C$_5$H$_5$N or H$_2$O), $M_r = 7084.54$, cubic, $Fm\bar{3}m$, $a = b = c = 26.5200(13)$ Å, $V = 18651.8(16)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.261$ g cm^{-3}, $2\theta_{max} = 50.0°$ ($-31 \le h \le 31$, $-31 \le k \le 18$, $-28 \le l \le 31$), $T = 173$ K, 22842 measured reflections, $R1 = 0.0602$ for 670 reflections ($I > 2\sigma(I)$), $wR2 = 0.1840$ for 891 independent reflections (all data) and 63 parameters, $GOF = 0.990$.

Data were collected on a Bruker SMART-APEX CCD diffractometer using Mo$_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), operating in the Ω and φ scan mode. All crystal data were corrected for Lorentz and polarization effects, and the SADABS[25] program was used for absorption correction. The structures were solved by direct methods and the structure solutions and refinements were based on $|F^2|$. All non-hydrogen atoms were refined with anisotropic displacement parameters, whereas hydrogen atoms were placed in calculated positions and given isotropic U values 20% higher than the atom to which they are bonded. All crystallographic calculations were conducted with the SHELXTL[26] software suite. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-156776 (**1**) and CCDC-156777 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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A Rationally Designed NH$_4^+$ Receptor Based on Cation–π Interaction and Hydrogen Bonding**

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Design and synthesis of ammonium ion receptors have received much attention, not only because ammonium binding is one of the fundamental problems of molecular recognition, but also because such receptors serve as an essential component of sensors used in clinical[1] and environmental analyses.[2] Most of the NH$_4^+$ receptors known to date harness hydrogen bonding in binding an ammonium ion.[3] For example, nonactin (see Scheme 1), a natural antibiotic agent and one of the most effective NH$_4^+$ receptors, utilizes four ethereal and four carbonyl oxygen atoms to bind NH$_4^+$ through hydrogen bonding.[4] While hydrogen bonding is most commonly involved in molecular recognition, cation–π interaction has drawn much attention in recent years.[5] In fact, cation–π interaction has been successfully employed in designing synthetic receptors for alkylammonium ions and alkali metal ions.[5, 6] Despite extensive theoretical studies on NH$_4^+$–π interaction, however, no synthetic NH$_4^+$ receptor exploiting cation–π interaction had been reported until recently. We recently reported a novel NH$_4^+$ receptor based on tris(pyrazol-1-ylmethyl)benzene that is highly selective for binding NH$_4^+$ over alkali metal ions.[7] Subsequent theoretical studies on this receptor by us[8] and others[9] suggest that the cation–π interaction between the substrate and the central benzene ring of the receptor plays a significant role in the binding affinity and selectivity of the tripodal receptor toward NH$_4^+$. Despite the high selectivity, however, the ion-selective electrode (ISE) based on this receptor shows low sensitivity and strong pH dependence of its performance in comparison to a nonactin-based ISE, and this hampers practical applications as a sensor. Here we present a rationally designed cage-type NH$_4^+$ receptor that binds the cation by both cation–π interaction and hydrogen bonding, with high sensitivity and selectivity comparable or superior to those of nonactin over a wide range of pH.

In designing the receptor, we considered the following stereoelectronic features: 1) spatial distribution of lone-pair

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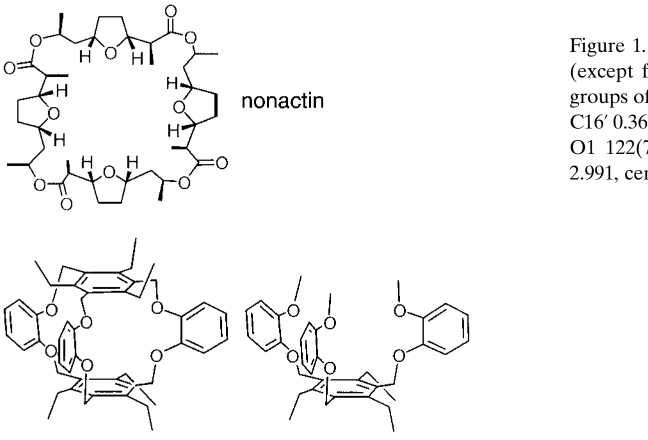
electrons for effective hydrogen bonding with the tetrahedral NH_4^+ ion, 2) benzene rings ideally positioned for strong cation–π interaction, and 3) a rigid framework with a cavity of correct size for binding NH_4^+. With this in mind, we designed receptor **1** in which two benzene rings are rigidly held together by three dialkoxybenzene units (Scheme 1). We chose phenolic oxygen atoms as hydrogen bonding acceptors because their pK_a values are larger than those of nitrogen atoms, and thus we can lower the pH dependence of the receptor performance. Molecular mechanics calculations[10] on **1** and its NH_4^+ complex showed that each dialkoxybenzene unit is almost ideally positioned to "bite" NH_4^+ through hydrogen bonding, while the two benzene rings are properly positioned at the top and bottom of the cage for cation–π interaction with NH_4^+, with an N ··· benzene centroid distance of about 3.0 Å. In addition, the cavity size of **1** is perfect for NH_4^+ but too large for smaller ions such as Li^+ and Na^+.



1 **2**

Scheme 1. Chemical structures of the ammonium receptors discussed here.

Receptor **1** is easily synthesized from the reaction of catechol with 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene[11] in two steps in good yield. The X-ray crystal structures[12] of **1** (see Supporting Information) and its NH_4^+ complex [**1**-NH_4]PF_6 (Figure 1) are in good agreement with those calculated by molecular modeling. These structures reveal that the only significant structural change in the receptor associated with NH_4^+ binding is that the mean distance between the two benzene rings increases from 5.588 to 5.966 Å. In [**1**-NH_4]PF_6, as expected, the NH_4^+ ion is located at the center of the receptor and forms hydrogen bonds with six oxygen atoms. A set of oxygen atoms (O2, O2A, and O2B) interacts with the NH_4^+ ion with O ··· N distances of 3.224(5) Å and N–H ··· O angles of 168(12)°, whereas the other set (O1, O1A, and O1B) has O ··· N distances of 3.226(5) Å and N–H ··· O angles of 122(7)°.[13] The average distance between the nitrogen atom of NH_4^+ and the center of the top or bottom benzene ring is 2.985 Å, which is in good agreement with the optimal distance for cation–π interaction between NH_4^+ and benzene suggested by theoretical studies.[5, 14] The PF_6^- counterion is located outside the cage with no apparent interactions.

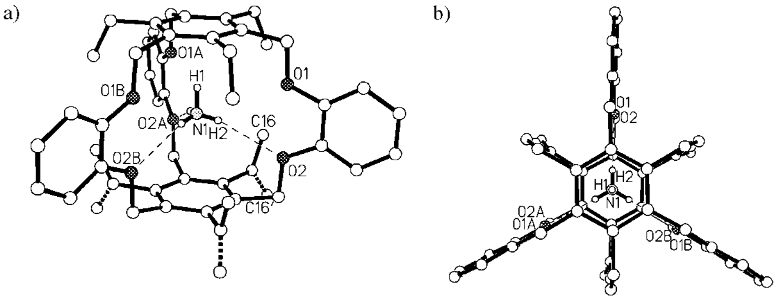


Figure 1. a) Side and b) top views of [**1**-NH_4]PF_6 in the solid state. Hydrogen atoms (except for those of NH_4^+) and the PF_6^- counterion are omitted for clarity. The ethyl groups of the "bottom" benzene ring are disordered over two sites (occupancy: C16 0.64, C16′ 0.36). Selected interatomic distances [Å] and angles [°]: O1 ··· N1 3.226(5), N1–H2 ··· O1 122(7), O2 ··· N1 3.224(5), N1–H2 ··· O2 168(12), centroid of "top" benzene ··· N1 2.991, centroid of "bottom" benzene ··· N1 2.980.

The performance of an ISE based on **1**[15] is comparable or even superior to that of a nonactin-based ISE in terms of sensitivity and selectivity (Figure 2): detection limit 3.2×10^{-6} M (**1**) versus 1.5×10^{-6} M (nonactin); selectivity coefficients $\lg K_{NH_4^+/K^+} = -0.97$ (**1**) versus -0.88 (nonactin), and $\lg K_{NH_4^+/Na^+} = -3.00$ (**1**) versus -2.85 (nonactin). Furthermore, it displays only a small pH dependence (see Supporting Information) which is also comparable to that of the nonactin-based ISE.

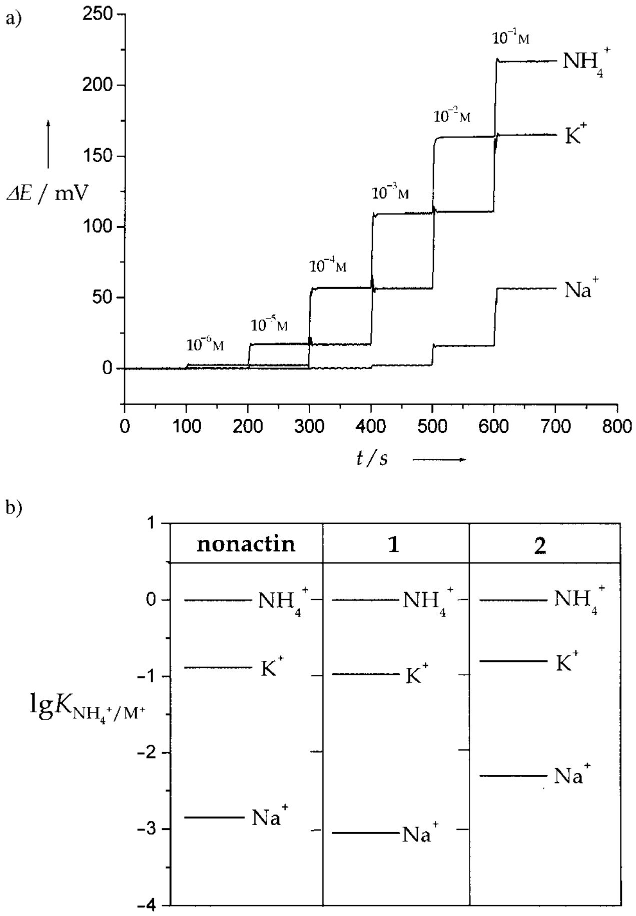


Figure 2. Responses of ISEs to NH_4^+, K^+, and Na^+ (background electrolyte: 0.05 M Tris–HCl, pH 7.2). a) Responses of an ISE based on **1**. b) Selectivity coefficients of ISEs based on nonactin, **1**, and **2**.

To understand the role of cation–π interaction in **1** in binding NH_4^+, we synthesized the modified receptor **2**, which does not have the "top" benzene ring (see Scheme 1). As expected, the binding affinity of **1** toward NH_4^+ is at least ten times higher than that of **2**: the association constants for binding of NH_4^+ to **1** and **2**, determined by the extraction method,[16] are 3.3×10^7 and $1.9 \times 10^6\,\text{M}^{-1}$, respectively.[17] This difference in binding affinity was also confirmed by a theoretical study. A gas-phase calculation[18] showed that the binding energies $-E_{\text{BSSE}}$ of **1** and **2** for NH_4^+ are 62.3 and 58.2 $\text{kcal}\,\text{mol}^{-1}$, respectively. The difference in binding energy between the two receptors (4.1 $\text{kcal}\,\text{mol}^{-1}$) is in reasonable agreement with the experimental value (ca. 1.7 $\text{kcal}\,\text{mol}^{-1}$)[19] calculated from the association constants if we consider solvation effects.[5, 20] These experimental and theoretical studies support a prominent role of cation–π interaction in the recognition of NH_4^+ by **1**.

In conclusion, we have presented a rationally designed cage-type receptor that binds NH_4^+ by cation–π interaction and hydrogen bonding, with high sensitivity and selectivity comparable or even superior to those of nonactin over a wide range of pH. In particular, this work demonstrates that an appropriate combination of hydrogen bonding and cation–π interaction can produce a large synergic effect in recognizing NH_4^+. The high performance, low cost, and easy synthesis may warrant practical applications of this receptor as an ammonium ion sensor.

Experimental Section

1: A solution of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (58 mg, 0.13 mmol) and 1,3,5-tris[(2-methoxyphenoxy)methyl]-2,4,6-triethylbenzene (69 mg, 0.13 mmol) in DMF (26 mL) was added to a suspension of K_2CO_3 (109 mg, 0.79 mmol) and [18]crown-6 (7 mg, 0.026 mmol) in DMF (6 mL) at 85 °C over 12 h. The resulting mixture was stirred for an additional 4 h and then cooled to room temperature. After addition of water and chloroform to the mixture, the aqueous layer was separated and extracted twice with chloroform. The combined organic layers were concentrated and purified by chromatography on silica to afford **1** (43 mg, 46 %). ^{1}H NMR ($CDCl_3$): $\delta = 6.92$ (s, 2H), 4.96 (s, 2H), 2.60 (q, 2H), 1.03 (t, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 149.6, 145.6, 131.8, 120.2, 111.1, 63.9, 23.1, 16.6$; MS (FAB): m/z: 727.3 [M^+]; satisfactory elemental analysis (C, H).

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[13] Although the distances between the ammonium nitrogen atom and receptor oxygen atoms O1 and O2 are essentially the same (3.226(5) and 3.224(5) Å, respectively), the different N–H ··· O angles (122(7) and 168(12)°, respectively) suggest that the ammonium ion forms a stronger hydrogen bond with O2 than with O1 in the solid state.

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[17] Furthermore, an ISE based on **1** is more selective and sensitive than that based on **2** for binding NH_4^+ over K^+ or Na^+ (see Figure 2b): detection limit 4.4×10^{-6} M (**2**).

[18] Ab initio calculations were performed with Gaussian 98.[21] The geometries were fully optimized with C_3 symmetry conditions at the B3LYP/3-21G* level. The binding energies of complexes were corrected for basis set superposition error (BSSE). The BSSE was calculated by using the counterpoise method[22] with a modification that takes account of the energy effect due to the change of geometries upon complexation.[23] Binding energies and BSSE were calculated at the B3LYP/6-31G** level.

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Macrocycles within Macrocycles: Cyclen, Cyclam, and Their Transition Metal Complexes Encapsulated in Cucurbit[8]uril**

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Jaheon Kim, Shigeru Sakamoto, Kentaro Yamaguchi,
and Kimoon Kim*

Dedicated to Professor Eiichi Kimura
on the occassion of his retirement

Inclusion of a macrocycle in a macrocycle, reminiscent of Russian Matrioshka dolls, is a rare phenomenon, although inclusion of crown ethers, cryptands, and their alkali metal complexes inside the cavity of γ-cyclodextrin has been known for many years.[1] Recently, the encapsulation of cryptands, crown ethers, and their alkali metal complexes in supramolecular capsules and cages held together by hydrogen bonds and coordination bonds, respectively, has also been reported.[2, 3] However, few examples of the inclusion of transition metal macrocyclic complexes in synthetic molecular or supramolecular host systems are available in the literature[4] even though such systems are potentially useful as catalysts with high specificity as a result of the unique microenvironment around the transition metal ion which is reminiscent of metalloenzymes.

Cucurbituril (CB[6]), a macrocycle comprising six glycoluril units, forms stable host–guest complexes with small molecules, such as aliphatic and aromatic amines.[5] Our recent discovery[6] of new cucurbituril homologues, cucurbit[*n*]uril (CB[*n*]; $n = 5$, 7, and 8), containing five, seven, and eight glycoluril units has opened up new opportunities to expand the host–guest chemistry of cucurbituril. For example, the largest member of the cucurbituril family, CB[8], has a cavity comparable to that of γ-cyclodextrin and can accommodate two aromatic guest molecules to form 1:2 host–guest complexes,[6] or 1:1:1 ternary complexes.[7] The large cavity prompted us to explore the inclusion of macrocycles and their transition metal complexes in CB[8]. Of the many potential candidates for the guest macrocycles we chose tetraazamacrocycles, not only because they are effective hosts for transition metal ions[8] but also because their transition metal complexes exhibit catalytic activities in many reactions, such as epoxydation and DNA hydrolysis.[9] Here we present novel macrocycles within macrocycles, in which cyclen (1,4,7,10-tetraazacyclododecane), cyclam (1,4,8,11-tetraazacyclotetradecane), and their transition metal complexes are encapsulated in CB[8].[10]

Heating an aqueous solution of CB[8] and cyclen tetrahydrochloride at 100 °C for 2 h, followed by slow cooling to room temperature produces colorless crystals of complex **1a**. The ^{1}H NMR spectrum of **1a** in D_2O reveals a shift of the cyclen signal to higher field relative to that of free cyclen, which is consistent with the formation of a 1:1 host–guest complex of CB[8], and cyclen.[11] The X-ray crystal structure of **1a** (Figure 1) confirms the encapsulation of a fully protonated cyclen macrocycle in the cavity of CB[8] with four Cl^- counterions residing outside CB[8]. The inner macrocyle is significantly tilted with respect to the outer macrocyle: the angle between the average planes of the inner

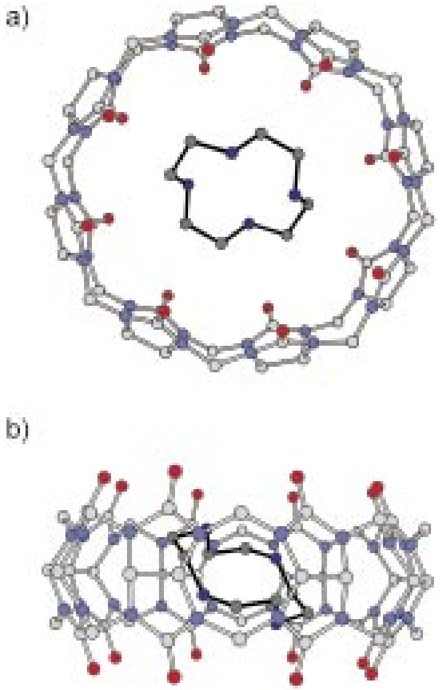

Figure 1. X-ray crystal structure of **1a**: a) top view and b) side view. Color code: oxygen: red, nitrogen: blue, carbon: gray. Hydrogen atoms, counterions (Cl^-), and solvent (H_2O) molecules are omitted for clarity.

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