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Polarized Naphthalimide CH Donors Enhance Cl^- Binding within an Aryl-Triazole Receptor

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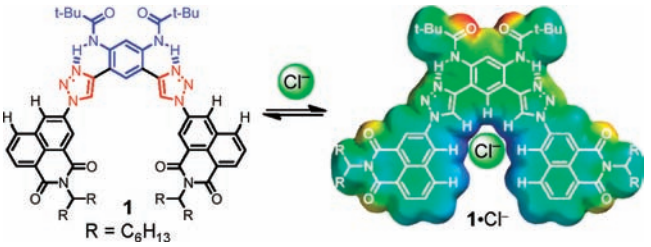
ABSTRACT



The dipolar character of 1,8-naphthalimide together with polarization of the C^4–H and C^5–H donors has been utilized in receptor 1 to effectively bind chloride alongside triazole and phenylene units. The Cl^- binding strength of 1 shows that the naphthalimide provides greater anion stabilization than an unactivated phenylene, and DFT calculations show that its collinear donor array can be a "urea-like" analog for CH···anion interactions.

The 1,8-naphthalimide building block, specifically 4-amino-1,8-naphthalimide, is typically employed as a *reporter*[1] for fluorescence sensing where binding of an analyte (cation, anion, H^+) affects the internal charge transfer from the electron-rich naphthalene to the electron-deficient imide.[1,2] While this phenomenon generates a highly polarized excited state, the inherent dipole within the *ground state* of the 1,8-naphthalimide moiety is also expected to generate polarized CH donors for cooperative hydrogen bonding interactions with anionic guests inside receptors.

Recent sensor designs[3−5] only hinted at the potential CH donors latent within 1,8-naphthalimide. These sensors utilized the NH donor of the 4-amino substituted 1,8-naphthalimide in the cooperative binding of anions alongside urea and thiourea motifs. While engaging with this NH donor led to enhanced affinities, further inspection of the ^{1}H NMR data showed a significant downfield shift ($\Delta\delta$ = 0.5 ppm) in the adjacent naphthalimide CH resonance. Given the growing evidence of effective CH···X^- interactions[6] stemming from triazoles[7] and other extrinsically polarized aryl CH groups,[6,8] this shift may have been a strong

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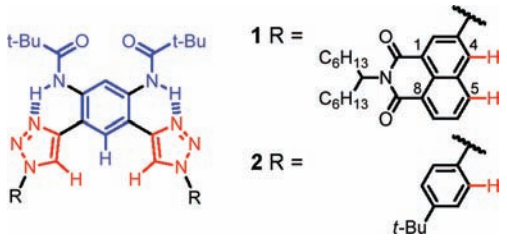


Figure 1. Preorganization provided by intramolecular NH···N[3] (triazole) hydrogen bonds (blue) was used to explore the CH donor strength of two naphthalimides (**1**) compared to that of two unactivated phenylenes (**2**).

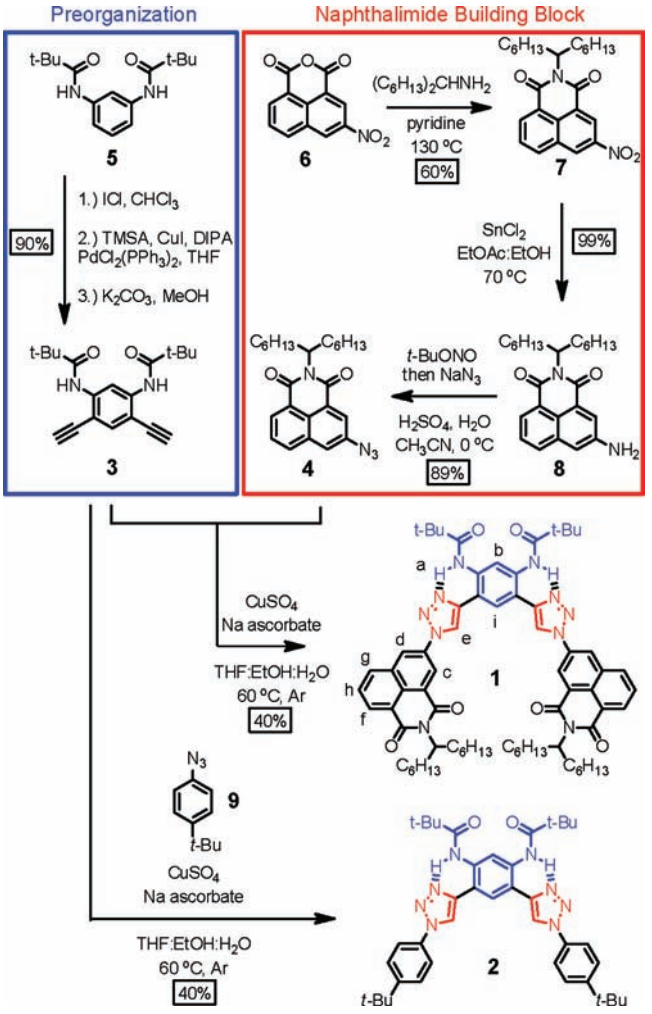
indication of this "nontraditional" hydrogen bond. In continuing to develop the assessment[6,7] and predictability[8] of CH hydrogen bonding, we hypothesized that through-bond polarization by the electron-withdrawing imide and the parallel alignment of the C^4–H and C^5–H bonds with the naphthalimide molecular dipole[9] (4.73 D) will turn on CH···X^- interactions.

Herein, we describe the synthesis and halide binding studies of receptor **1** (Figure 1) that demonstrates the utility of "nontraditional" naphthalimide CH hydrogen bonds in comparison to phenyl CH donors in receptor **2**. DFT analyses of the donors within receptor **1** demonstrate that the "urea-like" donor array of 1,8-naphthalimide provides more anion stabilization than both phenylenes and triazoles.

Receptors **1** and **2** were designed with intramolecular amido NH···N[3] (triazole) hydrogen bonds to direct the triazole donors toward a central anion-binding cavity and to aid in simplifying the conformational space for comparing the two receptors. The amido NH groups are expected to provide a distinct advantage over the previous use of phenolic OH moieties[7f,10] as (1) the amido NH groups are less susceptible to deprotonation and (2) the amide linkage provides a synthetic handle from which solubility can be added to the receptor. With this preorganized scaffold, we recognized that differences in Cl^- binding affinities (ΔG) between **1** and **2** could be rationalized by considering the different CH donors (Figure 1) presented by 1,8-naphthalimide and 4-*tert*-butylbenzene. We expect that the two polarized CH donors of 1,8-naphthalimide (C^4 and C^5) should result in stronger hydrogen bonding interactions and ultimately stronger anion binding for receptor **1**.

Receptors **1** and **2** were prepared using Cu(I)-catalyzed azide–alkyne cycloaddition[11] according to the synthetic route in Scheme 1. Intramolecular preorganization was introduced via dialkyne **3**, while azido-functionalized

Scheme 1. Synthesis[a] of Receptors **1** and **2**



[a] TMSA = trimethylsilylacetylene, DIPA = diisopropylamine.

naphthalimide **4** was prepared in four steps utilizing established[12] as well as some modified[13] conditions. 1-Heptylhexylamine[14] was installed to solubilize **1** in halogenated solvents.

The halide affinities of **1** and **2** were determined using both ^{1}H NMR and UV/vis spectroscopies by adding the corresponding tetrabutylammonium (TBA^+) salt in dichloromethane. The ^{1}H NMR titration of **1** with TBACl (Figure 2A) provided structural information about the receptor and its complexes present in solution. The downfield shift of the amido NH signal in empty receptor **1** (11.3 ppm) compared to its position (8.4 ppm) in alkyne building block **3** is indicative of intramolecular NH···N[3] (triazole) contacts. Upon receptor saturation, notable downfield shifts (Figure 2A) can be seen for the triazole H_e (2.2 ppm), phenylene H_i (1.1 ppm), and naphthalimide C^4–H (H_d, 0.7 ppm) hydrogens consistent with CH···Cl^- interactions within the receptor cavity.

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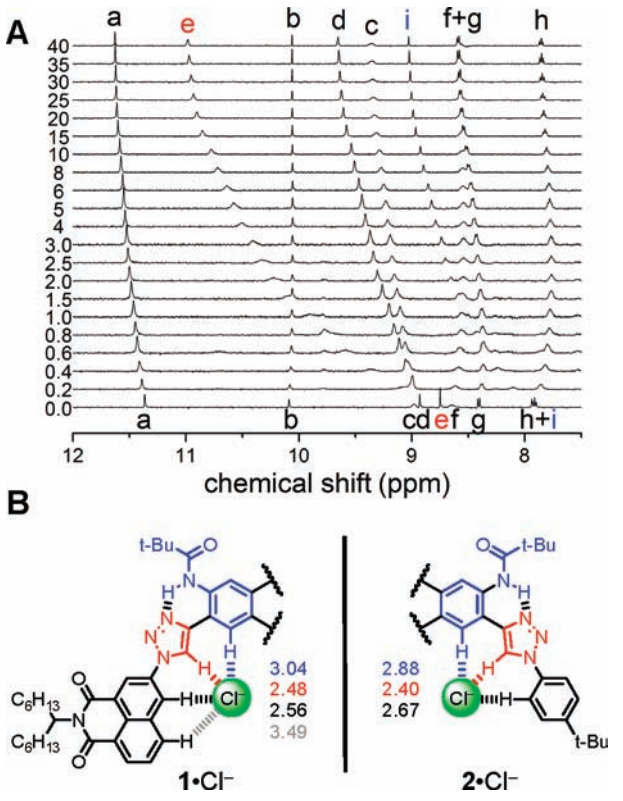

Figure 2. (A) ^{1}H NMR spectra of receptor **1** with increasing equivalents of TBACl (500 MHz, 500 μM, 298 K). (B) Calculated (B3LYP/6-31+G(d,p)) H-bond distances within **1**•Cl$^-$ and **2**•Cl$^-$ complexes.

The minor downfield shift observed for the naphthalimide C^5−H donor (H$_g$, 0.15 ppm) hints at weaker interactions with the bound Cl$^-$, which can be attributed to its more distant location. The predicted conformation of **1**•Cl$^-$ (Abstract graphic) was verified by 2D ROESY spectroscopy.[15]

The observation that the triazole (H$_e$) signal migrates to a greater extent upon Cl$^-$ binding than the central phenylene H$_i$ is consistent with its stronger hydrogen bonding interactions.[7d] The naphthalimide H$_d$ migrates less than the central phenylene H$_i$, a finding that appears to contradict expectations. However, the initial positions of the naphthalimide resonances in empty receptor **1** represent two rapidly interconverting rotamers[16] about each naphthalimide-triazole bond (resulting in four different conformations). By comparison, its final position is representative of a single conformation for **1**•Cl$^-$ (Abstract graphic). Therefore, it is not possible to utilize these $\Delta\delta$ values as a relative measure of hydrogen bonding stemming from the naphthalimides.

Rather, insight into the relative H-bond strengths was gained through geometry optimizations on the **1**•Cl$^-$ complex. Calculations (B3LYP/6-31+G(d,p))[15] show that the phenylene CH···Cl$^-$ distance in **1**•Cl$^-$ (3.04 Å) is significantly longer than that of the naphthalimide C$_4$−H (2.56 Å) and triazole (2.48 Å) donors (Figure 2B), which speaks to the more electropositive character of the latter two. The interaction of the naphthalimide's C^5−H donor is weakened by its substantially larger distance (3.49 Å) and nonideal angle (138°) relative to the chloride. By comparison, the CH···Cl$^-$ distances from the terminal phenylene CH donors in **2**•Cl$^-$ show longer contacts (2.67 Å) than the naphthalimide H-bonds. Presumably, this weakening causes contraction of the triazole (2.40 Å) and phenylene (2.88 Å) contacts in **2**•Cl$^-$.

These findings are further supported by the electronic binding energies (ΔE)[17] of the Cl$^-$ complexes for the individual CH donors within **1** (**NI**, naphthalimide; **T**, triazole). DFT calculations (Figure 3) showed that **NI**•Cl$^-$ adopts a bifurcated H-bond around Cl$^-$ (ΔE = −80 kJ/mol). For a more accurate representation of its expected binding geometry within the **1**•Cl$^-$ complex, the CH···Cl$^-$ angle was constrained to a linear angle (with respect to the C^4−H donor) causing a slight drop in the overall binding energy (ΔE = −72 kJ/mol) presumably due to weakening of the contribution of the C^5−H donor. Interestingly, the constrained **NI**•Cl$^-$ was found to provide greater stabilization than the analogous **T**•Cl$^-$ complex[18] (ΔE = −64 kJ/mol)! It is important to note that while most of the naphthalimide binding energy derives from the linear C^4−H···Cl$^-$ contact, the adjacent C^5−H also affects anion stabilization even though its angle and distance are less than ideal (Figure S29).[15] These calculated energies point to anion stabilization by the *entire* naphthalimide building block where the two parallel CH donors are analogous to the NH donors of urea.

If the CH donor array presented by the naphthalimide does indeed provide similar anion stabilization as the triazole CH, its incorporation into the receptor should result in stronger halide binding with **1** compared to **2**. To test this idea, the 1:1 anion binding energies of **1** and **2** need to be deconvoluted from the other solution equilbria.

The changes in peak position that take place during the ^{1}H NMR titration provides evidence for multiple complexes in solution. The hydrogens located distal to the binding cavity (H$_g$, H$_h$) are more sensitive to the formation of higher ordered species, which includes a 2:1 complex, **1**$_2$•Cl$^-$, as confirmed by mass spectrometry.[7c,19] The initial upfield shift of H$_h$ (2.0 equiv of Cl$^-$ added) is consistent with expected shielding from π−π stacking interactions within a **1**$_2$•Cl$^-$ complex while additional Cl$^-$ ultimately drives the equilibrium toward the **1**•Cl$^-$ complex. Titrations[15] with Br$^-$ and I$^-$ also provided corroborating evidence for the existence of such higher ordered complexes. Finally, our recent studies[7h] lead us to expect ion pairing to be present between TBA$^+$ and

(15) Supporting Information.

(16) The calculated (B3LYP/6-311++G(3df,2p)) rotational barrier for interconversion between the two rotamers was found to be 12 kJ/mol and consistent with rapid rotation on the NMR time scale.

(17) BSSE counterpoise corrected.

(18) The triazole calculation was performed with a linear constraint on the CH···Cl$^-$ angle.

(19) Evidence for these 1:1 and 2:1 complexes was obtained through electrospray ionization mass spectroscopy (ESI-MS) experiments conducted in the presence of 0.5 equiv of TBACl.[15]

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the halide[20] both competitively (K_{ion}) and within the receptor–anion complex (K_{ipc}).

Quantitative analysis of the halide binding strength of **1** was performed using the following equilibria:

$$\mathbf{1} + X^- = \mathbf{1}\bullet X^- \qquad K_1$$
$$\mathbf{1}\bullet X^- + \mathbf{1} = \mathbf{1}_2\bullet X^- \qquad K_2$$
$$TBA^+ + X^- = TBA^+\bullet X^- \qquad K_{ion}$$
$$\mathbf{1}\bullet X^- + TBA^+ = \mathbf{1}\bullet X^-\bullet TBA^+ \qquad K_{ipc}$$

Since it is expected[21] that all four equilibria are present at NMR concentrations (500 μM), K_1 values (Table 1) were determined separately by analysis of UV/vis titrations (<20 μM) where the weaker and higher ordered species could be diluted out. As dilution does not remove competitive ion pairing, the known values[22] for K_{ion} were used in the data fitting with the software Sivvu.[23] The ^{1}H NMR titration was then analyzed by HypNMR[24] using the previously calculated values for K_1 to allow determination of K_2 and K_{ipc}.[15]

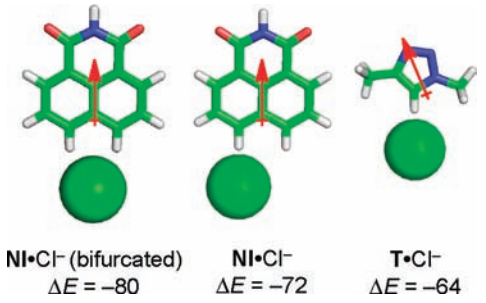

Figure 3. Optimized structures (B3LYP/6-31+G(d,p)) and electronic binding energies (kJ/mol, B3LYP/6-311+G(3df,2p)) for naphthalimide (**NI**•Cl$^-$) and triazole (**T**•Cl$^-$) complexes. The dipoles (B3LYP/6-31+G(d,p)) for the individual building blocks are shown in red.

The greater Cl$^-$ affinity ($\Delta\Delta G$ = 3 kJ/mol) of **1** as compared to **2** can only be rationalized by the incorporation of polarized naphthalimide donors within the binding cavity. The expected enthalpic benefit of the ideal C^4–H$\cdots$Cl$^-$ and nonideal C^5–H$\cdots$Cl$^-$contacts[15] is felt even after paying the energetic cost of organizing **1** for binding, as calculations show that the lowest energy conformation of **1** orients the two naphthalimide donors away from its electropositive cavity.[15] By comparison, the lowest energy conformation of receptor **2** is already ideal for Cl$^-$ binding. Entropically, the four low energy conformations of empty receptor **1** is reduced to one in the **1**•Cl$^-$ complex, whereas **2** has four conformations before and after Cl$^-$ binding.[25]

Table 1. Binding Constants[a] (M^{-1}), Free Energies (kJ/mol), and $\Delta\delta$ for Receptors **1** and **2**

	K_1 (**1**, UV) ΔG_1 (**1**)	K_1 (**2**, UV) ΔG_1 (**2**)	$\Delta\delta$ (H_e) (**1**, ppm)	$\Delta\delta$ (H_d) (**1**, ppm)
Cl$^-$	$1.4 \pm 0.2 \times 10^5$ -29.3 ± 0.4	$4.2 \pm 0.2 \times 10^4$ -26.3 ± 0.1	2.2	0.7
Br$^-$	$3.9 \pm 0.5 \times 10^4$ -26.2 ± 0.3	$1.1 \pm 0.1 \times 10^4$ -23.1 ± 0.2	1.9	0.9
I$^-$	$7.8 \pm 2 \times 10^3$ -22.2 ± 0.6	$<10^3$	1.6	1.0

[a] Values for K_2, K_{ion}, and K_{ipc} are in the Supporting Information.

While titrations of **1** with Br$^-$ and I$^-$ showed expectedly weaker binding (Table 1), we were surprised that the naphthalimide CH donors (H_d and H_g) responded with increasingly larger downfield shifts compared to the Cl$^-$ titration.[15] At the same time, the triazole showed smaller shifts. These observations indicate that these larger halides are not suited for strong H-bonding within the cleft defined by the central triazole-phenylene-triazole triad of receptor **1**. As seen in this and previous work,[6,7] the spatial relationship of these donors is ideal for Cl$^-$ to adopt strong H-bonding contacts. With increasing ionic radii, larger halides "migrate" away from the central triad thus forming stronger contacts with the naphthalimide C^4–H and C^5–H donors. These stronger contacts lead to the observed increase in $\Delta\delta$ values and thus provide experimental evidence for the bifurcated "urea-like" CH hydrogen bonds provided by the 1,8-naphthalimide building block.

In conclusion, receptor **1** shows strong Cl$^-$ binding as a result of (1) two polarized naphthalimide CH donors that act alongside triazole donors to effect anion stabilization and (2) receptor preorganization from intramolecular amido NH$\cdots$N[3] triazole H-bonds. The enhanced Cl$^-$ binding strength is indicative of significant CH$\cdots$Cl$^-$ contacts. DFT analysis of 1,8-naphthalimide shows how the parallel alignment of CH donors in a urea-like array leads to anion stabilization surpassing that of 1,2,3-triazole. Overall, this investigation shows how any *unconventional* CH donor can be easily diagnosed and assessed using well-understood concepts in physical organic chemistry.

Acknowledgment. The authors would like to thank the Department of Energy (Office of Basic Energy Sciences, DOE-BES) for funding.

Supporting Information Available. Syntheses, experimental procedures, compound characterization, computational details, titration, and data fittings. This material is available free of charge via the Internet at http://pubs.acs.org.

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