Tetrahedron Letters 51 (2010) 6516–6520

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Anion and cation binding by a new indole/pyridine/amine-based ion-pair receptor

Kristin N. Skala, Katelyn G. Perkins, Amna Ali, Robert Kutlik, Addie M. Summitt, Satyanarayana Swamy-Mruthinti, Farooq A. Khan *, Megumi Fujita *

Department of Chemistry and Department of Biology, University of West Georgia, 1601 Maple St., Carrollton, GA 30118, United States

ARTICLE INFO

Article history:
Received 26 July 2010
Revised 30 September 2010
Accepted 3 October 2010
Available online 28 October 2010

Keywords:
Indole
Ion-pair receptor
Cation binding
Anion binding
ESI-MS

ABSTRACT

A new ion-pair receptor bis(3-bromoindol-2-ylmethyl)(2-pyridylmethyl)amine (**1**) was synthesized and studied for its anion and cation binding behavior using ESI-MS and ^{1}H NMR spectroscopy. Among halides, **1** exhibits the strongest binding with Cl^- to form a 1:1 adduct ($K_a = 1042 \pm 21$ in CD_3CN). Among alkali metal ions, Li^+ and Na^+ showed the strongest binding in the formation of a **1**·M^+ complex. The simultaneous binding of Cl^- and Li^+ to **1** was confirmed by ^{1}H NMR titration of a 1:1 mixture of **1** and Cl^- with $LiPF_6$ in 83:17 v/v mixture of $CDCl_3$ and DMSO-d_6. DFT-optimized structures of **1**·Cl^-, **1**·Li^+, and **1**·Li^+·Cl^- are consistent with the chemical shift changes observed in ^{1}H NMR studies.

1. Introduction

Ion-pair receptors are molecules that are capable of binding both an anion and a cation simultaneously.[1] Such systems have drawn much attention in recent years, and the number of publications on this topic has grown rapidly in the past decade. Ion-pair receptors have potential applications in solubilization and extraction of salts from organic solvents or effluents, in the transfer of salts through lipophilic membranes, and as sensors for biological and environmental systems.[1]

The use of indole groups in anion or ion-pair receptors, along with related carbazoles, biindoles, and indolo[2,3-*a*]carbazoles, is fairly new.[2] The work from 2004 to 2008 on *anion* receptors with indole motifs is well summarized by Gale,[2] and more recent works are cited in Jeong's recent article on new indolocarbazole-based anion receptors.[3] However, the number of indole-based *ion-pair* receptors reported to date is still limited.[4] Jeong and co-workers have synthesized a biindole-based ion-pair receptor by coupling biindole with a diazacrown ether, which binds an alkali metal ion and a halide anion cooperatively.[4a] Ito and co-workers reported a series of indolylmethanes that bind anions and ion-pairs.[4b]

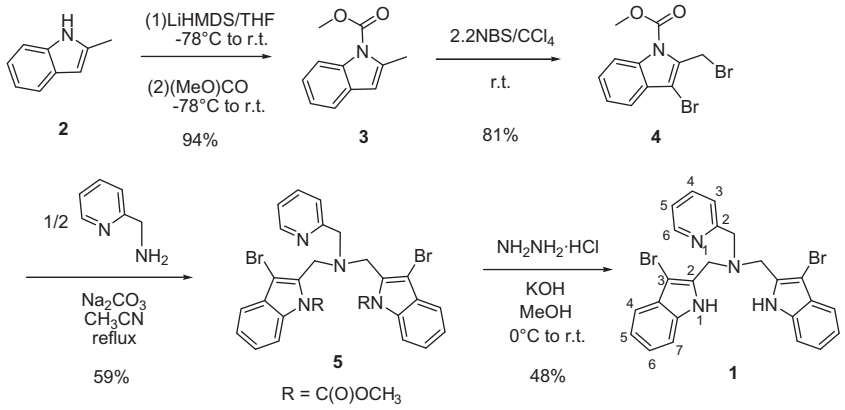
Herein we report a newly synthesized receptor bis(3-bromoindol-2-ylmethyl)(2-pyridylmethyl)amine (**1**, Scheme 1) that is capable of binding both an anion and a cation. This molecule contains two indole N–H groups that can potentially enable interaction with an anion through hydrogen bonding, and two amine/pyridine N atoms to allow a cation to bind. While it is a common approach to synthesize an ion-pair receptor by functionalizing well-known cation-binding macrocycles such as crown ethers, calixarenes or cholapods,[1a,e] receptor **1** is *acyclic* and contains a minimal number of cation-binding heteroatoms. The Br groups in the indolyl moieties of **1** are not directly involved in ion binding, yet were included in the synthesis to allow the possibility to substitute one or both with other groups to tune the molecule's electronic properties or to enhance colorimetric responses to ion binding.

The receptor **1** was synthesized in four steps starting from 2-methylindole **2** (Scheme 1). The first two steps, N-protection and dibromination by NBS, were modified from Nagarathnam's procedure.[5] The dibrominated compound **4** was coupled with 2-(aminomethyl)pyridine in 2:1 ratio to give **5** in 59 % yield. After N-deprotection of **5**, the final product **1** was obtained (48%).

We first examined the halide-binding behavior of **1** in methanol using ESI-MS. A series of methanol solutions of **1** with 5 equiv of $Bu_4N^+X^-$ ($X^- = F^-$, Cl^-, Br^- and I^-) was used for individual halide-binding assessment. A representative negative-ion mode spectrum with Cl^- is shown in Figure 1. This spectrum shows the 1:1 adduct **1**·Cl^- along with signals corresponding to the mono-deprotonated receptor $[\mathbf{1}-H^+]^-$ and $[Bu_4N^+\cdot(Cl^-)_2]^-$. Analogous peaks were also found with Br^- and I^-. With F^-, no 1:1 adduct was observed but instead the 2:1 adduct $(\mathbf{1})_2\cdot F^-$ ($m/z = 1067$) was detected with a small intensity. The signal intensities of the **1**·X^- species are in

* Corresponding authors. Tel.: +1 678 839 6024; fax: +1 678 839 6551 (M.F.).
E-mail address: mfujita@westga.edu (M. Fujita).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.10.012



Scheme 1. Synthesis of **1**.

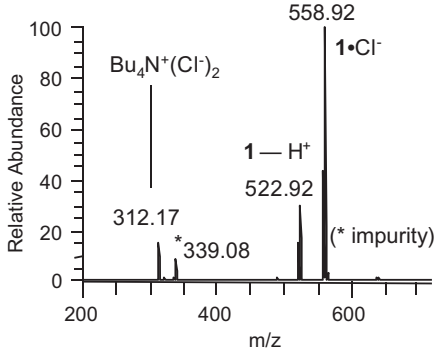


Figure 1. Negative-ion ESI mass spectrum of 1:5 mole ratio of **1**:Cl^- in methanol.

the order of $Cl^- > Br^- > I^-$, though for more quantitative comparison we used ^{1}H NMR titrations as discussed later.

We also examined the Group 1A cation binding to **1** in methanol by ESI-MS. A series of solutions of **1** with 5 equiv of MPF_6 (M = Li, Na and K) or $RbBF_4$ were used for individual cation-binding assessment. In the positive-ion mode, signals of a 1:1 adduct **1**·M^+ and the protonated receptor (**1** + H^+) were observed. A sample positive-mode spectrum of a mixture of **1** and Na^+ is shown in Figure 2. Among the first three cations, the **1**·M^+ signal intensities were roughly in the order of $Li^+ \sim Na^+ > K^+$ though further attempts to

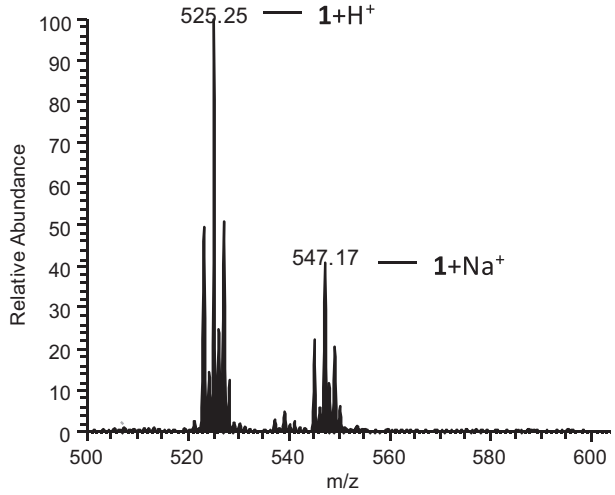


Figure 2. Positive-ion ESI mass spectrum of 1:5 mole ratio of **1**:$NaPF_6$ in methanol.

determine the relative order were made using ^{1}H NMR as discussed later. A complex of **1** with Rb^+ was not observed when $RbBF_4$ was used a Rb^+ source, but when RbF was used as a Rb^+ source a signal of **1**·Rb^+ was found, with the intensity comparable to **1**·K^+. It is not clear why the BF_4^- salt prevented the formation of **1**·Rb^+.[6]

^{1}H NMR studies of ion-binding behavior of **1** was carried out in three deuterated solvents: CD_3CN, $CDCl_3$, and an 83:17 mixture (by volume) of $CDCl_3$ and DMSO-d_6.[7] When **1** was titrated with $Bu_4N^+Cl^-$ in these solvents, notable downfield shift of the NH signal was observed. This indicates that **1** binds Cl^- through the NH···Cl^- hydrogen bonding. The titration curves in these solvents all fit to the formation of a 1:1 complex. The association constant K_a (M^{-1}) for the formation of **1**·Cl^- in CD_3CN, $CDCl_3$, and $CDCl_3$/DMSO-d_6 (83:17) was calculated as 1042 ± 21, 440 ± 23, and 177 ± 18, respectively, using a program WINEQNMR2.[8] Association constants in CD_3CN with other halides were also determined (Table 1). With F^-, K_a could not be calculated since the chemical shift changes caused by F^- were so small (Δ0.15 ppm change of the NH signal upon addition of 8 equiv $Bu_4N^+F^-$). The general order of the K_a values is $Cl^- > Br^- > I^- > F^-$, which is consistent with the ESI-MS observation.

Figure 3 shows the movement of chemical shifts of NH and aromatic protons of **1** upon titration with $Bu_4N^+Cl^-$ in CD_3CN. Upon addition of 6.8 equiv Cl^-, the NH signal had the most significant downfield shift by +2.35 ppm. The notable downfield shifts were also observed with the pyridyl proton at the 3rd position (Py 3) and the indolyl proton at the 7th position (In 7). These peaks moved by +0.85 and +0.24 ppm, respectively, upon addition of 6.8 equiv Cl^-, while other aromatic protons hardly moved or only slightly upfield shifted. Similar trend was observed in $CDCl_3$ and 83:17 $CDCl_3$/DMSO-d_6 as well. This indicates a possibility of weak hydrogen bonding-like interaction of Py 3 and In 7 protons with the Cl^-. The DFT-optimized structure of **1**·Cl^- (Figure 4), obtained by the program GAUSSIAN 09, is consistent with the ^{1}H NMR observation. The Cl^- ion is bound by the two indolyl NH groups of **1** in a propeller-like conformation. The N*H*···Cl^- distances are 2.14–2.15 Å, clearly within a range of hydrogen bonding.[9] The Py 3 H···Cl^- and In 7···Cl^- distances are 2.49 Å and 3.4–3.6 Å,

Table 1
The association constants K_a (M^{-1}) of the formation of **1**·X^- adducts from **1** and Bu_4NX (X = F, Cl, Br and I) based on titrations of 5 mM of **1** with 50 mM of Bu_4NX in CD_3CN.

Halide	F^-	Cl^-	Br^-	I^-
K_a	—	1042 ± 21	157 ± 9	12 ± 1

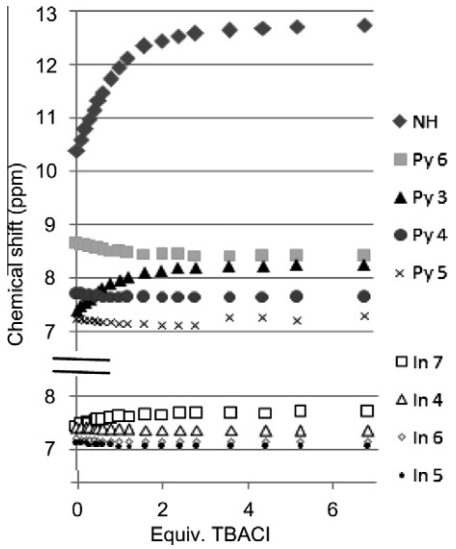


Figure 3. Chemical shift movement over titration of **1** with Bu_4NCl in CD_3CN. The pyridyl and indolyl proton signals are shown separately for clarity. See Scheme 1 for numbering of the aromatic protons.

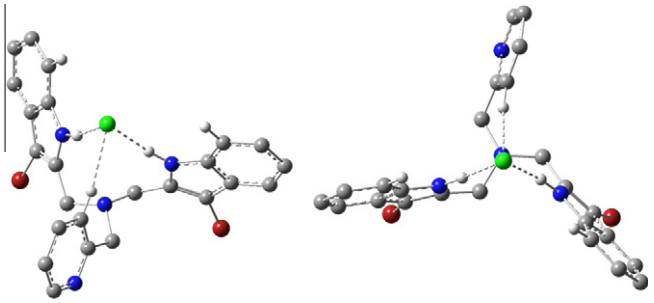


Figure 4. Two views of a DFT-optimized structure of **1**·Cl^-. Color scheme: Gray = C, white = H, blue = N, scarlet = Br, and green = Cl. Some hydrogen atoms are omitted for clarity.

respectively. The former is well in the range of reported CH···Cl^- hydrogen bonding distances.[10] Though aromatic CH bonds do not usually form hydrogen bonds, in this case the geometry of **1**·Cl^- brings these protons in proximity of Cl^- ion, within a possible range of some interaction.

The interaction between **1** and alkali metal cations from MPF_6 (M = Li, Na and K) was also examined in CD_3CN, 83:17 $CDCl_3$/DMSO-d_6, and $CDCl_3$. In the first two solvents, addition of 5 equiv MPF_6 caused very minimal changes (no more than Δ0.15 ppm, most peaks moved less than 0.01 ppm) in the ^1H NMR signals of **1**. Strong coordination of solvent molecules to the cations may be preventing a direct interaction between **1** and M^+.

In $CDCl_3$, due to poor solubility of MPF_6, we could not carry out a titration or quantitative addition of the cation source to **1**. We did a coarse experiment of saturating a 5 mM solution of **1** in $CDCl_3$ with MPF_6 by adding excess solid MPF_6 and shaking it vigorously. The ^1H NMR signals of **1** were affected by saturation with $LiPF_6$ and $NaPF_6$, but not by KPF_6. The chemical shift changes of **1** in $CDCl_3$ upon saturation with $LiPF_6$ and $NaPF_6$ are summarized in Table 2. Interestingly, the NH peak had a significant downfield shift upon addition of $LiPF_6$ and $NaPF_6$. This is not due to the hydrogen bonding of the NH groups to the anion PF_6^-, since in a separate experiment, Bu_4NPF_6 did not cause any changes in proton signals of **1**. The possible reason of the downfield shift of the NH protons is the coordination of the indolyl *N* atoms to the cation, making the

Table 2
Chemical shift changes of proton signals Δδ (ppm) of **1** in $CDCl_3$ upon saturation with $LiPF_6$ or $NaPF_6$.

	NH	Py 3	Py 4	Py 5	Py 6
$LiPF_6$	+0.78	+0.08	+0.15	−0.25	−0.38
$NaPF_6$	+0.78	+0.01	+0.11	−0.21	−0.11

	In 4	In 5	In 6	In 7	CH_2In	CH_2Py
$LiPF_6$	−0.11	−0.04	−0.09	−0.06	+0.32	+0.17
$NaPF_6$	−0.06	−0.11	−0.09	−0.002	+0.14	+0.06

N*H* more electron-deficient. The DFT-optimization of **1**·Li^+ indeed resulted in both indolyl N atoms in the coordination sphere of Li^+, in addition to the expected pyridyl N and the amine N (Figure 5).

Ion-pair binding behavior of **1** was also examined by ^1H NMR. In CD_3CN, addition of 4.5 equiv TBACl and 4.5 equiv $LiPF_6$ resulted in the precipitate formation (LiCl from excess Cl^- and Li^+), and the resulting solution matched the spectrum of 1:1 mixture of **1** and Cl^- from the titration experiment. Therefore 3.5 equiv of LiCl must have precipitated out, and 1 equiv Cl^- and 1 equiv Li^+ must have remained in solution, in which the Cl^- ions were interacting with **1**. But apparently Li^+ in solution does not have any influence on either **1** or the **1**·Cl^- complex. Therefore in CD_3CN, there was no cation binding even by **1**·Cl^-.

On the other hand, we detected evidences of simultaneous binding of Cl^- and Li^+ in 83:17 $CDCl_3$/DMSO-d_6. In Figure 6 the chemical shift changes of proton signals of **1** upon addition of (b) 10 equiv Li^+, (c) 10 equiv Cl^-, and (d) 10 equiv Cl^- and 10 equiv Li^+ are shown. The changes from (a) to (b), upon addition of Li^+, were relatively small, with most notable changes in the two methylene peaks, CH_2In and CH_2Py, by +0.14 and +0.17 ppm. The large changes from (a) to (c) upon addition of **10** Cl^- in the signals of NH (+1.00 ppm), Py 3 (+0.41 ppm), and In 7 (+0.16 ppm) were consistent with the strong (NH) and weak (Py 3 and In 7) hydrogen bondings to Cl^- as discussed earlier. When both 10 equiv Bu_4NCl and 10 equiv $LiPF_6$ were added (in either order) to **1** in 83:17 $CDCl_3$/DMSO-d_6, no precipitation occurred, therefore the solution contained 10 equiv each of Li^+ and Cl^-. The proton spectrum of the resulting solution (d) was quite different from **1** only, **1** plus Li^+, and **1** plus Cl^-. The effect of addition of Li^+ to the mixture of **1** + **10** Cl^- (c vs d) is obviously larger compared to the minimal effect of Li^+ to free **1** (a vs b), indicating that the complex **1**·Cl^- has a significant interaction with Li^+, possibly an inclusion of Li^+.

However, in the presence of excess of both ions, we cannot ascertain the stoichiometry of **1**:Cl^-:Li^+ in the ternary complex. In order to find the stoichiometry, We titrated a 1:1 mixture of **1** and Bu_4NCl with $LiPF_6$ in 83:17 $CDCl_3$/DMSO-d_6. We have already established the 1:1 stoichiometry of the **1**·Cl^- complex based on the titration as discussed earlier. In a 1:1 mixture of **1** and Bu_4NCl a mixture of free **1** and a complex **1**·Cl^- exist, but since we know that the interaction between free **1** and Li^+ is insignificant, any

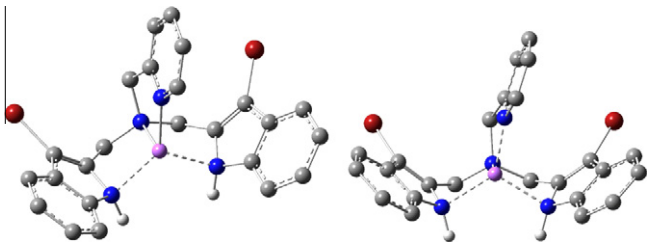


Figure 5. Two views of a DFT-optimized structure of **1**·Li^+. Color scheme: Gray = C, white = H, blue = N, and scarlet = Br, and pink = Li. Some hydrogen atoms are omitted for clarity.

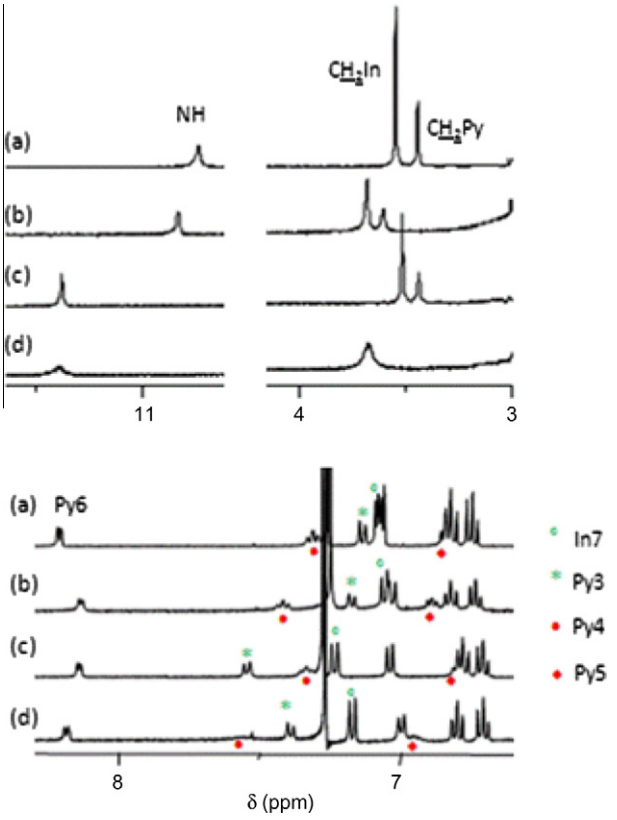


Figure 6. ^{1}H NMR spectra in 83:17 $CDCl_3$/DMSO-d_6 with (a) **1** only, (b) 1 + 10 $LiPF_6$, (c) 1 + 10 Bu_4NCl, and (d) **1** + 10 Bu_4NCl + 10 $LiPF_6$.

changes in the ^{1}H NMR spectrum can be attributed to the interaction of the **1**·Cl^- complex with Li^+. If the **1**·Cl^- complex incorporates Li^+ to form an ion-pair complex **1**·Cl^-·Li^+, the equilibrium of **1**·Cl^- formation (**1** + Cl^- ⇌ **1**·Cl^-) would shift toward the **1**·Cl^- which would become available for further incorporation of Li^+.

The resulting titration curves are presented in Figure 7. The curves of two signals, the NH and the Py 3 proton, had a subtle 'bending' at around 1 equiv point of the Li^+ addition. As discussed earlier, the NH and Py 3 signals were the most sensitive to the Cl^- binding environment due to their hydrogen bonding to Cl^-. The bending of the titration curves of these signals is an indication that the nature of the interaction between the **1**·Cl^- complex and Li^+ changed at the bending point. The Py 3 peak upfield-shifted up to around 1 equiv point, and then leveled off. The Py 3 peak's upfield shift suggests that the Py 3 H···Cl^- hydrogen bonding is weakened by incoming Li^+. The level-off of this upfield shift after the 1 equiv point suggests that the **1**·Cl^- complex is now saturated with 1 equiv of Li^+. This supports the formation of an ion-pair complex **1**·Cl^-·Li^+ with 1:1:1 ratio. Using WINEQNMR2,[8] we confirmed that the titration curve up to the 2.5 equiv point fit to the 1:1 equilibrium equation of [**1**·Cl^-] + Li^+ ⇌ [**1**·Cl^-·Li^+], and the association constant K_a was calculated as 189 ± 10 M^{-1}.

The NH signal, on the other hand, had a two-step shape: it downfield-shifted up to 1 equiv, leveled off, and after around 2 equiv point it started to downfield-shift again. The first downfield-shift leveled off at 1 equiv point, but the second downfield-shift was a continuous steady shift up to 15 equiv point (beyond the range shown in the graph). We propose that the first downfield shift is due to incorporation of 1 equiv of Li^+ to form a ternary complex **1**·Cl^-·Li^+, as proposed earlier using the Py 3 titration curve. The curve up to 1.7 equiv point reasonably fit to the 1:1 equilibrium equation of [**1**·Cl^-] + Li^+ ⇌ [**1**·Cl^-·Li^+] on the WINEQNMR2 program's curve fitting. The second downfield-shift is not specific to a certain stoichiometry, and it may be attributed to the excess Li^+ having less specific interaction with **1**·Cl^-·Li^+, such as cation-aromatic π electron interaction. The association constant K_a based on the NH shift was calculated as 28 ± 13 (M^{-1}). This is sevenfold smaller than the K_a value calculated based on the Py 3 proton, but the tale end of the 0–1.7 equiv region used for this K_a calculation was likely to be affected by the secondary non-specific interaction with excess Li^+.

Two proposed forms of the ion-pair complex **1**·Cl^-·Li^+ are depicted in Figure 8. Both structures were DFT-optimized. The first is an *intact* ion-pair complex (Figure 8a), in which Cl^- and Li^+ are held in proximity, literally an 'ion-pair' binding by **1.** After DFT geometry optimization the resulting structure had a covalent bond between Li^+ and Cl^- with an interatomic distance of 2.24 Å, which is a good match to the calculated and experimental bond distance

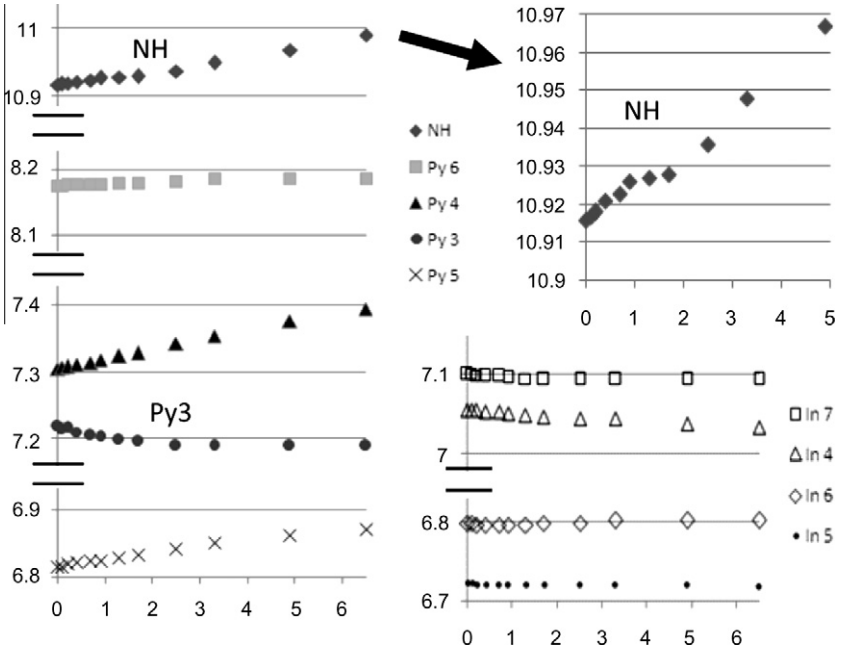


Figure 7. Chemical shift movement of ^{1}H NMR signals over titration of [**1** + 1 equiv Bu_4NCl] mixture with $LiPF_6$ in 83:17 $CDCl_3$/DMSO-d_6.

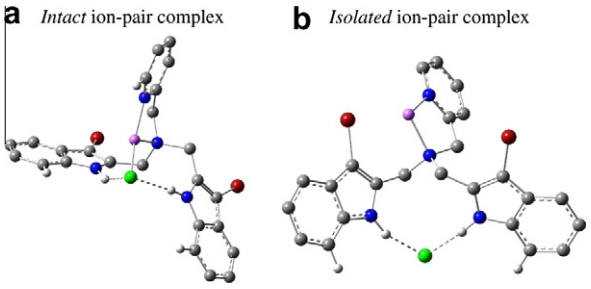


Figure 8. DFT-optimized structures of two possible modes of **1**·Cl^-·Li^+. Color scheme: Gray = C, white = H, blue = N, and scarlet = Br, and pink = Li. Some hydrogen atoms are omitted for clarity.

of a molecule of LiCl, reported as 2.02 Å by Dixon and co-workers.[11] The slightly longer Li···Cl bond distance in **1**·Cl^-·Li^+ is expected since both Li^+ and Cl^- ions have other interactions outside of the LiCl core. While both intact and isolated forms are consistent with the ^{1}H NMR observation, the former is probably more likely due to the extra stabilization energy from the formation of the Li···Cl bond. Calculations of energies using DFT show that the *intact* complex is more stable than the *isolated* complex by 25 kcal/mol (104 kJ/mol).

In conclusion, we have synthesized a new receptor **1** and demonstrated its ability to bind an anion and a cation separately or simultaneously. Anion binding was generally stronger than cation binding, and among halides the chloride ion had the strongest affinity to **1**. ^{1}H NMR titrations were used to show the stoichiometry of the ternary complex **1**·Cl^-·Li^+.

Acknowledgments

Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund for partial support of this research (Fujita: 45505-GB3; Khan: 50147-URG). Authors are also grateful for NSF MRI grants 0521238 (LC–MS (ESI)) and 00821504 (400 MHz NMR), and the University of West Georgia Technology Fee Grant (GAUSSIAN 09). The authors are grateful to Professor Michael Hynes for his help with the software WINEQNMR2.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.012.

References and notes

1. For selected reviews, see: (a) Katayev, E. A.; Melfi, P. J.; Sessler, J. L. In *Modern Supramolecular Chemistry: Strategies for Macrocycle Synthesis*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, Germany, 2008; pp 315–347; (b) Gale, P. A.; Garcia-Garrido, S. E.; Garric, J. *Chem. Soc. Rev.* **2008**, *37*, 151–190; (c) Itsikson, N. A.; Geide, I. V.; Morzherin, Y. Yu.; Matern, A. I.; Chupakhin, O. N. *Heterocycles* **2007**, *72*, 53–77; (d) Smith, B. D. In *Ion-pair Recognition by Ditopic Receptors, Macrocyclic Chemistry: Current Trends and Future*; Gloe, K., Antonioli, B., Eds.; Kluwer: London, UK, 2005; pp 137–152; (e) Kirkovits, G. J.; Shriver, J. A.; Gale, P. A.; Sessler, J. L. *J. Incl. Phenom. Macrocycl. Chem.* **2001**, *41*, 69–75; (f) Sutherland, I. O. *Adv. Supramol. Chem.* **1990**, *1*, 65–108.
2. Gale, P. A. *Chem. Commun.* **2008**, 4525–4540.
3. Lee, G. W.; Kim, N.-K.; Jeong, K.-S. *Org. Lett.* **2010**, *12*, 2634–2637.
4. (a) Chae, M. K.; Lee, J.-I.; Kim, N.-K.; Jeong, K.-S. *Tetrahedron Lett.* **2007**, *48*, 6624–6627; (b) Nishiki, M.; Oi, W.; Ito, K. *J. Incl. Phenom. Macrocycl. Chem.* **2008**, *61*, 61–69.
5. Nagarathnam, D. *Synthesis* **1992**, 743–745.
6. BF_4^- could potentially receive hydrogen bonding from **1** but we did not observe any signal corresponding to **1**·BF_4^-.
7. CD_3OD and pure DMSO-d_6 were tested as well, but the ^{1}H NMR signals of **1** were not affected upon addition of Bu_4NCl in these solvents. In the former, the NH peak disappeared upon H/D exchange.
8. Hynes, M. J. *J Chem. Soc., Dalton Trans.* **1993**, 311–312.
9. Mascal, M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1999–2001.
10. Balamurugan, V.; Hundal, M. S.; Mukherjee, R. *Chem. Eur. J.* **2004**, *10*, 1683–1690.
11. Vasiliu, M.; Li, S.; Peterson, K. A.; Feller, D.; Gole, J. L.; Dixon, D. A. *J. Phys. Chem. A* **2010**, *114*, 4272–4281.