed, with stabilization provided by cation−π interactions. With cucurbit[7]uril, the [2]pseudorotaxanes benefit from both the hydrophobic effects inside the cavity and the ion−dipole interactions at the portals.

The stability constants for the [2]pseudorotaxanes containing dicationic guests with the same decamethylene linker follow the trend of $1_{10}{}^{2+} > 3^{2+} > 4^{2+} > 2^{2+}$, indicating that for threads with the same alkyl chain length, the stability constant is related to charge diffusion on the peralkylonium end group. Changing the end groups from $NMe_3{}^+$ to $NEt_3{}^+$ ($1_{10}{}^{2+}$ vs 2^{2+}) or $PMe_3{}^+$ to $PEt_3{}^+$ (3^{2+} vs 4^{2+}) results in a lowering of $K_{CB[7]}$ by 1 order of magnitude as the less polar triethylonium groups have weaker ion−dipole interactions with the polar portals of CB[7] than the methyl analogues. Changing the decamethylene group to the bis(ester) linkage of the same backbone length in succinylcholine ($1_{10}{}^{2+}$ to 5^{2+}), however, reduces the stability constant by approximately 25 as the hydrophobicity of the central group is lowered. We have recently demonstrated that small polar solvent molecules such as acetone and methylacetate form relatively stable host−guest complexes with CB[7] ($K_{CB[7]} = 580 \pm 50$ and 1020 ± 100 M⁻¹, respectively) in aqueous

solution, in part due to interactions between the quadrupolar moment of the host and the dipole moment of the guests.[23] The values of $\Delta\delta_{lim}$ for succinylcholine suggest that the CB[7] may have a preference for encapsulating the acetyl groups in the center of the guest by virtue of these quadrupole−dipole interactions.

The 1:1 binding constant for guest 6^{2+} is similar to that of the *N*-methylquinuclidinium cation ($K_{CB[7]} = (5.8 \pm 1.3) \times 10^9$ M⁻¹, using the *p*-xylylenediammonium dication as the competitor guest[28]), while the 2:1 binding constant would be expected to be at least four times less on statistical grounds ($K_{CB[7]}/K_{2CB[7]} \geq 4$).[31] The 20-fold reduction of the second binding constant from the first is likely due to some degree of dipole−dipole repulsions between the carbonyl-lined rims of the two adjacent CB[7] hosts. For the 7^{2+} guest, which the ¹H NMR chemical shift changes of the guest suggests that the CB[7] is located over the phenyl groups, the 1:1 binding constant ($(1.3 \pm 0.2) \times 10^8$ M⁻¹) is similar to the value for the benzyltrimethylammonium cation ($(2.5 \pm 0.6) \times 10^8$ M⁻¹),[22] and somewhat larger than the values reported for the *p*-toluidinium ($(8.38 \pm 1.33) \times 10^6$ M⁻¹)[28] and dimethyl(*p*-tolyl)sulfonium ($(5.18 \pm 0.83) \times 10^7$ M⁻¹)[28] cations.

The equilibrium constants for the formation of the 2:1 host−guest complexes (other than with guest 6^{2+}) from the corresponding [2]pseudorotaxanes ($K_{2CB[7]}$) were determined from the ¹H and ³¹P NMR chemical shift titrations (Table 2).[32] The relative magnitudes of the 2:1 stability constants for the guest complexes containing $NR_3{}^+$ or $PR_3{}^+$ end groups parallel those of the corresponding $NR_4{}^+$ or $PR_4{}^+$, with $PMe_3{}^+ > NEt_3{}^+ > PEt_3{}^+ > NMe_3{}^+$.[22] As expected, the more hydrophobic allyldimethylphenylammonium (in 7^{2+}) and quinuclidinium (in 6^{2+}) end groups result in still higher stability constants for the 2:1 complexes.

The results of this study indicate that the affinities of the $NR_3{}^+$ and $PR_3{}^+$ end groups for both the carbonyl-lined portals and the hydrophobic cavity of the cucurbit[7]uril host molecule allow for the formation of two discrete supramolecular complexes in aqueous solution, depending on the host−guest ratio. The conversion of the 1:1 complex to the 2:1 host−guest complexes is illustrated in Scheme 1 with succinylcholine (5^{2+}) as the guest. There are two possible configurations for the 1:1 complex, with the host molecule residing over either the cationic end group (upper left structure) or the hydrophobic central linker (upper right structure). The addition of the second CB[7] host molecule

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may be expected to follow two possible pathways, starting with the two 1:1 configurations (top structures in Scheme 1), which would be in equilibrium with each other. With the guest 6^{2+}, this equilibrium would lie extensively to the left, such that addition of the second host would follow the red equilibrium arrows on the left side in Scheme 1. With the other guests for which there is evidence for a 2:1 host−guest complex (1_{10}^{2+}, 2^{2+}, 3^{2+}, 4^{2+}, 5^{2+}, and 7^{2+}), the formation from the 1:1 could involve the [2]pseudorotaxane (upper right structure) with the second CB[7] encapsulating one of the cationic end groups, which electrostatically repels the first host toward or onto the other cationic end group. Another possibility is that the addition of the second host occurs through the 1:1 species in which the first host is over an end group (upper left structure), resulting in the lower left 2:1 host−guest structure.

Conclusions

This study has demonstrated that established acetylcholinesterase inhibitors, such as decamethonium bromide, succinylcholine, and BW284c51, and other analogues form very stable [2]pseudorotaxanes with 1 equiv of cucurbit[7]uril in aqueous solution. With additional equivalents of the host, 2:1 host−guest complexes are formed with varying weaker affinities, dependent on the nature of the cationic headgroups and the hydrophobicity of the linker units. A particular practical application of the strong cucurbit[7]uril binding to this class of dicationic guests may be the ability to reverse the binding of guests such as succinylcholine and BW248c51 to their respective physiological receptors. In the former case, the CB[7] could act a drug reversal agent and, by "inhibiting" the inhibitor, reduce the potential side effects arising from the medicinal administration of succinylcholine as a depolarizing neuromuscular blocking agent. In analogy to Nau's use of CB[7] to inhibit proteases by complexing the substrates,[16b] this host could also be employed to modulate AChE activity by binding to substrates such as acetylcholine (and products such as choline)[10] or return activity by binding to selective AChE inhibitors such as BW248c51. We are currently pursuing this avenue of research with these dications, as well as with cationic nondepolarizing neuromuscular blocking agents bearing other types of peralkylated quaternary ammonium head groups, based on morpholine, pyrrolidine, and piperidine.

Experimental Section

Methods. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on 400 and 500 MHz spectrometers in D_2O, and 2D HSQC experiments were performed to assign the proton and carbon resonances. The electrospray-ionization time-of-flight high-resolution mass spectra of the guests and host−guest complexes were recorded on a MS/MS system in aqueous solutions. The 1:1 host−guest binding constants and the 2:1 host−guest binding constant for 6^{2+}, and the error limits, were determined from ^{1}H NMR competitive binding experiments using the method of Isaacs and co-workers.[28] The 2:1 binding constants for guests were determined from ^{1}H NMR chemical shift titrations (for guests 2^{2+}, 3^{2+}, 4^{2+}, and 7^{2+}) using a nonlinear least-squares fitting of the data beyond 1 equiv of the host or (for guests 1_{10}^{2+}, 2^{2+}, 4^{2+}, and 5^{2+}) from a double-reciprocal plot of the chemical shift change against concentration.[32] The pD of the solutions was

maintained at 4.75 using an acetate buffer system (0.050 M NaOAc-d_3 with 0.025 M DCl), and the temperature was maintained at 298 K.

Materials. Cucurbit[7]uril was prepared and characterized by the method of Day and co-workers.[33] The 1,6-bis(trimethylammonium)hexane dibromide ([1_6]Br$_2$), 1,10-bis(trimethylammonium)-decane dibromide ([1_{10}]Br$_2$), succinylcholine chloride ([5]Cl$_2$), and 1,5-bis(4-allyldimethylammoniumphenyl)pentan-3-one   bromide (B284c51, [7]Br$_2$) were commercially available and used as received. Quinuclidine was prepared by neutralizing quinuclidine hydrochloride with 0.10 M NaOH and subsequently extracting it with chloroform. Removal of the solvent by rotary evaporation yielded quinuclidine. The 1,8-bis(trimethylammonium)octane dibromide ([1_8]Br$_2$) and 1,10-bis(trimethylphosphonium)decane dibromide were prepared and characterized in a previous study.[25]

1,10-Bis(triethylammonium)decane dibromide ([2]Br$_2$). A solution of 0.832 g (2.77 mmol) of 1,10-dibromodecane and 1.112 g (11.09 mmol) of triethylamine in 10 mL of acetonitrile was heated at 70 °C under argon in a pressure tube for 48 h. The white precipitate was washed with ether and dried: yield 0.712 g (51%); mp 238−240 °C dec; ^{1}H NMR (D$_2$O, 400 MHz) δ 3.27 (q, 12H, CH$_2$, J = 7.2 Hz), 3.14 (t, 4H, Hα, J = 8.6 Hz), 1.67 (q, 4H, Hβ, J = 7.2 Hz), 1.36 (m, 8H, Hδ and Hγ), 1.32 (m, 2H, Hε), 1.27 (tt, 18H, CH$_3$, J = 7.2 Hz, J_{N-H} = 2.2 Hz); ^{13}C NMR (D$_2$O, 100 MHz) δ 56.6 (Cα), 52.4 (N$^+$-CH$_2$CH$_3$), 28.3 (Cδ or Cε), 28.2 (Cε or Cδ), 25.5 (Cγ), 20.8 (Cβ), 6.6 (N$^+$-CH$_2$CH$_3$); HR-ESI-MS calcd for C$_{22}$H$_{50}$N$_2$ [M − 2Br]$^{2+}$ m/z 171.1982, found m/z 171.1985.

1,10-Bis(trimethylphosphonium)decane Dibromide ([3]Br$_2$). The [3]Br$_2$ compound was synthesized using a method similar to that reported for the iodide salt in a previous study,[25] except that 1,10-dibromodecane was employed in place of the 1,10-diododecane: yield 0.389 g; mp 228−232 °C dec; ^{1}H NMR (D$_2$O, 500 MHz) δ 2.16 (m, 4H, $^2J_{H-P}$ = 13.2 Hz, J = 10.8 Hz, Hα), 1.81 (d, 18H, $^2J_{H-P}$ = 14.5 Hz, CH$_3$), 1.57 (sx, 4H, J = 6.4 Hz, Hβ), 1.43 (qn, 4H, J = 5.5 Hz, Hγ), 1.31 (m, 4H, Hδ), 1.29 (m, 4H, Hε); ^{13}C NMR (D$_2$O, 125 MHz) δ 30.0 (d, $^3J_{C-P}$ = 15.6 Hz, Cγ), 28.7 (s, Cδ), 28.3 (s, Cε), 23.1 (d, $^1J_{C-P}$ = 52.4 Hz, Cα), 21.1 (d, $^2J_{C-P}$ = 4.2 Hz, Cβ), 7.7 (d, $^1J_{C-P}$ = 55.2 Hz, CH$_3$); ^{31}P NMR (D$_2$O, 162 MHz) δ 25.91; HR-ESI-MS calcd for C$_{16}$H$_{38}$P$_2$ (M − 2Br)$^+$ m/z 146.1219, found m/z 146.1219.

1,10-Bis(triethylphosphonium)decane Dibromide ([4]Br$_2$). A solution of 0.602 g (2.01 mmol) of 1,10-dibromodecane and 8.00 mL of 1.0 M triethylphosphine (8.00 mmol) in THF was heated at 70 °C under argon in a pressure tube for 72 h. The hygroscopic white precipitate was washed with ether, and the solvent was removed by evaporating with a stream of nitrogen gas, yielding only about 2% of the theoretical yield (not optimized): mp 222−228 °C; ^{1}H NMR (D$_2$O, 500 MHz) δ 2.15 (dq, 12H, CH$_2$, $^2J_{H-P}$ = 13.0 Hz, J = 7.8 Hz), 2.13 (dt, 4H, Hα, $^2J_{H-P}$ = 13.0 Hz, J = 10.5 Hz), 1.53 (sx, 4H, Hβ J = 7.8 Hz), 1.41 (qn, 4H, Hγ, J = 7.0 Hz) 1.28 (m, 4H, Hδ), 1.26 (m, 4H, Hε), 1.17 (dt, 18H, CH$_3$, $^3J_{H-P}$ = 18.0 Hz, J = 7.8 Hz); ^{13}C NMR (D$_2$O, 125 MHz) δ 30.3 (d, $^3J_{C-P}$ = 14.6 Hz, Cγ), 28.7 (s, Cδ), 28.3 (s, Cε), 20.8 (d, $^2J_{C-P}$ = 4.5 Hz, Cβ), 16.9 (d, $^1J_{C-P}$ = 48.1 Hz, Cα), 11.3 (d, $^1J_{C-P}$ = 49.8 Hz, CH$_2$), 5.0 (d, $^2J_{C-P}$ = 5.5 Hz, CH$_3$); ^{31}P NMR (D$_2$O, 162 MHz) δ 38.54; HR-ESI-MS calcd for C$_{22}$H$_{50}$P$_2^{2+}$ (M − 2Br)$^{2+}$ m/z 188.1688, found m/z 188.1688.

1,10-Bis(quinuclidinium)decane Dibromide ([6]Br$_2$). To a solution of 0.587 g (5.28 mmol) of quinuclidine in 4 mL of DMF was added dropwise a solution of 0.720 g (2.40 mmol) of 1,10-dibromodecane in 2 mL of DMF. The solution was heated for 5 min at 50 °C with a white precipitate forming. The product was washed with ether and dried: yield 0.664 g (53%); mp > 300 °C;

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^{1}H NMR (D$_2$O, 400 MHz) δ 3.28 (t, 12H, H2, $J = 7.8$ Hz), 3.00 (t, 4H, Hα, $J = 8.4$ Hz), 2.09 (sp, 2H, H4, $J = 3.2$ Hz), 1.88 (m, 12H, H3), 1.61 (m, 4H, Hβ), 1.23 (m, 12 H, Hδ, Hε, Hγ); ^{13}C NMR (D$_2$O, 100 MHz) δ 64.4 (Cα), 54.6 (C2), 28.3 (Cε), 28.2 (Cδ), 25.7 (Cγ), 23.3 (C3), 21.4 (Cβ), 19.1 (C4); HR-ESI-MS calcd for C$_{24}$H$_{46}$N$_2$$^{2+}$ (M − 2Br)$^{2+}$ m/z 181.1825, found m/z 181.1821.

N-Methylquinuclidinium Iodide ([N-MeQuin]I). Iodomethane (0.649 g, 4.57 mmol) was added dropwise to a solution of 0.507 g (4.56 mmol) of quinuclidine in 10 mL of ethyl acetate and cooled in an ice bath. A white precipitate formed immediately: yield 0.746 g (65%); mp > 300 °C; ^{1}H NMR (D$_2$O, 400 MHz) δ 3.35 (t, 6H, H2, $J = 8.0$ Hz), 2.86 (s, 3H, CH$_3$), 2.13 (sp, 1H, H4 $J = 2.4$ Hz), 1.96 (m, 6H, H3); ^{13}C NMR (D$_2$O, 100 MHz) δ 57.0 (t, C2, $J = 3.0$ Hz), 51.9 (t, CH$_3$, $J = 4.5$ Hz), 23.5 (s, C3), 18.7 (t, C4,

$J = 4.8$ Hz); HR-ESI-MS calcd for C$_8$H$_{16}$N$^+$ (M − I)$^+$ m/z 126.1277, found m/z 126.1277.

Supporting Information Available: ^{1}H, ^{13}C, and ^{31}P NMR spectra of the novel guests, ^{1}H NMR spectra of the titrations of the guests with CB[7], and chemical shift titration curves. This material is available free of charge via the Internet at http://pubs.acs.org.