ORGANIC LETTERS

2003
Vol. 5, No. 21
4003−4006

Molecular Recognition of Anions through Hydrogen Bonding Stabilization of Anion–Ionophore Adducts: A Novel Trifluoroacetophenone-Based Binding Motif

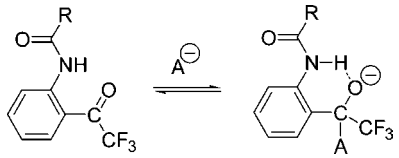
Young Kook Kim,[†] Yun-Ho Lee,[†] Hyang-Yeol Lee,[†] Mi Kyoung Kim,[‡] Geun Sig Cha,*[,‡] and Kyo Han Ahn*[,†]

Department of Chemistry and Center for Integrated Molecular Systems, Division of Molecular and Life Science, Pohang University of Science and Technology, San 31 Hyoja-dong, Pohang 790-784, Republic of Korea, and Department of Chemistry, Kwangwoon University, Seoul 139-701, Republic of Korea

ahn@postech.ac.kr

Received August 27, 2003

ABSTRACT



A novel trifluoroacetophenone-based binding motif has been developed that recognizes anions such as carboxylates through reversible formation of anion–ionophore adducts that are stabilized by intramolecular H-bonding. The intramolecular H-bonding resulted in more than 10-fold enhancement in the binding affinity and an enthalpy gain ($\Delta H°$) of 3.0 kcal/mol for the binding of an acetate ion when compared to the case without the intramolecular H-bonding.

The molecular recognition of anions with synthetic receptors has challenged many supramolecular chemists concerning the biological importance and molecular diversity of anions.[1] In the recognition of anions, molecular interactions such as electrostatic interactions, hydrogen bonding, and coordinative bond formation have been widely used. A variety of anion recognition systems developed to date thus contain cationic (organic or organometallic) or neutral groups that can provide these interactions. A different type of molecular interactions used for anion recognition involves "reversible covalent-bond formation" between an ionophore and an anion. This type of binding mode can be found in the recognition and sensing of carbonates and amines using trifluoroacetophenone (TFA)-based ionophores, which, introduced by Herman in 1974,[2] have been used as membrane components of ion-selective electrodes (ISE).[3] Surprisingly, with the exception of a few examples, this type of unique molecular interactions has not been fully appreciated in the area of molecular recognition

* Correspondence should be made to K. H. Ahn. Phone: +82-54-279-2105. Fax: +82-54-279-3399.
[†] Pohang University of Science and Technology.
[‡] Kwangwoon University.

(1) For selected reviews, see: (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609. (b) Antonisse, M. M. G.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 443. Kimura, E.; Koike, T. *Chem. Commun.* **1998**, 1495. (c) Snowden, T. S.; Anslyn, E. V. *Curr. Opin. Chem. Biol.* **1999**, *3*, 740. (d) Gale, P. A. *Coord. Chem. Rev.* **2000**, *199*, 181. (e) Hartley, J. H.; James, T. D.; Ward, C. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3155. (f) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486. (g) Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79. (h) Amendola, V.; Fabbrizzi, L.; Mangano, C.; Pallavicini, P.; Poggi A.; Taglietti, A. *Coord. Chem. Rev.* **2001**, *219*, 821. (i) Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 191.

(2) (a) Herman, H. B.; Rechnitz, G. A. *Science* **1974**, *184*, 1074. (b) Herman, H. B.; Rechnitz, G. A. *Anal. Chim. Acta* **1975**, *76*, 155. (c) Herman, H. B.; Rechnitz, G. A. *Anal. Lett.* **1974**, *8*, 147. For other receptors, see: (d) Hennrich, G.; Sonnenschein, H.; Resch-Genger, U. *Tetrahedron Lett.* **2001**, *42*, 2805.

10.1021/ol035624z CCC: $25.00
Published on Web 09/20/2003

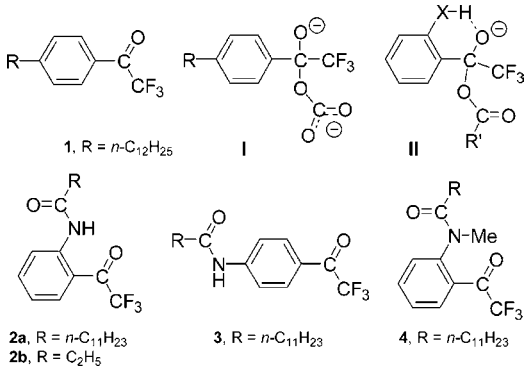


Figure 1. Trifluoroacetophenone-based anion receptors **1**−**4** and anion adducts I and II.

and sensing of anions.[4,5] One main reason may be found in its relatively weak binding affinity, which results from an unfavorable equilibrium toward the tetrahedral adduct that forms between the trifluoroacetyl group and an anion. If the binding affinity of the TFA moiety can be enhanced further, this unique binding motif can be greatly useful in the development of a variety of anion receptors. Herein, we wish to disclose a rational approach to enhance the binding affinity of the TFA motif. Our new TFA analogues have a neighboring group that stabilizes the TFA−anion adduct through intramolecular H-bonding, which shifts the equilibrium toward the adduct. One of our new TFA analogues, in its primitive form, is found to be an efficient ionophore toward simple carboxylate and cyanide ions.[6]

The TFADB **1** recognizes carbonate ion via a tetrahedral adduct I.[3] To shift the equilibrium toward adduct I, we have introduced a neighboring group at the ortho position of the trifluoroacetophenone system, a neighboring group that stabilizes the tetrahedral alkoxide adduct through intramolecular H-bonding (as adduct II in Figure 1).[7] Through the H-bonding, adduct II may gain additional stability, and thus the equilibrium can be shifted further toward adduct II. As for the H-bonding group, we have chosen a carboxamide group that can act either as an H-bond donor or acceptor.

The new TFA analogues, 2-trifluoroacetyl-carboxanilides (TFACAs) **2**, can be readily synthesized starting from 2-bromoacetanilide and its derivatives through a lithium−halogen exchange reaction followed by treatment with trifluoroacetic anhydride. As reference compounds, we synthesized **3**, a para analogue of **2a**, and TFACA **4**, an *N*-Me analogue of **2a**.

First, we have investigated the molecular interactions between **2b** and an acetate ion by NMR spectroscopy. A 1:1 mixture of **2b** and tetrabutylammonium acetate in $CDCl_3$ showed separate peaks for **2b** and the adduct, indicating that the equilibration is much slower on the NMR time scale.[8] The NH proton of **2b** itself appeared at 11.0 ppm, much downfield from that of **3** (7.68 ppm), due to its intramolecular H-bonding. Upon addition of an equivalent of acetate to **2b**, a series of peaks shifted upfield significantly from those of **2b** (Figure 2). The shifts can be explained by increased shielding upon formation of an anionic adduct such as II. A slight upfield shift observed for the NH proton (11.0 → 10.56 ppm) may be caused by a weakened H-bonding or the change in the hybridization of carbonyl carbon. In the case of **3**, a similar upfield shift of the NH proton was observed upon addition of acetate (7.68 → 7.49 ppm). Although the intramolecular H-bonding exists already in **2b** itself, that of the corresponding adduct is ionic, which usually forms a stronger H-bond than the corresponding neutral one.[9] Thus, we may not infer the weakening of the H-bond from the magnitudes of the NH chemical shifts, because the anionic species induces an upfield chemical shift through diamagnetic shielding. In fact, it is found that the strength of the H-bond changes little upon guest binding, judged by IR spectroscopy: the NH stretching frequency of **2b** (3330 cm^{-1}) is almost the same as that of its adduct (3334 cm^{-1}).[10]

The existence of intramolecular H-bonding is further supported by a larger binding affinity observed for ionophore **2b** compared to that of **3** or **4**.

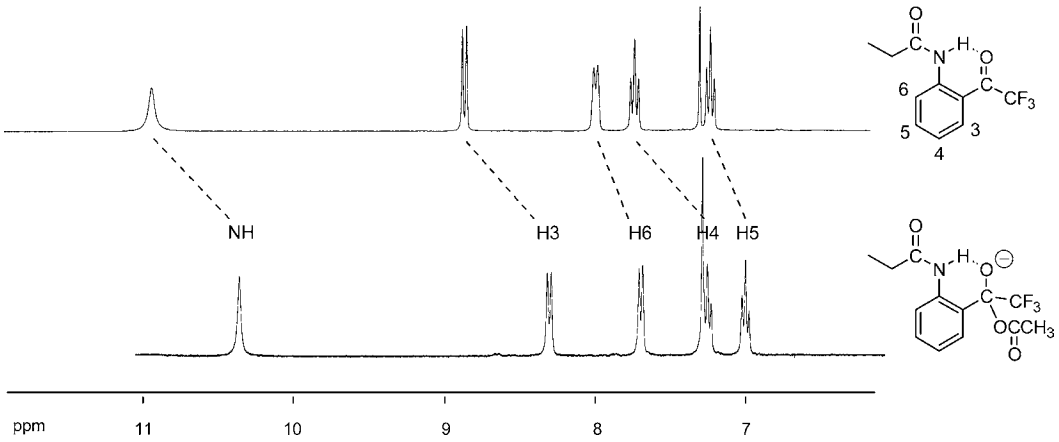


Figure 2. ^1H NMR spectra of TFACA **2b** and its acetate adduct in $CDCl_3$ at 25 °C (only NH and aromatic protons are shown; the peak assignment was done by ^1H COSY experiments).

To evaluate the effect of the intramolecular H-bonding on the binding affinity, we analyzed thermodynamic parameters for the molecular interactions between ionophores **2**−**4** and acetate ion by isothermal titration calorimetry (ITC).[11] The binding isotherm obtained with TFACA **2a** is shown in Figure 3. The 1:1 binding mode was also evident from the

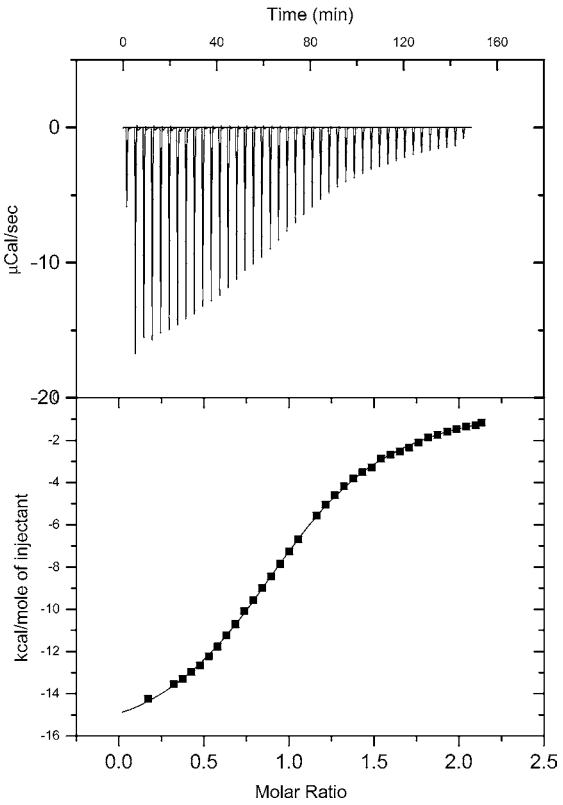


Figure 3. Titration of TFACA **2a** with acetate ion (*n*-Bu_4N^+ salt) at 30 °C in acetonitrile.

ITC analysis, judging from the binding stoichiometry values ($n = 1.0 \pm 0.05$). Comparison of the binding isotherms such as the step height ($\Delta H°$) and slope at the inflection point (K_a) clearly indicates that TFACA **2a** binds acetate more favorably than its analogues **3** and **4** (Supporting Information). Table 1 summarizes the thermodynamic data obtained by a nonlinear least-squares curve fit. A comparison of the thermodynamic data indicates that the adduct formation in all cases is driven by favorable enthalpy changes. The adduct formation results in negative entropy changes, as expected. The TFACA **2a** shows an enthalpy gain of $\Delta H° = 3.0$ kcal/mol in binding acetate compared to the para analogue **3**, which clearly indicates that the acetate adduct of **2a** is stabilized through the intramolecular H-bonding. In the case of TFADB **1**, the binding affinity was so weak ($K_a \ll 10^3$ M^{-1}) that ITC analysis resulted in a large error. The increased affinity in the case of **3** compared to **1** may be explained by interplay of intermolecular H-bonding involving the carboxamide group in the former case. The *N*-Me analogue **4** shows binding affinity lower than **2a** but similar to or slightly higher than **3**. These results indicate that the carboxamide group mainly acts as an H-bond donor, which forms six-membered ring, intramolecular H-bonding.[12]

Table 1. Thermodynamic Data for the Binding Process between TFACA **2**−**4** and Acetate Ion Determined by ITC Analysis[a]

	$\Delta H°$, kcal/mol	$-T\Delta S°$, kcal/mol	K_a, M^{-1}
2a	−16.8	10.7	2.5×10^4
3	−13.8	9.1	1.8×10^3
4	−10.7	5.7	2.7×10^3

[a] Determined in acetonitrile at 30 °C.

We evaluated the binding ability of the TFACA system toward various anions by ITC experiments using **2b**. On the basis of the established binding mode, the binding affinity is presumed to be dependent on the anion's nucleophilicity toward the trifluoroacetyl carbonyl carbon, which in turn is related to the electronic and steric nature of the anions.

The $\Delta H°$ and K_a values obtained in the cases of aliphatic carboxylates increase in the following order: $CH_3CO_2^-$ < $CH_3CH_2CO_2^-$ < $CH_3CH(CH_3)CO_2^-$ < $CH_3C(CH_3)_2CO_2^-$. This suggests that electronic effects are dominant over steric factors (Table 2). In the case of carboxylates with electron-withdrawing groups ($PhCO_2^-$, $ClCH_2CO_2^-$, and $CF_3CO_2^-$), the binding affinities dramatically decrease. The TFACA **2b** shows the highest affinity toward cyanide ion among the

(3) (a) Meyerhoff, M. E.; Pretsch, E.; Welti, D. H.; Simon, W. *Anal. Chem.* **1987**, *59*, 144. (b) Mohr, G. J.; Lehmann, F.; Grummt, U. W.; Spichiger-Keller, W. E. *Anal. Chim. Acta* **1997**, *344*, 215. (c) Mohr, G. J.; Citterio, D.; Spichiger-Keller, U. E. *Sens. Actuators B* **1998**, *49*, 226. (d) Shin, J. H.; Lee, J. S.; Lee, H. J.; Chu, J.; Pyun, H.-J.; Nam, H.; Cha, G. S. *J. Electroanal. Chem.* **1999**, *468*, 76. (e) Mohr, G. J.; Spichiger, U. E.; Jona, W.; Langhals, H. *Anal. Chem.* **2000**, *72*, 1084. (f) Lee, H. J.; Yoon, I. J.; Yoo, C. L.; Pyun, H.-J.; Cha, G. S.; Nam, H. *Anal. Chem.* **2000**, *72*, 4694. (g) Kim, Y. K.; Ha, J.; Cha, G. S.; Ahn, K. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1420.

(4) (a) Mohr, G. J. *Chem. Commun.* **2002**, 2646. (b) Sasaki, S.-i.; Hashizume, A.; Citterio, D.; Fujii, E.; Suzuki, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 3005. (c) Mertz, E.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2003**, *125*, 3424. (d) Whang, S. S.; Ko, S. W.; Oh, S. M.; Nam, K. C. *Bull. Korean Chem. Soc.* **2003**, *24*, 1. (e) Mertz, E.; Beil, J. B.; Zimmerman, S. C. *Org. Lett.* **2003**, *5*, 3127.

(5) Mohr referred to this type of receptors as "reactands"; see ref 4.

(6) For a recent review of carboxylate/carboxylic acid recognition, see: Fitzmaurice, R. J.; Kyne, G. M.; Douheret, D.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 841.

(7) An attempt at increasing the electrophilicity of the carbonyl carbon of the trifluoroacetyl group in TFADB **1** by substituting the phenyl ring with 2-pyridyl ring resulted in a significant increase of a hydrated form of the carbonyl group, which prevented such a direct approach.

(8) TFACA **2a** or **2b** did not show its hydrated form by ^1H and ^{19}F NMR analyses (See ref 7).

(9) (a) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, 1997; Chapter 3. (b) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382.

(10) IR analysis was carried out in $CHCl_3$ at 26 °C. The amide I bands (**2b**, 1682 cm^{-1}; **2b**-AcO^- adduct, 1677 cm^{-1}) indicate that the carboxamide oxygen is not associated in these cases.

(11) (a) Christensen, J. J.; Wrathall, D. P.; Oscarson, J. O.; Izatt, R. M. *Anal. Chem.* **1968**, *40*, 1713. (b) Smithrud, D. B.; Wyman, T. B.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 5420.

(12) We attempted to synthesize *N*-ethyl-2-(trifluoroacetyl)benzamide in which the carboxamide group may act as a hydrogen bond acceptor for the intramolecular H-bond stabilization but failed due to a rapid hydrolysis of the carboxamide group assisted by the neighboring hydrated trifluoroacetyl group.

Table 2. Thermodynamic Data for Molecular Interactions between TFACA **2b** and Various Anions[a]

	$\Delta H°$, kcal/mol	$-T\Delta S°$, kcal/mol	K_a, M
$CH_3CO_2^-$	−19.8	13.6	2.8×10^4
$CH_3CH_2CO_2^-$	−22.0	15.7	3.0×10^4
$CH_3CH(CH_3)CO_2^-$	−23.3	16.6	3.9×10^4
$CH_3C(CH_3)_2CO_2^-$	−24.7	17.3	5.3×10^4
$PhCO_2^-$	−19.0	13.3	1.1×10^4
$ClCH_2CO_2^-$ [b]			6.0×10^3
$CF_3CO_2^-$ [c]			$\ll 10^3$
^-CN	−13.1	6.0	1.2×10^5
$H_2PO_4^-$ [b]			3.2×10^3

[a] Determined in acetonitrile at 30 °C. [b] K_a was determined by ^1H NMR analysis. [c] Out of the measurement range.

tested anions, suggesting its potential use for the development of a sensor for this highly toxic anion.

Only phosphate ion showed an appreciable affinity among the other anions examined ($H_2PO_4^-$, HSO_4^-, ClO_4^-, F^-, Cl^-, and ^-SCN), and the others showed weaker or little binding. In the case of phosphate ion, dipodal or tripodal TFACA analogues can be envisaged, which may be synthesized if we use a dicarboxylic acid or a tricarboxylic acid as the *N*-acyl group of TFACA **2b**. With these di- or tripodal TFACA analogues, we may also expect an enhancement in the substrate specificity. Substrates such as dicarboxylates, amino acids, amines, and their analogues are potential guests for the TFACA analogues.

A potential application of TFACA **2** and its analogues is the use as an ion-selective electrode (ISE) membrane component for electrochemical sensing of anions such as carbonates.[13] Because TFACA **2a** has a long lipophilic alkyl chain, it can be directly used as the ISE membrane component for the electrochemical carbonates analysis.[14] An ISE study using a TFACA **2a**-based membrane showed a significant enhancement in the ion selectivity compared to the case of TFADB **1**, showing a significant decrease in the ion selectivity coefficients for all the ions tested (ClO_4^-, salicylate$^-$, SCN^-, NO_3^-, CO_3^{2-}, NO_2^-, Br^-, HPO_4^{2-}, and Cl^-) with respect to CO_3^{2-}.[15] In other words, TFACA **2a** responded more favorably toward carbonates compared to TFADB **1**. Although TFACA **2a** still shows stronger response toward salicylate ion, which is the most interfering ion for carbonate sensing, the significant improvement over the salicylate ion compared to TFADB **1** is an important step toward the development of a practically useful carbonate sensor for clinical purposes. An extension of the new receptor system to di- or tripodal analogues may provide more efficient carbonate sensors.[3f]

In summary, we have developed a novel trifluoroacetophenone-based receptor system that is useful for the recognition of anions such as carboxylates and cyanide. The receptor system recognizes anions by reversible covalent bond formation, which is stabilized by intramolecular H-bonding. The unique binding motif can find a greater utility in the development of new anion receptors/sensors with enhanced binding affinity and substrate specificity, which is actively under investigation.

Acknowledgment. This work was financially supported by the Korea Science and Engineering Foundation (the Basic Research Program, Grant No. R02-2002-000-00103-0) and the Center for Integrated Molecular Systems.

Supporting Information Available: Synthesis and characterization data of TFACAs **2**−**4** and ITC titration data of TFACAs **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035624Z

(13) For reviews on ISEs based on TFA derivatives, see: (a) Bühlmann, P.; Pretsch, E.; Baker, E. *Chem. Rev.* **1998**, *98*, 1593. (b) Baker, E.; Bühlmann, P.; Pretsch, E. *Chem. Rev.* **1997**, *97*, 3083.

(14) ISE membranes were prepared using 8.3 mg of an ionophore (**1** or **2a**), 60 mg of poly(vinyl chloride) as the supporting material, 92.6 mg of bis(2-ethylhexyl)adipate as the plasticizer, and 1 mg of tridodecyl(methyl)-ammonium chloride as the lipophilic additive. Potential differences were measured between the ion-selective electrodes and a double junction Ag|AgCl reference electrode. For the preparation of ISE membranes and analysis, see: (a) Hong, Y. K.; Yoon, W. J.; Oh, H. J.; Jun, Y. M.; Pyun, H.-J.; Cha, G. S.; Nam, H. *Electroanalysis* **1997**, *9*, 865. (b) Shin, J. H.; Sakong, D. S.; Nam, H.; Cha, G. S. *Anal. Chem.* **1996**, *68*, 221.

(15) Selectivity coefficients determined by the matched potential method at an interfering ion concentration of 0.1 M are as follows. For ISE composed of **2a**: ClO_4^- (1.22), salicylate$^-$ (1.6), SCN^- (0.34), NO_3^- (−1.34), NO_2^- (−1.88), Br^- (−2.5), Cl^- (−2.85), and HPO_4^{2-} ($\ll$−4). For ISE composed of **1**: ClO_4^- (2.56), salicylate$^-$ (2.47), SCN^- (1.79), NO_3^- (0.36), NO_2^- (−0.47), Br^- (−0.8), Cl^- (−4), and HPO_4^{2-} (<4). A detailed study will be reported elsewhere.