ChemComm

RSCPublishing

COMMUNICATION

View Article Online
View Journal | View Issue

Aryl C–H···Cl⁻ hydrogen bonding in a fluorescent anion sensor†

Blakely W. Tresca,[a] Lev N. Zakharov,[b] Calden N. Carroll,[a] Darren W. Johnson*[a] and Michael M. Haley*[a]

Cite this: *Chem. Commun.*, 2013, **49**, 7240

Received 18th June 2013,
Accepted 4th July 2013

DOI: 10.1039/c3cc44574g

www.rsc.org/chemcomm

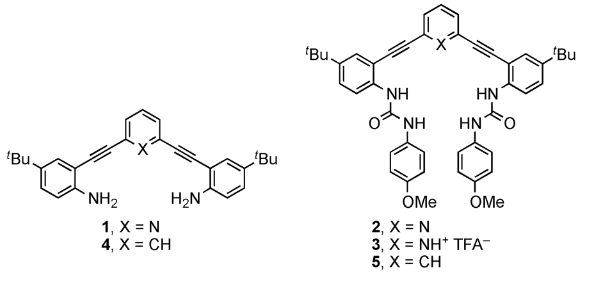
A new phenyl-acetylene receptor containing a carbonaceous hydrogen bond donor activates anion binding in conjunction with two stabilizing ureas. The unusual CH···Cl⁻ hydrogen bond is apparent in solution by large ^{1}H NMR chemical shifts and by a short, linear contact in the solid state.

Numerous supramolecular hosts for anionic guests have been developed, including polymers, macrocycles and cryptands.[1] Neutral hosts frequently combine a complementary geometry and strong hydrogen bond donors to selectively bind anionic guests.[2] A range of hydrogen bond donors that exhibit drastically different pK_as are found in supramolecular hosts. Some examples are amides (p$K_a^{\mathrm{DMSO}} \approx$ 23–25), sulfonamides (p$K_a^{\mathrm{DMSO}} \approx$ 13–18), phenols (p$K_a^{\mathrm{DMSO}} \approx$ 12–20), pyrroles (p$K_a^{\mathrm{DMSO}} \approx 23.0$) and ureas (p$K_a^{\mathrm{DMSO}} \approx$ 20–27).[3] These examples of hydrogen bond donors all rely on protic N- or O-groups. Highly electronegative elements are favored, but are not the only hydrogen bond donors extant. Of the donors employed in molecular sensors, the phenyl C–H $\left(\mathrm{p}K_a^{\mathrm{H_2O}} \approx 37\right)^{3b}$ donor is relatively underappreciated by supramolecular chemists.

The C–H donor was recognized early on by molecular biologists as an important component in the secondary structures of biomolecules.[4,5] Carbonaceous hydrogen bond donors have experienced a renaissance in recent years with the introduction of new functional groups, including imidazolium,[6] triazole,[7] diketopropylene–BF$_2$,[8] and benzene.[9] The 1,2,3-triazole functionality is a promising anion binding moiety in neutral receptors,[10] since the C–H hydrogen bond donor is activated by a strong dipole oriented through the nitrogen atoms.[11] As previously observed in other selective hosts, the anion binding ability of 1,2,3-triazoles is optimized when the receptor is preorganized in an appropriately sized macrocycle.[12]

Aryl groups are used as the rigid linkers in supramolecular hosts to provide the desired anion receptor geometry. As a result, phenyl protons are a frequent feature in anion binding pockets.[1] Despite their ubiquity, aryl protons play only a small role in the anion binding of most hosts. Contrary to this, calculations suggest phenyl protons can bind anions with association energies (ΔG) approaching -9.0 kcal mol^{-1} and volumes of crystallographic data exist for the general C–H···anion interaction.[9,13] Recent solution studies have demonstrated the action of C–H hydrogen bonds in supramolecular hosts, yet crystal structures of these complexes are still rare.[14]

2,6-Bis(2-anilinoethynyl)pyridine (**1**, Fig. 1) is an easily functionalized fluorescent core. Addition of sulfonamides or ureas (*e.g.*, **2**) has illustrated the versatility of this scaffold for the construction of fluorescent sensors.[15] Judicious modification of the substituents allows control of the fluorescent and coordinating properties.[16] Previous work in our labs has demonstrated the increased anion binding ability by the pyridine-protonated receptors (**3**), showing an almost two order of magnitude increase in anion binding.[17] The greater anion binding ability of the pyridinium host is limited by its pK_a. While the exact pK_a of **3** is not known, the pK_as for a series of similar ethynylpyridines have been measured in acetonitrile; the electron-withdrawing alkynes shift the pK_a of 2,6-bis(ethynyl)-pyridinium to 8.9[18] from 12.5 for pyridinium (MeCN).[19] This complicates any attempts to apply a pyridinium-based anion sensor in an environment such as cells where a low pH cannot be maintained.[18b] Replacement of the pyridine with a phenyl moiety



1, X = N
4, X = CH

2, X = N
3, X = NH$^+$ TFA$^-$
5, X = CH

Fig. 1 Structures of 2,6-bis(2-anilinoethynyl)arene cores **1** and **4** and anion receptors **2**, **3** and **5**.

---

[a] *Department of Chemistry & Biochemistry and the Materials Science Institute, University of Oregon, Eugene, OR 97403-1253, USA. E-mail: dwj@uoregon.edu, haley@uoregon.edu; Fax: +1-541-346-0487; Tel: +1-541-346-0456*

[b] *Center for Advanced Materials Characterization in Oregon (CAMCOR), University of Oregon, Eugene, OR 97403-1443, USA*

† Electronic supplementary information (ESI) available: Experimental details, spectroscopic data and X-ray analysis of receptors and titration experiments. CCDC 929532. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc44574g

in the ethynyl core (*e.g.*, **4**, **5**) will maintain the same geometry, while altering the electronic and anion binding properties. The phenyl C–H hydrogen bond offers an opportunity to expand the working conditions of this sensor and explore the nature of C–H hydrogen bonds. Herein, we introduce an aryl hydrogen bond donor in place of the pyridine–pyridinium moiety and report the anion binding characteristics of this new receptor.

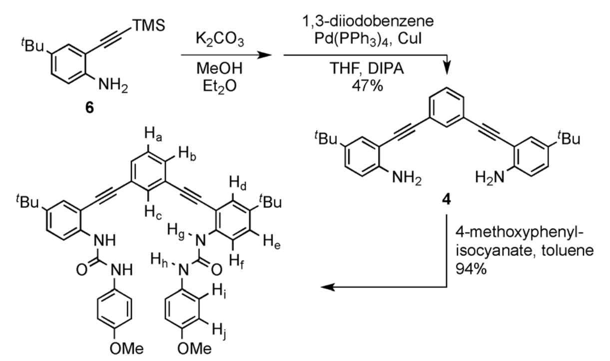
Phenyl core **4** was obtained by deprotection and subsequent Sonogashira cross-coupling of ethynylaniline **6** with 1,3-diiodobenzene in 47% yield (Scheme 1). Reaction of **4** with 4-methoxyphenyl isocyanate gave bisurea receptor **5** in 94% yield. The anion binding properties of **5** were analyzed using ^{1}H NMR and UV-Vis spectroscopy. Titrations were performed in water-saturated chloroform with anions added as tetra-*n*-butylammonium (TBA) salts. A representative ^{1}H NMR titration experiment with **5** and Cl^- is shown in Fig. 2. The $\Delta\delta$ of urea proton H_g was fit using non-linear regression in MatLab to determine association constants (K_a).[20] A 1 : 1 host : guest binding model was used to fit the data as this agrees with previous binding studies on similar systems.[17] In addition, the model is supported by UV-Vis spectroscopic evidence and solid-state structures. Association constants for **5** and comparison with data for structurally similar hosts **2** and **3** are reported in Table 1.

Pyridine host **2**, with only four hydrogen bond donors, has the lowest K_a for the tested anions. As previously reported, protonation of this class of receptor activates anion binding, increasing the K_a from 700 M^{-1} to 40 700 M^{-1} for $\mathbf{3}\cdot Cl^-$.[17] The difference in K_a between **2** and **3** can be separated into three influencing factors: (1) the repulsive effect of the nitrogen lone pair on **2**, (2) the additional hydrogen bond in **3**, and (3) the electrostatic interaction of Cl^- with **3**. For the three hosts, receptor **2** has the lowest energy interaction due to the repulsion between the pyridine lone pair. The inclusion of an aryl C–H hydrogen bond donor in **5** increases the K_a by an order of magnitude for Cl^- (Table 1). The difference in energy ($\Delta\Delta G = \Delta G\ \mathbf{2}\cdot Cl^- - \Delta G\ \mathbf{5}\cdot Cl^-$) is 1.33 kcal mol^{-1}. This $\Delta\Delta G$ is very close to the value (1.44 kcal mol^{-1}) reported by Sessler *et al.* for strapped pyrroles containing benzene or furan.[21] The additional electrostatic attraction in protonated receptor **3** leads to 1.07 kcal mol^{-1} added stabilization ($\Delta\Delta G$). This value is perhaps smaller due to competition from the trifluoroacetate counter ion.

Table 1 Anion association constants (K_a) obtained by fitting titration data using MatLab for ^{1}H NMR data or Hyperquad for UV-Vis data[a]

Host	Cl^-/M^{-1}	Cl^- ΔG/kcal mol^{-1}	Br^-/M^{-1}	I^-/M^{-1}
2	700[b]	−3.88	—	—
5	6700[c]	−5.21	1600[b]	150[b]
3	40 700[c]	−6.28	—	—

[a] Anions added as tetrabutylammonium salts in water-saturated $CHCl_3$ or $CDCl_3$ at 298 K. Error is *ca.* ±10% and the values represent an average of three titrations. [b] Titrations performed using ^{1}H NMR. [c] Titrations performed using UV-Vis.



Scheme 1 Synthesis of receptor **5**. Proton assignments determined *via* ^{1}H–^{13}C HSQC and ^{1}H–^{1}H ROSY NMR spectroscopy.

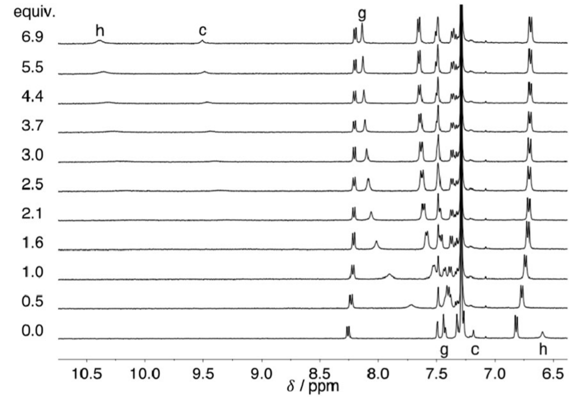


Fig. 2 ^{1}H NMR titration of **5** with TBA^+Cl^- at 298 K; [**5**] = 0.69 mM in water saturated $CDCl_3$. Peak assignments refer to Scheme 1.

2-D HSQC and ROSY NMR spectroscopy were used to assign the urea and aryl peaks in the proton NMR spectrum of **5** (see Fig. S20–S22 in the ESI†). The urea protons (H_h and H_g) shift downfield upon addition of Cl^-. A close examination of the aryl peak H_c reveals a large downfield shift, $\Delta\delta > 2$ ppm. The magnitude of $\Delta\delta$ suggests a strong aryl hydrogen bond, but may also be influenced by structural changes induced by anion binding. The other aromatic peaks shift very little or slightly upfield likely as a result of weak CH–π interactions. The lack of a significant $\Delta\delta$ for H_a or H_b contraindicates the influence of alternative binding conformations, although multiple conformations have been previously observed in **2** and **3** by rotation about the ethynyl linkers.[16a,17,22] The stronger urea hydrogen bond to Cl^- is formed with the more distant proton from the core, H_h, which is apparent in the large shift ($\Delta\delta$ 3.8 ppm) as compared to the interior urea H_g. Similar shifts are observed upon titration with Br^- and I^- (Fig. S4 and S7, ESI†).

Evidence of hydrogen bonding was also observed in the X-ray crystal structure of $\mathbf{5}\cdot Cl^-$, which is shown in Fig. 3.[23] The chloride resides within a binding pocket created by the aryl proton and the urea arms with a TBA^+ cation in close proximity. The central phenylacetylene carbons (C_1–C_9, C_{27}–C_{29}) form a plane (±0.033 Å), which the chloride sits slightly above (0.257(4) Å). The urea arms are twisted with one slightly above the plane and the other slightly below the plane. The $C(H_c)\cdots Cl$ distance is 3.579(3) Å and the $C(H_c)\cdots Cl$ angle is 169°. The $N(H)\cdots Cl$ distances vary greatly with the shortest distance at 3.212(3) Å and the longest distance measuring 3.732(3) Å. The $N(H)\cdots Cl$ angles vary from 146° to 170°. The $C(H_c)\cdots Cl$ total distance is less than the sum of the van der Waals radii for the component elements and is shorter than previously reported examples of arene $C(H)\cdots Cl$ contacts in anion hosts (3.538–3.793 Å).[14] The large angle and short distance fall well within

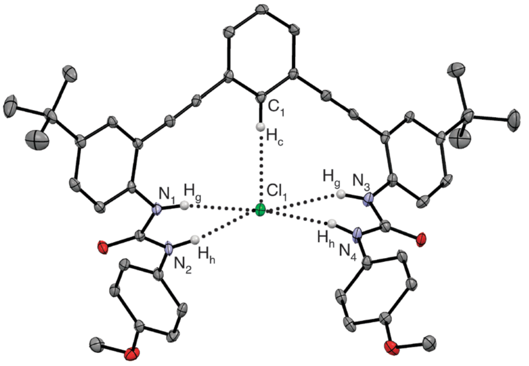


Fig. 3 X-ray crystal structure of **5**·Cl^- shown as ORTEP representation. Hydrogen bond interactions are shown as dashed lines. Non-coordinating hydrogens, TBA^+ counter cation and solvent have been omitted for clarity. Ellipsoids drawn at 50% probability level.

previously defined criteria for an aryl hydrogen bond ($\theta > 140^\circ$, $d < 3.86$ Å)[4,24] and add credence for the importance of this C–H hydrogen bond in anion binding.

The urea hydrogen bond distances provide further evidence for the binding conformation observed in solid-state studies to exist in solution. The urea hydrogen bonds are divided into two asymmetric groups, where N_2/N_4 are on average 0.41 Å closer to Cl than N_1/N_3 (H_h and H_g, respectively). The average distance for $N(H_g)\cdots Cl$ is 3.637 Å and the average distance for $N(H_h)\cdots Cl$ is 3.213 Å. A longer $N(H_g)\cdots Cl$ distance would account for the smaller downfield shift observed by ^1H NMR spectroscopy. The solution and solid state experiments provide a relative rank of the hydrogen bond lengths to Cl^-, and perhaps strengths as follows: $N(H_h) > C(H_c) > N(H_g)$.

UV-Vis and fluorescence spectroscopy experiments were performed to evaluate the sensing ability of compound **5** (see Fig. S11 and S15 in the ESI†). The color change of **5** was modest but allowed for the determination of binding constants. Cl^- titrations of **5** have an isosbestic point at 312 nm indicating a clean transition from free host and guest to the final host:guest complex, which lends credence to the 1 : 1 host : guest model used for K_a determination. Crystallographic evidence points to a higher order complex (1 : 2 or 2 : 1 host : guest) being unlikely and these larger complexes would require an intermediate complex, which is not evident in solution. Receptors **2** and **3** were previously shown to be good fluorescent sensors,[16] and the conjugated core of **5** should also lend itself to this application. Excitation at 320 nm produced a fluorescence emission at 381 nm with a Stoke's shift of 5000 cm^{-1}. Addition of one equivalent TBACl caused a marked decrease in the fluorescence. The turn-off fluorescent response for chloride is the same as previously observed with receptor **3**. The fluorescence response of this class of sensors can be controlled by substitution at the *para* position of the phenylureas. In the pyridine sensors **2** and **3**, an electron donating group (OMe) produced an "on–off" response; however, electron withdrawing groups (NO_2) led to an "off–on" response.[16]

In summary, replacement of a pyridyl unit with a phenyl moiety in the bis(anilinoethynyl)arene class of anion receptors has provided a new avenue of inquiry into aryl C–H hydrogen bonding. The importance of the phenyl hydrogen bond donor has been demonstrated with solution and solid-state evidence for a strong C–H to Cl^- contact. In addition, the structural modification has not negatively affected the selectivity or electronic properties of the host. Related computational modeling has shown that substitution with electron withdrawing groups can increase the hydrogen bond energy of benzene closer to that of pyrrole.[9] Further experiments with the phenyl core may help to elucidate the mechanism of fluorescence in this class of sensor, especially the influence of the pyridine ring in the parent receptor. Work is underway to explore substituted phenyl cores with the goal of achieving K_as on the same order or greater than found for **3**.

This work was supported by NIH grant R01-GM087398; see the ESI† for complete acknowledgments.

Notes and references

1 J. L. Sessler, P. A. Gale and W.-S. Cho, *Anion Receptor Chemistry*, Royal Society of Chemistry, Cambridge, 2006.
2 P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed.*, 2001, **40**, 486–516.
3 (*a*) F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456–463; (*b*) There appears to be discrepancy for the pK_a of benzene in water, with values of 37 and 43 appearing most commonly. We chose to use the value reported in: E. V. Anslyn and D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, Sausalito, CA, 2006, p. 280.
4 G. R. Desiraju and T. Steiner, *The Weak Hydrogen Bond: in Structural Chemistry and Biology*, Oxford University Press, Oxford, New York, 1999.
5 H.-J. Schneider, *Angew. Chem., Int. Ed.*, 2009, **48**, 3924–3977.
6 N. G. White, S. Carvalho, V. Felix and P. D. Beer, *Org. Biomol. Chem.*, 2012, **10**, 6951–6959.
7 Y. Li and A. H. Flood, *Angew. Chem., Int. Ed.*, 2008, **47**, 2649–2652.
8 (*a*) H. Maeda, Y. Haketa and T. Nakanishi, *J. Am. Chem. Soc.*, 2007, **129**, 13661–13674; (*b*) B. Dong, T. Sakurai, Y. Honsho, S. Seki and H. Maeda, *J. Am. Chem. Soc.*, 2013, **135**, 1284–1287; (*c*) Y. Terashima, M. Takayama, K. Isozaki and H. Maeda, *Chem. Commun.*, 2013, **49**, 2506–2508.
9 V. S. Bryantsev and B. P. Hay, *J. Am. Chem. Soc.*, 2005, **127**, 8282–8283.
10 Y. Hua and A. H. Flood, *Chem. Soc. Rev.*, 2010, **39**, 1262–1271.
11 K. P. McDonald, Y. Hua and A. H. Flood, *Top. Heterocycl. Chem.*, 2010, **24**, 341–366.
12 Y. Hua, R. O. Ramabhadran, J. A. Karty, K. Raghavachari and A. H. Flood, *Chem. Commun.*, 2011, **47**, 5979–5981.
13 V. S. Bryantsev and B. P. Hay, *Org. Lett.*, 2005, **7**, 5031–5034.
14 (*a*) H. Juwarker, J. M. Lenhardt, D. M. Pham and S. L. Craig, *Angew. Chem., Int. Ed.*, 2008, **47**, 3740–3743; (*b*) C.-H. Lee, H.-K. Na, D.-W. Yoon, D.-H. Won, W.-S. Cho, V. M. Lynch, S. V. Shevchuk and J. L. Sessler, *J. Am. Chem. Soc.*, 2003, **125**, 7301–7306; (*c*) F. Szemes, D. Hesek, Z. Chen, S. W. Dent, M. G. B. Drew, A. J. Goulden, A. R. Graydon, A. Grieve, R. J. Mortimer, T. Wear, J. S. Weightman and P. D. Beer, *Inorg. Chem.*, 1996, **35**, 5868–5879.
15 (*a*) C. N. Carroll, J. J. Naleway, M. M. Haley and D. W. Johnson, *Chem. Soc. Rev.*, 2010, **39**, 3875–3888; (*b*) O. B. Berryman, C. A. Johnson II, L. N. Zakharov, M. M. Haley and D. W. Johnson, *Angew. Chem., Int. Ed.*, 2008, **47**, 117–120.
16 (*a*) J. M. Engle, C. N. Carroll, D. W. Johnson and M. M. Haley, *Chem. Sci.*, 2012, **3**, 1105–1110; (*b*) C. N. Carroll, B. A. Coombs, S. P. McClintock, C. A. Johnson, O. B. Berryman, D. W. Johnson and M. M. Haley, *Chem. Commun.*, 2011, **47**, 5539–5541.
17 C. N. Carroll, O. B. Berryman, C. A. Johnson, L. N. Zakharov, M. M. Haley and D. W. Johnson, *Chem. Commun.*, 2009, 2520–2522.
18 (*a*) J. M. Heemstra and J. S. Moore, *Org. Lett.*, 2004, **6**, 659–662; (*b*) It should be noted that this value is determined in CH_3CN; in water the bis(ethynyl)pyridiniums should still be more acidic than pyridinium and thus have pK_as < 5.
19 I. Kaljurand, A. Kütt, L. Sooväli, T. Rodima, V. Mäemets, I. Leito and I. A. Koppel, *J. Org. Chem.*, 2005, **70**, 1019–1028.
20 P. Thordarson, *Chem. Soc. Rev.*, 2011, **40**, 1305–1323.
21 D.-W. Yoon, D. E. Gross, V. M. Lynch, J. L. Sessler, B. P. Hay and C.-H. Lee, *Angew. Chem., Int. Ed.*, 2008, **47**, 5038–5042.
22 J. M. Engle, P. S. Lakshminarayanan, C. N. Carroll, L. N. Zakharov, M. M. Haley and D. W. Johnson, *Cryst. Growth Des.*, 2011, **11**, 5144–5152.
23 Crystallographic data for **5** can be found in the ESI† and as CCDC 929532.
24 (*a*) R. Taylor and O. Kennard, *J. Am. Chem. Soc.*, 1982, **104**, 5063–5070; (*b*) B. P. Hay and V. S. Bryantsev, *Chem. Commun.*, 2008, 2417–2428; (*c*) P. A. Wood, F. H. Allen and E. Pidcock, *CrystEngComm*, 2009, **11**, 1563–1571.