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Origin of the High Affinity and Selectivity of Novel Receptors for NH_4^+ over K^+: Charged Hydrogen Bonds vs Cation–π Interaction

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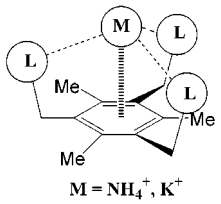
ABSTRACT



Given the recent report of a novel pyrazole receptor exhibiting a high selectivity for NH_4^+ over K^+, it would be interesting to investigate the origin of this selectivity and affinity so that better receptors could be designed. On the basis of extensive theoretical studies, we conclude that the origin arises from a subtle interplay of charged H-bonds and cation–π interactions. The approach employed herein would be very useful in the rational design of novel functional molecular systems.

Given the stellar role of molecular recognition in diverse fields of modern chemistry over the past two decades, in particular, host−guest complexation, a lot of interest has been evinced in understanding the underlying factors leading to high binding selectivities and affinities. This understanding has led to the design of novel receptors having high specificity, in particular, for systems exhibiting similar characteristics.[1−6] In this Letter, we focus our attention on the recognition of NH_4^+, since ammonium-containing compounds are very important in chemical, biological, and physiological molecular systems.[7] One of the major problems in the recognition of NH_4^+ is the nearly equivalent sizes of NH_4^+ and K^+. Thus, nonactin which is used in ion selective electrodes (ISE) is an effective NH_4^+ receptor but shows only about a 10-fold selectivity for NH_4^+ over K^+.[7] Recently, the

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use of benzene-based tripodal receptors as a model for studying the recognition of a variety of guest molecules has attracted much interest.[2,3] Using such a tripodal system, Chin et al.[8] observed a remarkable selectivity of NH_4^+ over K^+ ($10^{2.6}$) in the pyrazole receptor (comprised of a trimethylated phenyl ring with three pyrazole subunits **1**) which Hartshorn and Steel[3] synthesized as a new class of metal-encapsulating ligands. However, since the affinity of this compound for NH_4^+ is smaller than that of nonactin, it is desirable to design more potent receptors exhibiting greater affinity and higher selectivity for NH_4^+. Toward this end, we have investigated the origin of the selectivity and affinity for NH_4^+ using ab initio calculations[9] and predicted possible potent receptors.

To exhibit a high selectivity for NH_4^+, receptors should have an optimal space to capture NH_4^+ and strong interactions with NH_4^+. Since the radius of K^+ is almost the same as that of NH_4^+, the spatial differentiation may not be useful. Nevertheless, the receptor should have an optimal space for both cations to have high affinities. Our calculations indicate that the pyrazole receptor possesses both an optimal space and a good capability to distinguish between NH_4^+ and K^+. Thus, the predicted selectivity for NH_4^+ over K^+ ($10^{3.4}$ in $CHCl_3$ solution and $10^{2.4}$ in the gas phase) for the receptors with three subunits **1** is in reasonable agreement with the experimental value[8] ($10^{2.6}$ in $CHCl_3$ solution). The origin of this selectivity and affinity can be explained using the concepts of charged H-bond[10] and cation$-\pi$ interactions.[4,5] In particular, the strong proton-withdrawing power by subunits is responsible for both the selectivity and affinity and the cation$-\pi$ interaction, for the affinity.[11] Keeping this tenet in mind, we investigated receptor systems that have a trimethylated phenyl ring with three strong proton-withdrawing subunits.

Our next design strategy was to harness some of the differences between NH_4^+ and K^+ to develop further new receptors. Since the pK_a of NH_4^+ is 9.0, we considered several strong proton-withdrawing subunits (that are highly related to pK_a) such as azoles and azolines:[12] pyrazole **1** (pK_a = 2.5), pyrazoline **2**, oxazole **3** (pK_a = 0.8), oxazoline **4** (pK_a = 5.0), imidazole **5** (pK_a = 7.0), and imidazoline **6** (pK_a = 11.0), as shown in Figure 1. Since the imidazoline

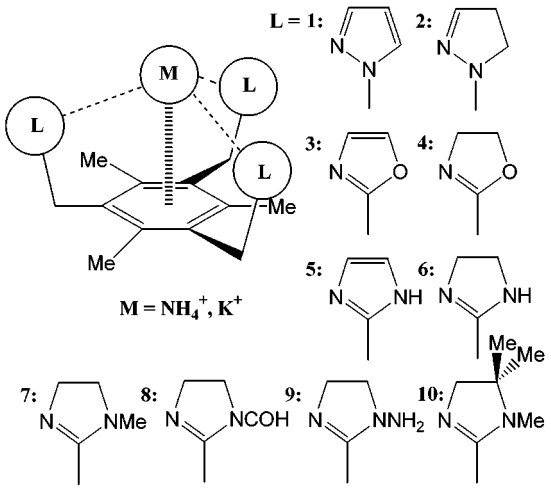

Figure 1. Schematics of receptors with subunits (**1**−**10**).

subunit is found to have the best selectivity for NH_4^+ among the six subunits (Table 1), we studied the imidazoline derivatives with electron donor or acceptor groups (**7**−**10**) to search for receptors with better proton-withdrawing power to strengthen the charged H-bonds. We also considered the cation$-\pi$ interaction. The strong cation$-\pi$ interaction between the benzene ring and cation (NH_4^+/K^+) is found to increase the affinity but to marginally decrease the selectivity.[13]

The effect of the solvent was investigated by calculating the binding energies [$E^R_{sol}(NH_4^+)$] and the preferential binding energies for NH_4^+ over K^+ [$\Delta E^R_{sol} = E^R_{sol}(NH_4^+) - E^R_{sol}(K^+)$] of selected receptors (with subunits **1**, **4**−**7**) in $CHCl_3$ solution. Compared to the gas phase, the binding energies of the receptors in $CHCl_3$ decrease by 40−50 kcal/mol.[14] However, the preferential binding energies slightly increase by 1−2 kcal/mol. Apart from maintaining their efficacy in solvent, the receptors also need to possess solvent access-blocking groups (such as Me), which replace H atoms attached to C atoms adjacent to the N atoms. In this way, the coordination number of the receptors is limited to no more than 4. Sine NH_4^+ and K^+ favor the coordination numbers of 4 and 6,[15] respectively, the optimally solvated NH_4^+ in the presence of receptors is more energetically favored than the under-solvated K^+, as suggested by Chin et al.[8,16] Our results indicate that the imidazoline receptors

(8) Chin, J.; Walsdorff, C.; Stranix, B.; Oh, J.; Chung, H. J.; Park, S.-M.; Kim, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 2756. The association constant of the pyrazole receptor (with subunits **1**) for binding of the NH_4^+ is $10^{6.15}$ M^{-1}.

(9) Hartree−Fock (HF) calculations [and Moller−Plesset second-order perturbation (MP2) calculations for few systems] and calculations of self-consistent-reaction field method (IPCM) in $CHCl_3$ solution were carried out using a Gaussian suite of programs (Frisch et al. *Gaussian 94*; Gaussian Inc.: Pittsburgh, PA, 1995).

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(13) Although the cation$-\pi$ interactions of a benzene molecule with NH_4^+ and K^+ are almost equivalent at their optimal distances, the interactions are stronger in the case of K^+ than NH_4^+ in the present receptor systems (Table 1) wherein the benzene−cation distances (~3.0 Å) are slightly longer than the optimal distances for NH_4^+ (~2.8 Å) and K^+ (~2.9 Å) by ~0.2 and ~0.1 Å, respectively.

(14) When the receptors are in water, the binding energies are further decreased. In the case of **1**, $E^R_{sol}(NH_4^+) = -12.6$ kcal/mol and $\Delta E^R_{sol}(NH_4^+/K^+) = -1.7$ kcal/mol.

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(16) For the same reason, in solution the trimethylated or triethylated phenyl ring would have better selectivity than the nonsubstituted phenyl ring.

(17) In a strongly charged H-bonding case such as **6**, **7**, or **10**, the receptor can be protonated according to ab initio calculations. In the presence of H_3O^+, the receptor is protonated with deprotonation of H_3O^+, and therefore the protonated receptor interacts with H_2O. In the presence of NH_4^+, the receptor is not protonated. The H_3O^+ issue was raised due to a comment from Prof. J. Chin.

Table 1. Interaction Energies [$E(NH_4^+)$] of the Receptors with Subunits (**1**−**10**) Interacting with NH_4^+ and Their Preferential Interaction Energies [$\Delta E = E(NH_4^+) - E(K^+)$] over K^+ [a]

receptor	E^R_{gas}	ΔE^R_{gas}	E^S_{gas}	ΔE^S_{gas}	E^π_{gas}	ΔE^π_{gas}	$\Delta E^{3S+\pi}_{gas}$	E^R_{sol}	ΔE^R_{sol}
1	−63.34	−3.33	−24.29	−2.56	−15.24	3.45	−4.24	−21.3	−4.6
2	−64.48	−1.84	−23.99	−1.93	−15.31	3.78	−2.01		
3	−67.26	−3.38	−22.71	−2.64	−14.91	4.16	−3.77		
4	−68.48	−4.31	−24.94	−3.08	−15.11	4.01	−5.23	−24.1	−4.6
5	−72.58	−4.12	−29.84	−3.06	−15.65	3.43	−5.75	−24.6	−6.1
6	−80.94	−4.96	−30.04	−3.54	−15.82	3.29	−7.32	−36.9	−6.5
7	−80.67	−5.54	−30.78	−3.79	−15.97	3.16	−8.21	−33.1	−7.6
8	−63.44	−4.93							
9	−78.27	−5.09							
10	−85.37	−5.35							

[a] The data listed are the HF/6-31G* values in kcal/mol. The MP2 data (calculated for limited cases due to the large size of the molecular systems) are consistent with the HF results. In particular, the differences in relative energies between the HF and MP2 results are not significant. For the receptors with **1**−**7** and **10**, the cation−π binding energy of the benzene with NH_4^+/K^+ is ∼15.5/∼19 and ∼17/∼19.5 kcal/mol at the HF/6-31G* and MP2/6-31G* levels, respectively. At the MP2/6-311+G** optimal geometry, the binding energy of the benzene with NH_4^+/K^+ is 16.9/16.8 kcal/mol.[5a] Superscripts "R" and "S" denote receptor and subunit, respectively. E^R/E^S is the binding energy of the receptor/subunit with NH_4^+. E^π denotes the cation−π interaction energy. The sum of the binding energy component differences ($\Delta E^{3S+\pi} = 3\Delta E^S + \Delta E^\pi$) is correlated to the receptor binding energy difference ΔE^R, and therefore this analysis can be utilized to predict new receptors for NH_4^+. The reason ΔE^R is smaller in magnitude than $\Delta E^{3S+\pi}$ (i.e., the subadditive effect) is mainly due to the induction effect. The values of E^R and ΔE^R for selected receptors (**1**, **4**−**7**) in $CHCl_3$ solution [E^R_{sol} and ΔE^R_{sol}] were obtained using the IPCM method.[9]

with **6** and **7** can be potent receptors for NH_4^+ (∼10^2 higher in selectivity and ∼10^4 greater in affinity than the pyrazole receptor with **1**).[18,19] The present approach to the design of novel receptors with high affinity and selectivity employed in this study would be a useful aid in the design of novel functional molecular systems. In addition, our results would be very useful in molecular recognition studies of nanostructures in the gas phase[20] wherein the origin of pure interaction forces in the absence of solvent effects is elucidated.

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(18) In $CHCl_3$ solution, the relative selectivities of receptors with **4**, **5**, **6**, and **7** with respect to the receptor with **1** are predicted to be 1, $10^{1.1}$, $10^{1.4}$, and $10^{2.2}$, respectively. When a K^+ ion is solvated, the enthalpy change is almost the same as the binding energy (E), but the free energy change is only ∼40% of the binding energy.[15] Assuming a similar correlation, the free energy changes in receptors with **4**, **5**, **6**, and **7** interacting with an NH_4^+ ion are expected to be around 8.5, 9.6, 9.8, 14.8, and 13.2 kcal/mol, respectively. These correspond to the association constants for NH_4^+(K_a), which are $10^{6.2}$, $10^{7.1}$, $10^{7.2}$, $10^{10.8}$, and $10^{9.7}$ M^{-1}, respectively.

(19) While this manuscript was in the review process, Ahn and co-workers reported the affinity and selectivity of the receptor with subunits **4** in $CHCl_3$ solution. [Ahn, K. H.; Kim, S.-G.; Kim, K.-H.; Jung, J.; Kim, J.; Chin, J.; Kim, K. *Chem. Lett.* **2000**, 170.] For the oxazoline receptor (with subunits **4**), the association constant for binding of the NH_4^+ is $10^{7.38}$ M^{-1} and the selectivity for binding NH_4^+ over K^+ is $10^{2.65}$. Thus, this association constant and the relative association constant ($10^{1.23}$) with respect to the pyrazole receptor are very close to our estimated values, and the oxazoline receptor has almost the same selectivity as the pyrazole receptor.[18] Therefore, this experiment has verified one of our predictions.

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