JOC*Note*

Molecular Recognition of Fluoride Anion: Benzene-Based Tripodal Imidazolium Receptor

Sunggoo Yun,† Hyejae Ihm,† Heon Gon Kim,† Chi-Wan Lee,† Bandyopadhyay Indrajit,† Kyung Seok Oh,† Young Jun Gong,† Jung Woo Lee,† Juyoung Yoon,‡ Hee Cheon Lee,† and Kwang S. Kim*,†

National Creative Research Initiative Center for Superfunctional Materials, Department of Chemistry, Division of Molecular and Life Sciences, Pohang University of Science and Technology, San 31, Hyojadong, Namgu, Pohang 790-784, Korea, and Department of Chemistry, Ewha Womans University, Seoul, Korea

kim@postech.ac.kr

Received August 26, 2002

Abstract: A benzene-based tripodal imidazolium receptor utilizing the strong $(C-H)^+\cdots X^-$ hydrogen bonding interaction between imidazolium moieties and halide anions is extensively investigated both theoretically and experimentally. Ab initio calculations predict that this receptor has a very high affinity for fluoride ion (F^-). The association constant and free energy gain of the *N*-butyl receptor **2** for F^- in acetonitrile were measured to be 2.1×10^5 M^{-1} and −7.25 kcal/mol, respectively, showing that the receptor has a high affinity for F^- in highly polar organic solvents.

The design of new receptors for molecular recognition has attracted considerable interest in the recent past.[1] In particular, the studies of novel receptors with various degrees of affinity and selectivity toward anions such as F^-, Cl^-, $H_2PO_4^-$, and carboxylates, are quite intriguing.[2] We are particularly interested in F^- because of its beneficial effects in human physiology such as prevention of dental caries[3] and treatment of osteoporosis,[4] etc.

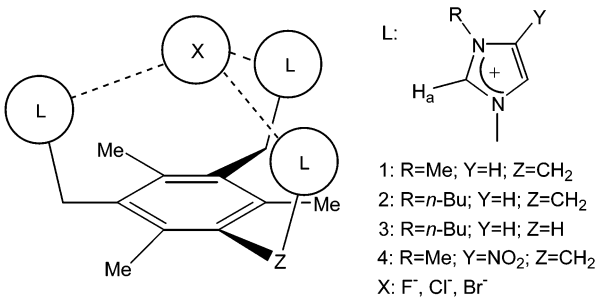

FIGURE 1. Schematics of imidazolium receptors.

Recently, Sato et al.[5] proposed the benzene-based tripodal imidazolium receptor **2** for halide anions based on a new type of interaction, $(C-H)^+\cdots X^-$ hydrogen bonding (Figure 1). This novel type of charged hydrogen bonding is very interesting in comparison with many other types of hydrogen bonding.[6] Although the tripodal imidazolium receptor has shown large association constants for Cl^-, Br^-, and I^-, its binding to F^- was not reported possibly due to analytical difficulties (vide infra). To enhance the anion binding strength, we have designed and synthesized a modified tripodal imidazolium receptor **4**[7] by adding a nitro group to the imidazolium sidearm to utilize both charge−charge interaction and charge−dipole interaction.[8] This receptor has shown enhanced anion affinity for Cl^- compared to Sato's receptor. However, the recognition of F^- by **4** was not possible due to the reaction between the receptor and F^- (as a nucleophile). Here we investigated the affinity and selectivity of the tripodal imidazolium receptors **1** and **2** to the F^- ion both theoretically and experimentally.

For this study, we carried out ab initio calculations to find out if the receptors can have high affinity and selectivity for F^-. The optimized structure of the complex of the *N*-methyl tripodal imidazolium receptor **1** with F^- ions shows C_{3v} symmetry as shown in Figure 2. The strength of ionic hydrogen bond interaction depends on the hydrogen bond distance and angle. The predicted structures of complexes of **1** with halide anions (Table 1) show that the ionic hydrogen bond distance for F^- (1.82 Å) is shorter than those for Cl^- and Br^- (2.40 and 2.56 Å), and the hydrogen bond angle for F^- (168.3°) is much more linear than those for Cl^- and Br^- (163.4 and 162.1°). The distances between the benzene centroid and the halide anions, F^-, Cl^-, and Br^-, are 3.24, 3.84, and 4.02 Å, respectively, and the binding energies are 247.2, 217.0, and 211.3 kcal/mol in the gas phase, respectively.

* To whom correspondence should be addressed. Phone: 82-54-279-2110. Fax: 82-54-279-8137.
† Pohang University of Science and Technology.
‡ Ewha Womans University.

(1) (a) Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Eds.; *Comprehensive Supramolecular Chemistry*; Elsevier: Amsterdam, 1996; Vols. 1−11. (b) Niikura, K.; Metzger, A.; Anslyn, E. V. *J. Am. Chem. Soc.* **1998**, *120*, 8533−8534. (c) Bission, A. P.; Lynch, V. M.; Monahan, M.-K. C.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2340−2342. (d) Stack, T. D. P.; Hou, Z.; Raymond, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 6466−6467. (e) Gallivan, J. P.; Dougherty, D. A. *Org. Lett.* **1999**, *1*, 103−106. (f) Hong, B. H. et al. *Science* **2001**, *294*, 348−351. (g) De Wall, S. L.; Barbour; L. J.; Gokel, G. W. *J. Am. Chem. Soc.* **1999**, *121*, 8405−8406. (h) Kim, H. G. et al. *Org. Lett.* **2002**, *4*, 3971−3974. (i) Choi, H. S. et al. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12094−12099. (j) Oh, K. S. et al. *Org. Lett.* **2000**, *2*, 2679−2681. (k) Choi, H. S.; Kim, K. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2256−2258; *Angew. Chem.* **1999**, *111*, 2400−2402. (l) De Wall, S. L. et al. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 6271−6276. (m) Yun, S. et al. *Org. Lett.* **2002**, *5*, 471−474.

(2) (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609−1646. (b) Antonisse, M. M. G.; Reinhoudt, D. N. *Chem. Commun.* **1998**, *4*, 443−448. (c) Black, C. B.; Andrioletti, B.; Try, A. C.; Ruiperez, C.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 10438−10439. (d) Mizuno, T.; Wei, W.-H.; Eller, L. R.; Sessler, J. *J. Am. Chem. Soc.* **2002**, *124*, 1134−1135. (e) Kim, K. S. et al. *J. Phys. Chem. B* **1998**, *102*, 461−463. (f) Dietrich, B. et al. *Helv. Chim. Acta* **1996**, *79*, 569−587. (g) Yamaguchi, S.; Akiyama, S.; Tamao, K. *J. Am. Chem. Soc.* **2001**, *123*, 11372−11375.

(3) Kirk, K. L. *Biochemistry of the Halogens and Inorganic Halides*; Plenum Press: New York, 1991; p 58.

(4) Kleerekoper, M. *Endocrinol. Metab. Clin. North Am.* **1998**, *27*, 441.

(5) Sato, K.; Arai, S.; Yamagishi, T. *Tetrahedron Lett.* **1999**, *40*, 5219−5222.

(6) (a) Kim, K. S. et al. *Chem. Rev.* **2000**, *100*, 4145−4185. (b) Oh, K. S. et al. *Biochemistry* **2000**, *39*, 13891. (c) Kim, K. S. et al. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 6373. (d) Tarakeshwar, P. et al. *J. Am. Chem. Soc.* **2001**, *123*, 3323. (e) Kim. K. S. et al. *Biochemistry* **2002**, *41*, 5300.

(7) Ihm, H.; Yun, S.; Kim, H. G.; Kim, J. K.; Kim, K. S. *Org. Lett.* **2002**, *4*, 2897−2900.

(8) Cui, C.; Cho, S. J.; Kim, K. S. *J. Phys. Chem. A* **1998**, *102*, 1119−1123.

10.1021/jo0263519 CCC: $25.00 © 2003 American Chemical Society
Published on Web 02/15/2003

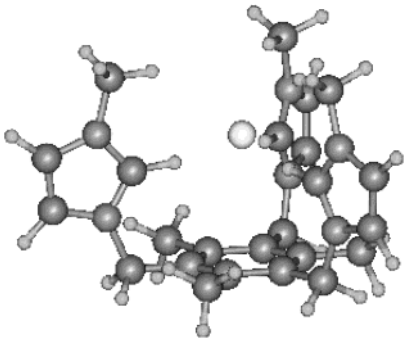

FIGURE 2. Calculated structure of **1** with fluoride anion.

Although the binding energies are large in the gas phase, those values are much reduced in polar solvents because the ionic hydrogen bond strength is dependent on the solvent polarity and the effective charges on atoms in **1** are also reduced. In solvents with a dielectric constant greater than 10, the binding energies (which are larger than 200 kcal/mol in the gas phase) decrease to only ~30 kcal/mol. The calculated binding energies of **1** with F^- and Cl^- in the solvent medium with the dielectric constant of acetonitrile ($\epsilon = 36.64$) are −29.4 and −17.9 kcal/mol, respectively. From the relative binding energies, the host **1** should recognize F^- more effectively than Cl^- or Br^- in highly polar solvents as well as in the gas phase.

Since ab initio calculations predict that the hydrogen bonding interactions of **1** with F^- is particularly strong in polar solvents, we have investigated its affinity for F^- in solution by ^1H NMR titration. Hosts **1** and **2** (which was already synthesized by Sato et al.)[5] were synthesized by reaction of the corresponding 1-alkyl-substituted imidazole and 2,4,6-tris(bromomethyl)mesitylene. In acetonitrile-d_3, addition of tetrabutylammonium fluoride, chloride, or bromide to host **1** resulted in a white precipitate. Therefore, host **2**, which has *n*-butyl group at N(3) of the imidazolium ring, was used.

In acetonitrile-d_3, the association constant of **2** with F^- is too large to be measured using the conventional NMR titration method. To determine the association constant of **2** for F^-, a competitive method[9] between hosts **2** and **3**[5] was used (see Experimental Section). In other cases, the association constants were determined from their titration curves by using a nonlinear curve-fitting program.[10] Stoichiometry for the binding of **2** to F^- was determined to be 1:1 using a Job plot. By using a competitive method, we found that **2** has a very high affinity for F^- with an association constant of 2.1×10^5 M^{-1} and a free energy gain of −7.25 kcal/mol. It was also observed that **2** showed a high affinity for Cl^- and Br^- with association constants of 7.6×10^4 M^{-1} and 4.6×10^4 M^{-1}, respectively, which are in good agreement with Sato's data.[5] It should be noted that **2** is more selective for the fluoride anion than for chloride and bromide anions (the selectivity of **2** for F^- over Cl^- is 2.8, and that for F^- over Br^- is 4.6).

The association constant of **2** for F^- is over 200 times larger than that of **3**. This indicates that the three imidazolium groups in **2** provide a much more favorable environment for anion complexation than the two imidazolium groups in **3**. It is interesting to note that the X-ray structure of **2** (under guest-free conditions) reveals that the three imidazolium groups are not on the same side of the benzene ring (Supporting Information). However, upon complexation with F^-, all three imidazolium units of **2** are expected to be on the same side of the benzene rings by $(C-H)^+\cdots F^-$ hydrogen bonding interactions, as predicted in our calculation. This is corroborated by a previous X-ray characterization[11] of a tripodal system similar to ours.

Nevertheless, the association constant of **2** with F^- is somewhat smaller than the theoretical prediction. In our experiments, it was also not possible to eliminate water molecules completely, because tetrabutylammonium fluoride salt is trihydrated. Since the complexation of F^- with water molecules is very strong compared to other halide anions,[12,13] the interaction of the host with the remnant water would have caused the discrepancy. Similar discrepancies in the affinity for F^- between experiments and calculations have already been noted by a few groups.[14] For example, though bis(phenylurea) *p-tert*-butylcalix[4]arene is theoretically expected to show the highest affinity among halide anions, it actually does not bind F^-,[14a] unlike other halide anions.

To clarify the difference between the theoretical prediction and the experimental results, we calculated the binding energies of three water molecules with F^- and Cl^- in acetonitrile solution because the trihydrate form of F^- was used in experiments. The two calculated binding energies are −14.0 and −4.9 kcal/mol, respectively. These results imply that the actual binding energies of **1** with F^- and Cl^- in the presence of a small amount of water molecules in acetonitrile solution are −15.4 and −13.0 kcal/mol. Because the free energy change is often no more than ~40% of the binding energy in the solvated ion systems, the calculated binding free energies for F^- and Cl^- in acetonitrile are expected to be around −6 and −5 kcal/mol, respectively. These values are in good agreement with the experimental results for **2** with F^- and Cl^- in acetonitrile solution (7.3 and 6.7 kcal/mol) in consideration that the difference between **1** and **2** is small.

We further investigated the affinity of the tripodal imidazolium receptor **2** for the F^- ion in more polar solvent media as shown in Table 3. The NMR titration experiments of hosts **1** and **2** were done on the 1:1 mixture of DMSO-d_6 and acetonitrile-d_3 or only DMSO-d_6. As we have shown that the binding affinity of host **4** depends on the polarity of the solvent,[7] the binding of hosts with halide anions decreased drastically in a more

(9) Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 3910−3915.

(10) Connors, K. A. *Binding Constants, The Measurement of Molecular Complex Stability*; Wiley: New York, 1987.

(11) Chin, J. et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 2756−2759.

(12) (a) Kim, J. et al. *J. Chem. Phys.* **2000**, *113*, 5259−5272. (b) Baik, J. et al. *J. Chem. Phys.* **1999**, *110*, 9116−9127. (c) Majumdar, D. et al. *J. Chem. Phys.* **2000**, *112*, 101−105. (d) Lee, H. M.; Kim, K. S. *J. Chem. Phys.* **2001**, *114*, 4461−4471.

(13) Savage, P. B.; Holmgren, S. K.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 4069−4070.

(14) (a) McDonald, N. A.; Duffy, E. M.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1998**, *120*, 5104−5111. (b) van Hoorn, W. P.; Jorgensen, W. L. *J. Org. Chem.* **1999**, *64*, 7439−7444. (c) Wu, Y.-D.; Wang, D.-F.; Sessler, J. L. *J. Org. Chem.* **2001**, *66*, 3739−3746.

TABLE 1. Selected Geometrical Parameters and Binding Energies for the Complexes of 1 with Halide Anions[a]

halides	R ($X^-\cdots\phi$)[b]	R ($X^-\cdots H_a$)[c]	∠ ($X^-\cdots H_a-C$)[d]	ΔE_{gas} ($\Delta\Delta E_F$)[e]	$\Delta E_{acetonitrile}$ ($\Delta\Delta E_F$)[e]
F^-	3.24	1.82	168.3	−247.2 (0.00)	−29.4 (0.00)
Cl^-	3.84	2.40	163.4	−217.0 (30.2)	−17.9 (11.5)
Br^-	4.02	2.56	162.1	−211.3 (35.9)	f

[a] Distances are in Å; angles are in degrees; energies are in kcal/mol. "ϕ" denotes the benzene centroid. [b] Distances between an anion and a benzene centroid. [c] Hydrogen bond distances. [d] Hydrogen bond angles. [e] Relative binding energies with respect to that of the complexation by F^-. [f] SCRF binding energy for **1** with Br^- is not reported because of a convergence problem in calculations.

TABLE 2. Association Constants K_a and Binding Free Energies $\Delta G°_{298}$ for 1:1 Complexes of 2 and 3 with Halide Anions in Acetonitrile-d_3 at 298 K[a]

hosts	halides[b]	K_a (M^{-1})/10^3	$\Delta G°_{298}$ (kcal/mol)
2	F^-	210[c]	−7.25
2	Cl^-	76[d]	−6.65
2	Br^-	46	−6.35
3	F^-	0.99	−4.08

[a] Errors in K_a are estimated to be less than 10%. [b] Anions used in this assay were in the form of their tetrabutylammonium salts. [c] Determined by a competitive binding experiment. K_{rel} of host **2**/host **3** is 212.1. [d] These values are in good agreement with Sato's result (ref 5).

TABLE 3. Association Constants K_a and Binding Free Energies $\Delta G°_{298}$ for 1:1 Complexes of Host 1 and 2 with F^- and Cl^- Anions in Various Solvent Mixtures of DMSO-d_6 and Acetonitrile-d_3 at 298 K[a]

hosts	halides[b]	DMSO-d_6(%) in acetonitrile-d_3	K_a (M^{-1})/10^3	$\Delta G°_{298}$ (kcal/mol)
1	F^-	50	8.6	−5.36
1	F^-	100	1.3	−4.25
1	Cl^-	50	8.3[c]	−5.34
1	Cl^-	100	1.1[c]	−4.15
2	F^-	50	10	−5.45
2	F^-	100	2.4	−4.61
2	Cl^-	50	5.3	−5.08
2	Cl^-	100	1.5[c]	−4.33

[a] Errors in K_a are estimated to be less than 10%. [b] Anions used in this assay were in the form of their tetrabutylammonium salts. [c] Reported in ref 7.

polar solvent probably due to the strong interaction between DMSO and the cationic imidazolium receptor.[15] In particular, the selectivity for the fluoride anion over the chloride anion also decreased in a more polar solvent compared to that in acetonitrile-d_3. This trend would be explained by the hydration effect of water existing in DMSO. In a 50% DMSO-d_6 mixture, the association constant and free energy gain of host **1** with F^- were found to be 8600 M^{-1} and 5.36 kcal/mol, whereas those of host **2** with F^- increased moderately to 10 000 M^{-1} and 5.45 kcal/mol probably due to the nonpolar sidearm of the butyl group, which would block the direct interaction of the fluoride ion with the solvent molecules and reduce the microenvironmental polarity around the binding site.[16] The same trend is noted in 100% DMSO-d_6. The selectivity of **2** for F^- over Cl^- (1.9 in 50% DMSO-d_6 and 1.6 in 100% DMSO-d_6) is much higher than that of **1** (1.04 in 50% DMSO-d_6 and 1.2 in 100% in DMSO-d_6). Although the affinity of host **2** for F^- is weak in the more polar DMSO solution, the affinity in the polar acetonitrile solution is very high, comparable to any highly selective receptor in nonpolar organic solvents.

In conclusion, we predicted from ab initio calculations that the tripodal imidazolium receptors **1** and **2** would have a high affinity for F^-, and this prediction has been confirmed by NMR titration. In acetonitrile solution, the *N*-butyl tripodal imidazolium receptor **2** showed a high affinity for F^- (2.1×10^5 M^{-1}). This is in contrast to many other receptors, which show high affinities for F^- only in nonpolar organic solvents. In more polar solvents such as DMSO and the 1:1 mixture of DMSO and acetonitrile, though the affinities for F^- and Cl^- are much reduced due to the polar solvent, the selectivity of **2** for F^- over Cl^- is much enhanced compared with that of **1**, due to the butyl group. It is likely that this butyl group effect not only blocks the hydration but also reduces the microenvironmental polarity around the binding site.

Experimental Section

Imidazolium Receptor (1). To a solution of 1-methylimidazole (0.16 mL, 2.0 mmol) in MeCN (20 mL) was added 2,4,6-tris(bromomethyl) mesitylene (0.20 g, 0.50 mmol). The mixture was heated under reflux overnight. After the mixture was cooled to room temperature, the solvent was evaporated in vacuo. The residue was dissolved in water (1 mL), and a saturated aqueous solution of NH_4PF_6 (2 mL) was added to the solution. The precipitate was filtered off and washed with water. The obtained crude product was recrystallized from MeCN and EtOH to give a colorless crystalline product (0.35 g, 85%): mp 328−330 °C; ^{1}H NMR ($(CD_3)_2SO$, 500 MHz) δ 8.79 (s, 3H), 7.75 (s, 3H), 7.61 (s, 3H), 5.53 (s, 6H), 3.81 (s, 9H), 2.17 (s, 9H); ^{13}C NMR ($(CD_3)_2SO$, 125.8 MHz) δ 141.04, 136.04, 129.38, 123.83, 122.09, 47.56, 35.90, 16.19; MS (FAB) *m*/*z* 695.38 $[M - PF_6]^+$. Anal. Calcd for $C_{24}H_{33}N_6F_{18}P_3 \cdot 1/2CH_3CH_2OH$: C, 34.74; H, 3.82; N, 9.73. Found: C, 34.80; H, 3.80; N, 9.33.

Imidazolium Receptor (2). The synthesis of the imidazolium receptor **2** was performed according to Sato's procedure (ref 5): MS (FAB) *m*/*z* 821.2 ($[M - PF_6]^+$, 100). Anal. Calcd for $C_{33}H_{51}N_6P_3F_{18}$: C, 41.00; H, 5.32; N, 8.70. Found: C, 41.27; H, 5.26; N, 8.76. Colorless crystals of **2** were obtained by recrystallizing from acetonitrile and ethanol. Crystal data for **2**: 0.15 × 0.25 × 0.50 mm, $C_{33}H_{51}N_6P_3F_{18}$, $M_r = 966.71$, monoclinic, space group $P2_1/n$, $a = 19.4352(4)$ Å, $b = 9.1274(2)$ Å, $c = 26.1977(3)$ Å, $\alpha = 90$, $\beta = 111.51$, $\gamma = 90$, $V = 4323.54(14)$ Å^3, $Z = 4$, $T = 238$ K, $\rho_{calcd} = 1.485$ g/cm^3, 6775 independent reflections, $R_1 = 0.1051$, w$R_2 = 0.2656$ [$I > 2\sigma(I)$], $R_1 = 0.1494$, w$R_2 = 0.3041$ (all data), GOF = 1.049.

Calculations. The geometry optimization was done at the Hartree−Fock (HF) level of theory using 6-31+G* for

(15) (a) Gutmann, V. *The Donor−Acceptor Approach to Molecular Interactions Phenomena*; New York, 1978. (b) Gutmann, V.; Wychera, E. *Inorg. Nucl. Chem. Lett.* **1966**, *2*, 257.

(16) (a) Camiolo, S.; Gale, P. A. *Chem. Commun.* **2000**, 1129−1130. (b) Anzenbacher, P., Jr.; Jursíková, K.; Lynch, V. M.; Gale, P. A.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 11020−11021.

(17) Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311−312.

halide anions and 6-31G* for all other atoms (Frisch, M. J. et al. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1999). The self-consistent reaction field (SCRF) calculations in the solvent medium (dielectric constant $\epsilon = 36.64$ for acetonitrile) were carried out using a (static) isodensity surface-polarized continuum model (IPCM) at the HF/6-31G*-optimized geometries.

NMR Titration. All NMR experiments were performed on a 500 MHz spectrometer at 298 K. A solution (1 mM or 2 mM) of hosts in a mixture of $(CD_3)_2SO$ and/or CD_3CN was titrated with an aliquot of a stock solution (10 mM or 20 mM) of guests as tetrabutylammonium salts in the same solvent. The chemical shift changes of the C(2) proton of imidazolium moieties in hosts were monitored. Data analysis was performed using the WinEQNMR[17] computer program. Every titration was repeated at least once until consistent values were obtained.

Competition Method. Various amounts of tetrabutylammonium chloride were added to a solution (1 mM) of the two hosts **2** and **3** (to be compared) in 0.5 mL of CD_3CN. From comparison of the observed downfield chemical shift ($\delta_0 - \delta_{obsd}$) of the C(2) proton to that of the chemical shift of the complex ($\delta_0 - \delta_{complex}$), F_1 and F_2 were obtained, and K_{rel} was calculated (eq 1). The chemical shifts of the C(2) proton in the complexes were assumed to be the values observed when the guest−host ratio was large.

$$K_{rel} = K_2/K_1 = (1/F_1 - 1)/(1/F_2 - 1) \quad (1)$$

$$F_i = \delta_0 - \delta_{obsd}/\delta_0 - \delta_{complex} \quad (2)$$

Acknowledgment. We are grateful for financial support from Creative Research Initiative of the Korean Ministry of Science and Technology. The crystal structure was obtained courtesy of Prof. Kimoon Kim in POSTECH.

Supporting Information Available: Crystal data of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0263519