Communications to the Editor

On Binding Forces between Aromatic Ring and Quaternary Ammonium Compound

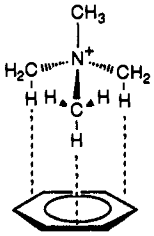
Kwang S. Kim,*,† Jin Yong Lee,† Sang Joo Lee,†
Tae-Kyu Ha,*,‡ and Dong H. Kim*,†

Center for Biofunctional Molecules and
Department of Chemistry, Pohang University of
Science and Technology, San 31, Hyojadong
Pohang 790-784, Korea
Laboratory of Physical Chemistry
Swiss Federal Institute of Technology
CH-8092 Zurich, Switzerland

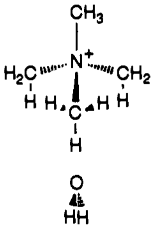
Received December 30, 1993

Recently, the cation-π interaction has received considerable attention as a new type of binding force that is important in biological systems. Several propositions have been formulated on the basis of experimental findings and theoretical calculations on the nature of the force at the molecular level.[1-3] Of these, the proposition of Dougherty et al.[2] is of particular interest. According to them the cation-π interaction is responsible for not only the ion selectivity of potassium channel but also the binding of acetylcholine (ACh) to its deactivating enzyme, acetylcholinesterase (AChE). This enzyme has long been served as a target molecule in designing potential therapeutic agents of various ailments such as myasthenia gravis, glaucoma, and possibly Alzheimer's desease.[4] Until recently, it was generally believed that at the active site of AChE there is present an anionic subsite consisting of carboxylate groups, which accommodates the charged quaternary moiety of the neurotransmitter.[4c] But, recent X-ray structure analysis of AChE revealed that at the active site there are 14 aromatic amino acid residues but no more than one acidic group which is slightly far from the charged moiety in a protonated form or with a counterion nearby.[3]

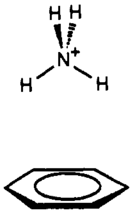
In an effort to shed light on the character of the binding forces of ACh to AChE as well as to better understand the nature of the cation-π interaction, we carried out extensive *ab initio* calculations for the complexes of tetramethylammonium cation (Me_4N^+) with benzene (**1**) and with water (**2**), and the complexes of ammonium cation (H_4N^+) with benzene (**3**) and with water (**4**). The calculations involve the Hartree–Fock (HF) and Möller–Plesset second-order perturbation (MP2) treatments with 6-311+G** basis sets at optimized geometries using Gaussian 92,[5] and the results are summarized in Table 1.



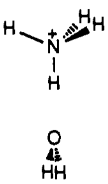
1



2



3



4

It is seen that the MP2-predicted enthalpy and free energy changes (ΔH_r, ΔG_r) for the complex formations agree reasonably well with the experimental data.[6] In the case of **2** the charge–dipole interaction ($\Delta E_{+,\mu}$ = −9.8 kcal/mol) constitutes a major binding force. In the case of **1** not only the charge-quadrupole ($\Delta E_{+,Q}$ = −7.7 kcal/mol) and charge-polarizability ($\Delta E_{+,\alpha}$ = −3.2 kcal/mol) interactions but also the electron correlation effect ($\Delta E_{cor} = -8.4 \pm 1.5$ kcal/mol) is important. From the comparison of the HF and MP2 results, we find that the electron correlation effect enhances the interaction energies of $\Delta E_{+,Q}$ and $\Delta E_{+,\alpha}$ by 1.5 and 1.1 kcal/mol, respectively. The sum of the electrostatic interaction energy (ΔE_{es}) and ΔE_{cor} is much larger in magnitude than the binding energy (ΔE^N). A major portion of this energy difference (~7.6 kcal/mol) is likely to be due to the exchange repulsion (see footnote *f* of Table I).

The large difference between the HF and MP2 results, large ΔE_{cor}, arises mostly because a small fraction of the LUMO electron clouds is taken into account in the MP2 results, but not in the HF results. In the π-LUMOs of **1** the π orbital lobes are much highly prolate from benzene to Me_4N^+ compared with those in the HOMO (Figure 1).[7] The respulsive interaction between the delocalized π electron clouds over the benzene ring and the electron clouds of Me_4N^+ tends to be mitigated through a transfer of the π electrons in the benzene ring to the σ^*_{C-H} orbitals in Me_4N^+, (i.e., π–σ^* through-space interaction, which is a very novel type of interaction). Namely, a portion of the π-LUMO electron clouds surrounds the partially positively charged H atoms in Me_4N^+, so that ΔE_{cor} contributes significantly in the binding of Me_4N^+ to benzene.

On the other hand, in the case of **2** the hydrogen atoms in Me_4N^+ approach to the electron-donating lone pair electrons localized around the oxygen nucleus of H_2O, which results in a σ electron transfer. Owing to the lack of π-electrons in **2** and **4**, their ΔE_{cor} are small (-2.9 ± 0.9 kcal/mol and -2.6 ± 1.0 kcal/mol, respectively). In comparison, ΔE_{cor} for **3** (-6.2 ± 1.1 kcal/mol) is large but smaller (by ~2.2 kcal/mol) in magnitude than that for **1**, because the π and σ^*_{C-H} orbitals in **1** are ligned up to

---

† Pohang University of Science and Technology.

‡ Swiss Federal Institute of Technology.

[1] (a) Hasan, F. B.; Elkind, J. L.; Cohen, S. G.; Cohen, J. B. *J. Biol. Chem.* **1981**, *256*, 7781–7784. (b) Dhaenens, M.; Lacombe, L.; Lehn, J.-M; Vigneron, J.-P. *J. Chem. Soc., Chem. Commun.* **1984**, 1097–1099. (c) Schneider, H.-J.; Guettes, D.; Schneider, U. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 647–649; *J. Am. Chem. Soc.* **1988**, *110*, 6449–6454. (d) Quinn, D. M.; *Chem. Rev.* **1987**, *87*, 955–979. (e) Petti, M. A.; Shepodd, T. J.; Barrans, R. E.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825–6840. (f) Dhaenens, M.; Lehn, J.-M.; Fernandez, M.-J.; Vigneron, J.-P. *New J. Chem.* **1991**, *15*, 873–877. (g) Radic, Z.; Gibney, G.; Kawamoto, S.; MacPhee-Quigley, K.; Bongiorno, C.; Taylor, P. *Biochem.* **1992**, *31*, 9760–9767. (h) Dhaenens, M.; Vigneron, J.-P.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, 129–131. (i) Duffy, E. M.; Kowalczyk, P. J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1993**, *115*, 9271–9275. (j) Schwabacher, A. W.; Zhang, S.; Davy, W. *J. Am. Chem. Soc.* **1993**, *115*, 6995–6996. (k) Garel, L.; Lozach, B.; Dutasta, J.-P.; Collet, A. *J. Am. Chem. Soc.* **1993**, *115*, 11652–11653. (l) Miller, C. *Science* **1993**, *261*, 1692–1693.

[2] (a) Dougherty, D. A.; Stauffer, D. A. *Science* **1990**, *250*, 1558–1560. (b) McCurdy, A.; Jimenez, L.; Stauffer, D. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 10314–10321. (c) Kumpf, R. A.; Dougherty, D. A. *Science* **1993**, *261*, 1708–1710. (d) Kearney, P. C.; Mizoue, L. S.; Kumpf, R. A.; Forman, J. E.; McCurdy, A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1993**, *115*, 9907–9919.

[3] (a) Sussman, J. L.; Harel, M.; Frolow, F.; Oefner, C.; Goldman, A.; Toker, L.; Silman, I. *Science* **1991**, *253*, 872–879. (b) Harel, M.; Schalk, I.; Ehret-Sabatier, L.; Bouet, F.; Goeldner, M.; Hirth, C.; Axelsen, P. H.; Silman, I.; Sussman, J. L. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 9031–9035.

[4] (a) Krogsgard-Larsen, P. In *A Textbook of Drug Design and Development*; Krogsgard-Larsen, P., Bundgaard, H., Eds.; Harwood Academic Publ.: Chur, Switzerland, 1991; pp 419–428. (b) Egan, T. M.; North, A. *Nature* **1986**, *319*, 405–407. (c) Elbeiu, A. D. In *Comprehensive Medicinal Chemistry*; Sammens, P. G., Ed. Pergamon: Oxford, 1990; Vol. 2, pp 365–389.

[5] Frisch et al. *Gaussian 92*; Gaussian, Inc.: Pittsburg, 1992.

[6] Meot-Ner(Mautner), M.; Deakyne, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 469–474.

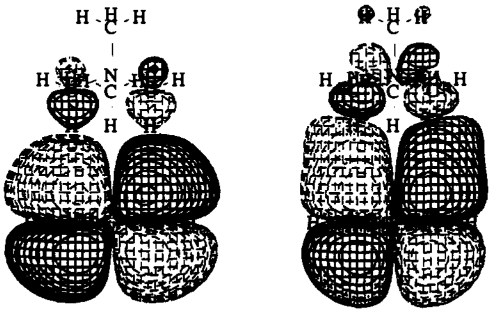
[7] The first LUMO is a σ orbital and the second LUMOs are degenerate π orbitals. Since the enhancement of charge–polarizability interaction by electron correlation arises mainly from an easy transfer of the delocalized π electrons from the HOMOs to LUMOs, one of the degenerate π-LUMOs is shown.

0002-7863/94/1516-7399$04.50/0

Table 1. Complexation Energies of **1–4**[a]

	1	**2**	**3**	**4**
ΔE_e^N	-11.72	-11.52	-18.97	-21.70
ΔE_e^B	-8.67	-9.72	-16.88	-19.76
ΔE_e	-10.20 ± 1.53	-10.62 ± 0.90	-17.93 ± 1.05	-20.73 ± 0.97
ΔE_0	-9.66 ± 1.53	-8.98 ± 0.90	-16.99 ± 1.05	-18.93 ± 0.97
ΔH_r	-9.49 ± 1.53	-8.95 ± 0.90	-16.75 ± 1.05	-18.85 ± 0.97
ΔH_r^{exp} [b]	-9.4 ± 1.	-9.0 ± 1.	-19.3 ± 1.[c]	
ΔG_r [d]	-4.08 ± 1.53	-3.61 ± 0.90	-12.79 ± 1.05	-13.87 ± 0.97
ΔG_r^{exp} [b]	-3.5	(-2.6 ± 1.6)	(-12.4 ± 1.6)[c]	
d_{N-R} [e]	4.217	3.936	2.915	2.993
$\Delta E_{+,\mu}$	0.00	-9.78	0.00	-16.91
$\Delta E_{+,Q}$	-7.71	-0.37	(-23.35)	-0.85
$\Delta E_{+,\alpha}$	-3.23	-0.53	(-6.88)	-1.58
$\Delta E_{\alpha,\mu}$	0.00	-0.25	0.00	-0.20
ΔE_{es}	-10.94	-10.93	(-30.23)	-19.54
$\Delta E'_{cor}$ [f]	-4.71 ± 1.53	-1.55 ± 0.90	-3.64 ± 1.05	-1.49 ± 0.97
ΔE_{cor} [f]	-8.40 ± 1.53	-2.89 ± 0.90	-6.19 ± 1.05	-2.56 ± 0.97

[a] All energies are given in kcal/mol. ΔE_e^N and ΔE_e^B denote the binding energies without and with basis set superposition error (BSSE) correction, respectively. Although the latter energy is generally accepted to be more reliable, there is a trend that the latter is still underestimated, while the former is overestimated.[8] Thus, the median value plus/minus a half value of the BSSE, ΔE_e, was chosen to represent both ΔE_e^B and ΔE_e^N as the upper and lower bounds, respectively. All other thermodynamic quantities were represented in the same way: ΔE_0 is the zero point energy, while ΔH_r and ΔG_r are the enthalpy and Gibbs free energy at 1 atm and 298 K, respectively. All geometries were optimized with MP2/6-311+G** calculations. To obtain thermal energies, the MP2/6-31G* vibrational frequencies were used for all the complexes except for **1** for which the MP2/6-31G frequencies were used due to the calculational limitation. Each contribution term for the electrostatic interactions between Me_4N^+/H_4N^+ and C_6H_6/H_2O is denoted by $\Delta E_{+,\mu}$, $\Delta E_{+,Q}$, and $\Delta E_{+,\alpha}$ in which the first subscript denotes the + charge in Me_4N^+/H_4N^+, while the second subscript denotes the dipole, quadrupole, and polarizability in C_6H_6/H_2O, respectively. $\Delta E_{\alpha,\mu}$ is the interaction energy between the polarizability of Me_4N^+/H_4N^+ and the dipole of C_6H_6/H_2O. Since the electrostatic interactions due to high multipole moments and hyperpolarizabilities are either zero or negligible, the total electrostatic interaction energy (ΔE_{es}) is approximately the sum of $\Delta E_{+,\mu}$, $\Delta E_{+,Q}$, $\Delta E_{+,\alpha}$, and $\Delta E_{\alpha,\mu}$, unless there is not much molecular orbital interaction in complexation. (But, for a complex like **3** in which the two inner molecules are separated only by a short distance with high redistribution of electrons, the multipole expansion may not be a useful representation; thus, the corresponding values are given in parentheses. [b] Experimental values from ref 6. ΔG_r^{exp}'s in parentheses were estimated from the experimental enthalpy and estimated entropy with the errors of 1 kcal/mol and 2 cal/mol/K, respectively. [c] From Figure 1 in ref 6, one can note that the slope of the van't Hoff plots was to be drawn somewhat steep near room temperature region, indicating that the value of -19.3 is likely to be reduced down to -17. [d] ΔG_r's are not reliable enough due to a few low frequency modes. The lowest frequency mode of **1**/**3** was treated as internal free rotation by C_6H_6 and Me_4N^+/H_4N^+ at room temperature. [e] d_{N-R} is the distance (Å) between N and the centroid of benzene-quadrupole/water-dipole. [f] The electron correlation energies are defined as follows. $\Delta E'_{cor}/\Delta E_{cor}$ is the value of E_e(MP2) at the MP2 optimized geometry subtracted by E_e(HF) at the HF/MP2 optimized geometry. Since the benzene complexes have high repulsive energies between the benzene π-electrons and the countermolecule electrons, the complex structure at the MP2 optimized geometry is located at highly repulsive hard wall potential region at the level of the HF theory. This results in a large electron correlation energy difference between $\Delta E'_{cor}$ and ΔE_{cor}. Since the MP2 structure should be considered much more realistic, only ΔE_{cor} is discussed in the text.



HOMO π-LUMO

Figure 1. π-LUMO and HOMO of the complex of Me_4N^+ with benzene.

give the maximum overlap, while the π and σ^*_{N-H} orbitals in **3** are tilted. Further, the portion of ΔE_{cor} in the binding is much smaller in **3** than **1**. Apparently, since the positive charge enhances polarizability and charge transfer in the π-LUMO, ΔE_{cor} becomes much larger in magnitude than the ordinary dispersion energy between neutral molecules.

In conclusion, the results of our *ab initio* calculations confirm that the important binding forces in the complexing of Me_4N^+ with benzene arises from the charge-quadrupole and charge-polarizability interactions in agreement with the proposition of Dougherty and Stauffer.[2a] What is even a more important finding for the binding is that ΔE_{cor} is as important as the charge–quadrupole interaction and plays a key role in the binding so that Me_4N^+ binds benzene slightly more strongly than water. This is important, considering the fact that H_4N^+ binds water more strongly than benzene. Apparently, a tetramethyl quaternary ammonium ion is an exceptional cation that forms a complex efficaciously with aromatic rings, and now we may understand why nature has chosen a cation such as ACh for interaction with aromatic rings in AChE. Finally, the present study may provide a theoretical background for designing of efficient aromatic host-charged guest supramolecules.[9]

Acknowledgment. We are grateful to the Korea Science and Engineering Foundation for geneous support of this study. It is acknowledged that most of the calculations were performed at SERI/KIST and the ETH computer center.

---

(8) (a) Davidson, E. R.; Chakravorty, S. J. *Chem. Phys. Lett.* **1994**, *217*, 48–54. (b) Chakravorty, S. J.; Davidson, E. R. *J. Phys. Chem.* **1993**, *97*, 6373–6383. (c) Racine, S. C.; Davidson, E. R. *J. Phys. Chem.* **1993**, *97*, 6367–6372. (d) Kim, K. S.; Mhin, B. J.; Choi, U.-S.; Lee. K. *J. Chem. Phys.* **1992**, *97*, 6649–6662. (e) Mhin, B. J.; Lee, S. J.; Kim, K. S. *Phys. Rev. A* **1993**, *48*, 3764–3770.

(9) (a) Petti, M. A.; Shepodd, T. J.; Barans, Jr., R. E.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825–6840. (b) Shinai, S.; Araki, K.; Matsuda, T.; Nishiyama, N.; Ikeda, H.; Takasu, I.; iwamoto, M. *J. Am. Chem. Soc.* **1990**, *112*, 9053–9058. (c) Araki, K.; Shimizu, H.; Sinkai, S. *Chem. Lett.* **1993**, 205–208.