Nitrogen−Halogen Intermolecular Forces in Solution

Paul L. Wash, Shihong Ma, Ulrike Obst, and Julius Rebek, Jr.*

The Skaggs Institute for Chemical Biology and The Department of Chemistry, The Scripps Research Institute 10550 North Torrey Pines Rd., La Jolla, California 92037

Received May 13, 1999

Molecular recognition studies using synthetic receptors have achieved a level of sophistication that allows even very weak intermolecular forces to be evaluated directly. Edge-to-face aromatic interactions and methyl−π interactions have been determined in organic solvents,[1,2] while hydrogen bonds and salt bridges have been evaluated in water.[3,4] These forces are all in the subkilocalorie range, and their determination involves carefully constructed control systems. This research was undertaken to provide a measure of the nitrogen−halogen interactions in an organic solvent. The interactions proved measurable through the use of a synthetic cleft-like receptor with affinities ranging from several hundred calories/mole to almost 1 kcal/mol in benzene.

Nitrogen−halogen interactions have often been observed in the solid state[5−7] where their presence is deduced from nitrogen−halogen intermolecular distances that are less than the sum of their van der Waals radii. Recent examples include the crystal structure of cyanuryl chloride[8] **1**, the TMEDA−1,2-diiodotetrafluoroethane[9] complex **2** (Figure 1), and the assembly of molecular tapes.[10] Calculations have estimated the strength of the nitrogen−chlorine affinity in the gas phase to be 1.2−2.5 kcal/mol,[6,8] but attempts to evaluate the nitrogen−halogen interaction in solution by means of **3** gave only very low binding constants ($<1\ M^{-1}$).[11] Kochi obtained evidence for charge transfer between DABCO and carbon tetrabromide **4** in a number of solvents and measured association constants in the 0.03−4.5 M^{-1} range.[12]

Cleft molecules **5a**−**c** (Figure 2) offer an inviting environment to certain nitrogen-containing heterocycles: hydrogen bonding of the base to the carboxylic acid can occur and π-stacking interactions of an aromatic heterocycle with the perylene floor are available. When these forces act simultaneously on, say, phenazine, the remaining heterocyclic nitrogen presents its lone pair to the "X" group as shown. The relative energies of the nitrogen−X interactions follow from the association constants (K_A) of **5a**−**c** and phenazine as a function of X.[13] As controls that offer comparable acids and π frameworks, we chose their S-shaped isomers (**5d**−**f**). Earlier studies established that hindered rotation around the imide N−xanthene bond prevents interconversion of the C (cleft) and S-shaped isomers at ambient temperatures.

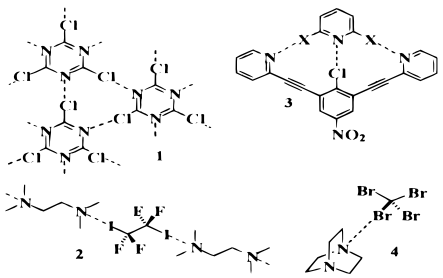

Figure 1. Examples of observed nitrogen−halogen interactions.

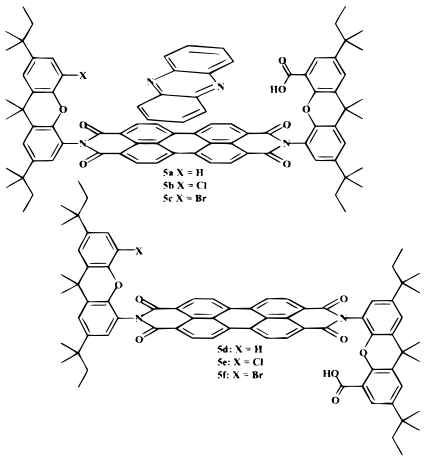

Figure 2. C-and S-shaped clefts designed to probe interactions between aromatic nitrogens and halogens.

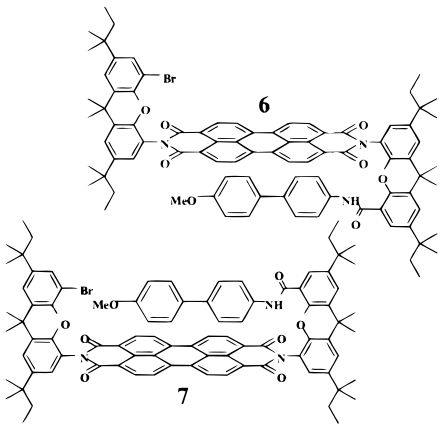

Figure 3. Amides **6** and **7** prepared for nOe studies to determine the identities of C and S cleft isomers.

Exhaustive spectroscopic studies of the individual C and S isomers failed to provide an unambiguous assignment for their structures, so we turned to derivatization. Accordingly, amides **6** and **7** (Figure 3) were prepared from the corresponding bromo acids **5c** and **5f**. Modeling suggested that the methoxy groups on the biphenyl amide had better access to the *tert*-amyl group of

(1) Paliwal, S.; Geib, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1994**, *116*, 4497−4498.
(2) Adams, H.; Carver, F. J.; Hunter, C. A.; Morales, J. C.; Seward, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1542−1544.
(3) Kato, Y.; Conn, M. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 3279−3284.
(4) Kato, Y.; Conn, M. M.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 1208−1212.
(5) Bent, H. A. *Chem. Rev.* **1968**, *68*, 587−648.
(6) Lommerse, J. P. M.; Stone, A. J.; Taylor, R.; Allen, F. H. *J. Am. Chem. Soc.* **1996**, *118*, 3108−3116.
(7) Desiraju, G. R.; Harlow, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 6757−6764.
(8) Xu, K.; Ho, D. M.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 105−110.
(9) Amico, V.; Meille, S. V.; Corradi, E.; Messina, M. T.; Resnati, G. *J. Am. Chem. Soc.* **1998**, *120*, 8261−8262.
(10) Reddy, D. S.; Panneerselvam, K.; Pilati, T.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1993**, 661−662.
(11) Xu, K.; Ho, D. M.; Pascal, R. A. *J. Org. Chem.* **1995**, *60*, 7186−7191.
(12) Blackstock, S. C.; Kochi, J. K.; Lorand, J. P. *J. Org. Chem.* **1987**, *52*, 1451−1460.
(13) Initial studies involving symmetrically substituted cleft compounds (containing two convergent aromatic bromines in the C isomer) failed to show interaction with such guests as phenazine, DABCO, and 1,4-benzoquinone; all suitable guests with nucleophilic heteroatoms are presented in the required collinear arrangement. In these cases, C and S isomers of the dibromides were assigned by the X-ray structure determination of a suitable crystal grown of the *S* isomer. A standard crystallographer's report can be found in the Supporting Information.

10.1021/ja991653m CCC: $18.00
Published on Web 08/17/1999

the remote xanthene in the S isomer than in the C isomer, and pointed to an nOe experiment. Indeed, only one amide cleft exhibited a rOe (rotating-frame nOe) between the methoxy and *gem*-dimethyl groups of the *tert*-amyl side chain. The assignments of C and S were then extrapolated to the two remaining sets (**5a,d** and **5b,e**) used in the study. Although the C isomer is preorganized with convergent functionality, pyramidalization[14] and partial rotations about the imide allow a range of distances between the opposing functions.

The xanthene *tert*-amyl side chains provided sufficient solubility of the synthetic receptors in benzene, a solvent that proved ideal for the titrations. Preliminary ^{1}H NMR (600 MHz, benzene-d_6) dilution studies of hydrogen-acid isomers, **5a** and **5d**, showed their chemical shifts to be concentration dependent. However, changes in shifts ceased upon reaching 1.3×10^{-5} M for the C isomer and 1.9×10^{-5} M for the S isomer. The spectra recorded for those respective concentrations also showed significantly sharpened line shape compared to spectra obtained at higher concentrations. This gave us confidence that the species present at the low concentrations were monomeric. As a point of comparison (although an imperfect one), benzoic acid, a significantly less hindered aromatic acid, in this solvent shows a dimerization constant of 245 M^{-1} (25 °C).[15] Similar hydrogen-bonded dimerization of the cleft acids causes severe steric clashes elsewhere in the structures. In addition, the possibility of intramolecular hydrogen bonding to the xanthene oxygen is expected to reduce self-association of the acids by hydrogen bonding. More likely, the aggregation of the molecules at hand involves their large aromatic surfaces. Attempts at NMR titrations at such low concentrations proved impractical due to long acquisition times needed to obtain reliable chemical shift data. Instead, UV/vis spectral analysis emerged as the appropriate method for binding studies.

The polyaromatic perylene diimide core of the receptors imparts a bright, brick-red color to the compounds, and boasts extinction coefficients greater than 75000 in benzene solution. The primary absorbances of the perylene chromophore (ca. 490 and 535 nm) are suitably free from occlusion by the longest wavelength absorbance of phenazine (ca. 400 nm): a solution containing 500 equiv of phenazine and hydrogen-acid cleft **5d** revealed phenazine end absorption eclipsing only as far as 470 nm. Samples were prepared by transfer of receptor and phenazine solutions via microliter syringe to waiting 3 mL volumetric flasks followed by dilution to the mark. The receptor concentration was held constant while anywhere from 50 to 650 equiv of phenazine were present in the samples. For a typical example, Figure 4 shows overlaid UV/vis spectra obtained from measuring hydrogen-acid S isomer (**5d**) solutions in benzene having 0−460 equiv of added phenazine. It is seen that the receptor's maximum absorbance ($\lambda_{max} \sim 535$ nm) remains free from phenazine absorbance. Both hypo- and bathochromic behavior, supportive of π-stacking,[16] is observed, and the distinct isosbestic points at 495, 510, and 532 nm confirm a 1:1 stoichiometry of binding. Benesi−Hildebrand[17] treatment of the data shows the required linear relationship, and gave a binding constant of 780 ± 80 M^{-1} for this example. Table 1 contains the binding data collected for all six compounds (**5a**−**f**) with phenazine.

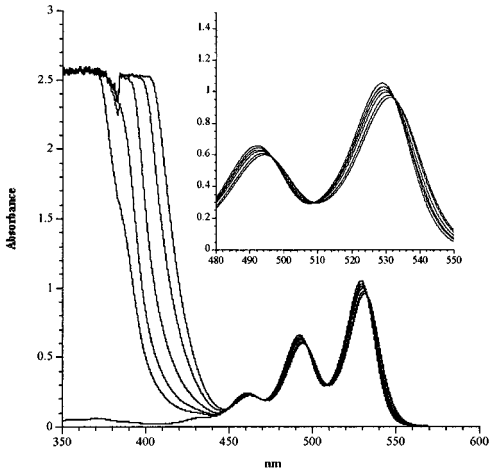

Figure 4. Overlaid UV/vis spectra obtained from titrations of S cleft **5d** with phenazine in benzene (25 °C).

Table 1

cleft	$K_{A(293)}$ (M^{-1})	ΔG_{293} (kcal/mol)	cleft	$K_{A(293)}$ (M^{-1})	ΔG_{293} (kcal/mol)
5a	480 ± 50	-3.6 ± 0.1	**5d**	780 ± 80	-3.9 ± 0.1
5b	1100 ± 100	-4.1 ± 0.1	**5e**	900 ± 90	-4.0 ± 0.1
5c	2200 ± 200	-4.5 ± 0.1	**5f**	760 ± 80	-3.9 ± 0.1

All S isomers performed as expected, with association constants falling within experimental error of each other. The difference in affinities (ca. 0.3 kcal/mol) seen for the C and S hydrogen-acid isomers (**5a**,**d**) is puzzling, but probably due to steric effects in the cleft. The striking difference is seen in the halogen-containing clefts. A favorable binding trend emerges as the X substituent is changed: chlorine binds better than hydrogen by approximately 0.5 kcal/mol, and a bromine increases the binding affinity by an additional 0.4 kcal/mol. A measurable attractive interaction exists then between heterocyclic nitrogens and aryl halogens in benzene solution. The force of the attraction is small compared to, say, a hydrogen bond, but can still be observed when the binding environment is appropriately constructed.

In summary, cleft-like shapes are well-suited for the investigation of weak intermolecular forces because they provide convergent functional groups: the acid for hydrogen bonding, the large perylene surface for π-stacking, and the halogen for interaction with the substrate held within. The values of 0.5 and 0.9 kcal/mol for nitrogen−chlorine and nitrogen−bromine interactions are estimates. These numbers reflect three different forces acting in concert, and cooperative binding effects, which may be stronger than the sum of the three forces acting alone, are possible. The strength of a solitary nitrogen−halogen interaction may be less, but the present measurement provides a reasonable upper limit.

Acknowledgment. We are grateful to the Skaggs Foundation and the National Institutes of Health for support, to Dr. Emily Maverick for crystallographic studies and to Dr. Derek Nelson for experimental contributions.

Supporting Information Available: A listing of crystallographic data and refinement parameters, thermal ellipsoid drawing of the asymmetric unit, ball-and-stick drawing of the entire molecule, fractional coordinates, interatomic distances, and bond angles; titration experimental details and graphical analysis (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA991653M

(14) Shimizu, K. D.; Dewey, T. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 5145−5149. Similar solid-state evidence of pyramidalization at the imide nitrogen is present in the X-ray structure described in ref 13.

(15) Huq, A. K. M. S.; Lodhi, S. A. K. *J. Phys. Chem.* **1966**, *70*, 1354−1358.

(16) Langhals, H.; Ismael, R. *Eur. J. Org. Chem.* **1998**, *1915*, 5−1917. Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793−1796.

(17) Benisi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703−2707.