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Spectrometric Study of the Size Discrimination of Quaternary Ammonium Cations by Tetracyanoresorcin[4]arene

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The inclusion complexes of tetracyanoresorcin[4]arene with six quaternary ammonium cations—biologically important acetylcholine and choline, tetramethyl ammonium, tetraethyl ammonium, tetrapropyl ammonium and tetrabutyl ammonium—were studied by means of electrospray ionization mass, fluorescence and NMR spectrometries. The results indicate that tetracyanoresorcin[4]arene shows high affinity toward these ammoniums and is capable of recognizing their sizes.

Keywords: Resorcin[4]arene; Quaternary ammonium; Recognition; Spectrometry

INTRODUCTION

The selective recognition of cationic species by synthetic receptors with specific and high affinities has attracted considerable interests in supramolecular chemistry [1]. In these aspects, resorcin[4] arenes, readily available from the acid-catalyzed condensation of resorcinol with aldehydes, are actively explored as fascinating supramolecular architecture motifs that have wide applications, for example, in the direct complexation of cations and other polar organic compounds [2,3]. Due to their concave aromatic structures, resorcin[4]arenes are especially attractive as strong synthetic receptors for biologically important acetylcholine and other quaternary ammonium cations [4–15]. In the complexation of resorcin[4]arenes with ammonium cations, size complementarity and noncovalent interactions (e.g. cation-π [16]) between the electron-rich cavity of resorcin[4]arene and the positively charged ammonium cation play a crucial role.

Unsubstituted resorcin[4]arenes possess modest cavities and can surround only a small fraction of the target molecules. As a consequence, unsubstituted resorcin[4]arenes exhibit binding preference for small quaternary ammonium cations such as tetramethyl ammonium, whereas the potential of resorcin[4]arenes to selectively host other bulkier quaternary ammoniums is relatively unexplored [17]. In this paper, we describe the study of the size discrimination of an enlarged resorcin [4]arene derivative, tetracyanoresorcin[4]arene **1** toward six quaternary ammonium cations, by means of electrospray ionization mass (ESI-MS), fluorescence and NMR spectrometries. The ammoniums explored in this study are acetylcholine ($AcCh^+$), choline (Ch^+), tetramethyl ammonium (Me_4N^+), tetraethyl ammonium (Et_4N^+), tetrapropyl ammonium (Pr_4N^+) and tetrabutyl ammonium (Bu_4N^+) (Scheme 1). Tetracyanoresorcin[4]arene **1** was synthesized according to the methods previously described by us [18,19].

ESI-MS DETECTION

Firstly, the inclusion complexes of compound **1** with the six quaternary ammonium cations were detected by using ESI-MS. This is because ESI-MS spectrometry has been actively utilized as a rapid, sensitive and effective analytical technique to

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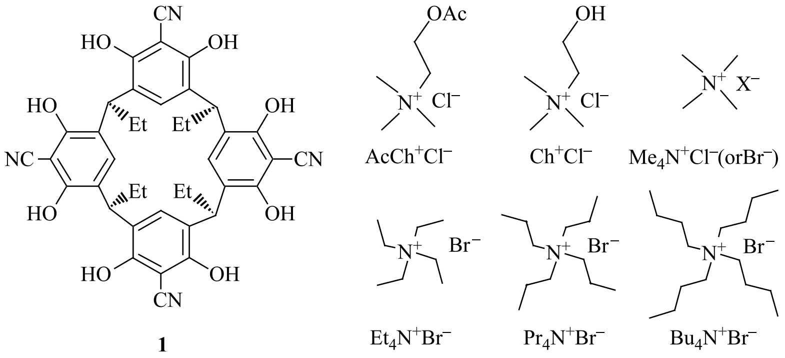

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SCHEME 1 Tetracyanoresorcin[4]arene **1** and quaternary ammonium cations explored in this study.

detect the complexes of cationic species with resorcin[4]arenes [20–22], and also because ESI-MS results are assumed to reflect the complexation phenomena in solution [23–25]. The obtained negative ESI-MS spectra are shown in Fig. 1.† In the negative ESI-MS spectrum (Fig. 1a) of compound **1**, only one ion peak at *m/z* 699.4 was observed, which is assignable to one-charged monomeric **1** ([**1** − H]$^-$). This result indicates that compound **1** does not form self-assembled species in the present ESI-MS detection conditions (1:1 methanol-water). This behavior is different from unsubstituted resorcin[4]arenes which usually form capsular dimers or other self-assembly in solution through intermolecular hydrogen bonding [26–29]. The reason why compound **1** is incapable of forming dimeric or other self-assembled species may be that the linearly aligned cyano groups prohibit the formation of (stable) hydrogen bonding between the molecules of **1**.

It is clear from Fig. 1b–g that compound **1** can form stable 1:1 inclusion complexes with the six quaternary ammoniums. In Fig. 1b, for example, in addition to the ion peak at *m/z* 699.4 ([**1** − H]$^-$), an abundant ion peak at *m/z* 844.4 was observed. This ion peak is assignable to the 1:1 complex of **1** with AcCh$^+$([**1** @AcCh$^+$ − 2H]$^-$). The high relative abundances of the complexes of **1** with these quaternary ammoniums suggest the high affinities of **1** toward these ammoniums. It should be noted that compound **1** is capable of binding bulky Pr$_4$N$^+$ and Bu$_4$N$^+$ (Fig. 1f and 1g) which cannot be encapsulated by unsubstituted resorcin [4]arenes [7].

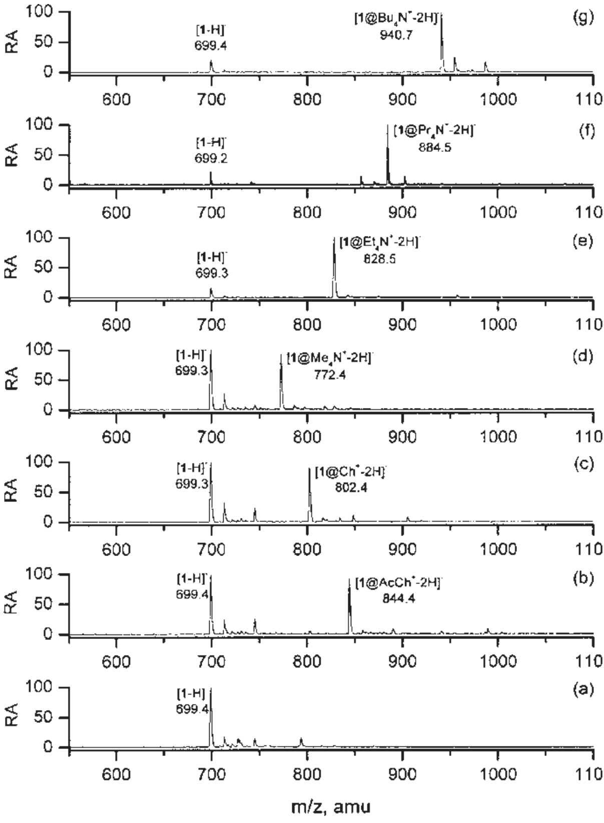

FIGURE 1 Negative ESI-MS spectra of (a) **1** and its complexes with (b) AcCh$^+$, (c) Ch$^+$, (d) Me$_4$N$^+$, (e) Et$_4$N$^+$, (f) Pr$_4$N$^+$ and (g) Bu$_4$N$^+$ in the 2:1 guest/host molar ratios in 1:1 methanol–water. RA denotes relative abundance in Fig. 1 and the following figure.

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† Under the ESI-MS detection conditions (1:1 water-methanol), compound **1** should exist as polyanionic species because of its p$K_{a1\sim3}$ in the physiological pH region [18,19]. Therefore we used the negative ion mode to detect compound **1** and its complexes with the quaternary ammoniums, though the use of positive ions appears to be more logical for studying the complexation of resorcin[4]arenes with ammonium cations. Also because compound **1** exists as polyanionic species, higher than 1:1 complexes can be detected by ESI-MS in the presence of large excess of ammonium cations. For example, when AcCh$^+$/**1** molar ratio increased to 8, a new ion peak at *m/z* 989.4, in addition to the ion peaks at *m/z* 699.2 ([**1** − H]$^-$) and *m/z* 844.4 ([**1** @AcCh$^+$ − 2H]$^-$), was observed in the negative ESI-MS spectrum. This new peak was assignable to the 1:2 complex ([**1** @AcCh$_2^+$-3H]$^-$) in which the first AcCh$^+$ is thought to be specifically encapsulated into the cavity of **1** while the second AcCh$^+$ may be complexed with negatively charged **1** through nonspecific (e.g. electrostatic) interactions. Under the conditions of ammonium/host molar ratios being 2, high relative abundance of the 1:1 complexes could be obtained while the 1:2 complexes were negligible.

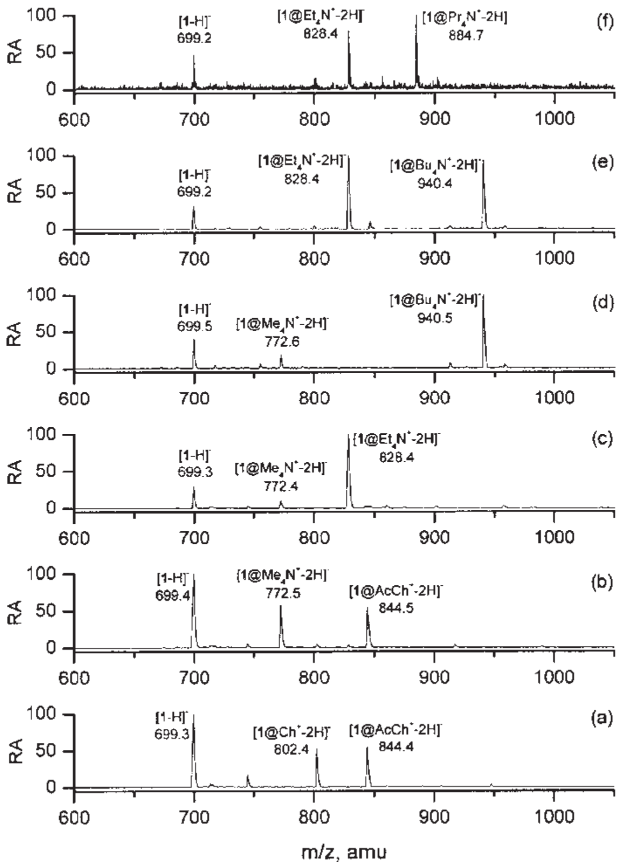

FIGURE 2 ESI-MS competitive binding spectra of (a) $AcCh^+$-Ch^+, (b) $AcCh^+$-$Me_4N^+(Cl^-)$, (c) $Me_4N^+(Br^-)$-Et_4N^+, (d) $Me_4N^+(Br^-)$-Bu_4N^+, (e) Et_4N^+-Bu_4N^+ and (f) Et_4N^+-Pr_4N^+ to **1** in 1:1:1 host/guest 1/guest 2 molar ratios in 1:1 methanol-water.

TABLE I Complexation-induced ^1H NMR shifts (*CIS*)[a] and association constants[b] (K_a's, M^{-1}) of six ammoniums with **1**

Guest	Proton	CIS	K_a
$AcCh^+$	/	/	$(6.22 \pm 1.97) \times 10^{5c}$
Ch^+	/	/	$(5.80 \pm 2.21) \times 10^5$
Me_4N^+	CH_3	−0.87	$(7.63 \pm 3.71) \times 10^5$
Et_4N^+	CH_3	−0.78	$(1.00 \pm 0.40) \times 10^6$
	CH_2	−0.89	
Pr_4N^+	3-CH_3	−0.51	$(1.10 \pm 0.50) \times 10^6$
	2-CH_2	−0.41	
	1-CH_2	−0.35	
Bu_4N^+	4-CH_3	−0.22	$(8.40 \pm 4.23) \times 10^5$
	3-CH_2	−0.17	
	2-CH_2	−0.12	
	1-CH_2	−0.07	

[a] ^1H NMR spectra were measured in CD_3OD at room temperature. The host/guest molar ratio was 2:1 for Me_4N^+, 5:1 for Et_4N^+, 7:1 for Pr_4N^+ and 4:1 for Bu_4N^+, respectively. [b] Obtained from fluorescent competitive detection using pyrene-modified *N*-methylpyridium cation as a fluorescent indicator, in pH 7.0 aqueous solutions buffered with 10 mM phosphate at room temperature. [c] From reference [19].

The relative binding affinity of **1** toward the six quaternary ammoniums was established by ESI-MS competitive binding experiments. In these experiments, compound **1** of fixed concentration was mixed with equimolar amounts of two different ammoniums and the corresponding negative ESI-MS spectra (Fig. 2) were measured. These experiments allow the easy determination of which ammonium of the two ammoniums in the mixture preferentially binds to **1**. For example, the spectrum (Fig. 2a) of an equimolar mixture of $AcCh^+$ and Ch^+ with **1** gave intense signals for both 1:1 complexes ([**1**@ $AcCh^+ - 2H]^-$ at *m/z* 844.4 and [**1** @ $Ch^+ - 2H]^-$ at *m/z* 802.4) with apparent preference for **1** @ $AcCh^+$ over **1** @ Ch^+. By directly comparing the relative abundance of the noncovalent complexes, we can establish the following order of the pairs of the complexes: $AcCh^+ \geqq Ch^+$ (Fig. 2a), $Me_4N^+ \geqq AcCh^+$ (Fig. 2b), $Et_4N^+ > Me_4N^+$ (Fig. 2c), $Bu_4N^+ > Me_4N^+$ (Fig. 2d), $Et_4N^+ > Bu_4N^+$ (Fig. 2e) and $Pr_4N^+ > Et_4N^+$ (Fig. 2f). Thus, the overall binding order with **1** is $Pr_4N^+ > Et_4N^+ > Bu_4N^+ > Me_4N^+ \geq AcCh^+ \geq Ch^+$.

MEASUREMENT OF ASSOCIATION CONSTANTS

To quantitatively assess the binding affinity of **1** toward the six quaternary ammoniums, the association constants (K_a's) in neutral aqueous solution were measured by fluorescent competitive detection using pyrene-modified *N*-methylpyridium cation as a fluorescent indicator.[‡] The result is shown in Table I and illustrated in Fig. 3. These association constants clearly suggest that these ammoniums can be strongly bound to **1** in the order of $Pr_4N^+ > Et_4N^+ > Bu_4N^+ > Me_4N^+ \geq AcCh^+ \geq Ch^+$, which is in full agreement with the results obtained from ESI-MS detection. Thus, compound **1** can discriminate these quaternary ammoniums based on their sizes. The high binding affinity of **1** toward these ammoniums indicates that compound **1** may be exploitable as

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[‡] The fluorescent competitive detection using pyrene-modified *N*-methylpyridium cation as a fluorescent probe was conducted, using the methods similar to those previously described [19]. Typically, to a solution of **1** (8.0×10^{-7} M) and fluorescent probe (2.0×10^{-7} M) in pH 7.0 aqueous solutions buffered with 10 mM phosphate was added quaternary ammonium of increasing concentrations ($0 \sim 1.6 \times 10^{-3}$ M), and their corresponding fluorescence spectra were measured at room temperature (ex 430 nm, ex/em 10 nm/10 nm). Association constants (K_a's) were derived from nonlinear curve fitting, using the equation: $[A]_0 = ((I_\infty - I)/((I - I_0) \times K_d \times K_a) + 1) \times ([CN]_0 - (I - I_0) \times K_d/(I_\infty - I) - [P]_0 \times (I - I_0)/(I_\infty - I_0))$, wherein $[A]_0$, [CN] and $[P]_0$ are the initial analytical concentrations of quaternary ammonium, compound **1** and fluorescent probe, respectively. I, I_0 and I_∞ represent the fluorescence intensities (at em 570 nm) of the sample, fluorescent probe alone and the intensity when fluorescent probe is totally bound by **1**, respectively. K_d ($= 2.01 \times 10^{-8}$ M) is the disassociation constant between **1** and fluorescent probe under the same conditions [19].

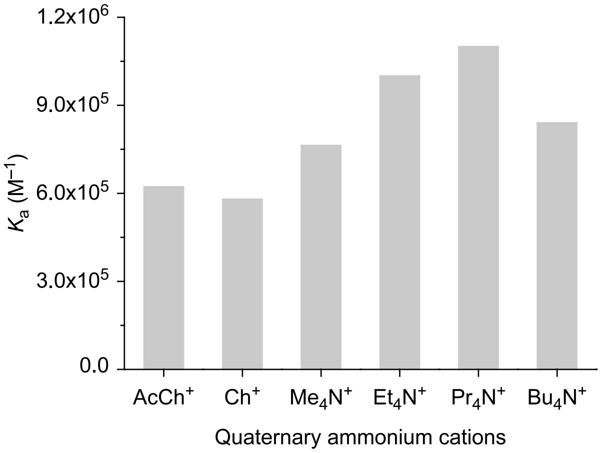

FIGURE 3 Association constants of **1** with the six quaternary ammonium cations in pH 7.0 aqueous solutions buffered with 10 mM phosphate at room temperature.

their potential receptors with high sensitivity (10^{-6} M) under neutral aqueous conditions.

^{1}H NMR INVESTIGATION

Since structural information about the complexes cannot be obtained from mass spectrometric experiments, the ^{1}H NMR spectra of the complexes of **1** with Me_4N^+, Et_4N^+, Pr_4N^+ and Bu_4N^+ were measured as to provide unambiguous evidence for the accommodation of these quaternary ammoniums into the cavity of **1**. The ^{1}H NMR spectra were measured in CD_3OD because **1** is not so soluble in D_2O or D_2O/CD_3OD (1:1, v/v) to give well-resolved NMR spectra. In all cases, the signals of the guest protons were observed as average single resonances because of the fast exchange on the NMR time scale between the free and the complexed guest. As shown in Table I, the guest protons experienced large complexation-induced upfield shift (CIS), owing to the shielding effect from the aromatic wall of compound **1**. These upfield shifts clearly indicated that Me_4N^+, Et_4N^+, Pr_4N^+ and Bu_4N^+ were encapsulated into the cavity of **1**. The methyl groups in Pr_4N^+ and Bu_4N^+ showed the largest upfield shifts, suggesting that the ammonium heads of Pr_4N^+ and Bu_4N^+ were not bound into, but resided above, the cavity of **1**.

The foregoing results can be rationalized if the structural characteristics inherent in **1** and the size complementarity between **1** and the quaternary ammoniums are taken into account. Compared with unsubstituted resorcin[4]arenes, tetracyanoresorcin [4]arene **1**, thanks to the linearly aligned cyano groups, has a widened and enlarged concave electron-rich cavity and therefore has more space to accommodate bulky guests, such as Pr_4N^+ and Bu_4N^+. The very high binding affinity of **1** toward the six quaternary ammoniums is ascribed to the enhanced electrostatic and cation-π interactions between **1** and these quaternary ammoniums, due the introduction of electron-withdrawing cyano groups, as recently described by us [19].

In summary, the inclusion complexes of six quaternary ammoniums with tetracyanoresorcin [4]arene have been studied by means of ESI-MS, fluorescence and NMR spectrometries. The results indicate that tetracyanoresorcin[4]arene does not only exhibit high affinities toward the six quaternary ammoniums, but also can discriminate their sizes. The high binding affinity toward these ammoniums makes tetracyanoresorcin[4]arene exploitable as their potential receptors with high sensitivity under neutral aqueous conditions, which is actively in progress in our laboratories.

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