Communication of electronic information over nanometer distances with supramolecular transduction. An experimental and density functional investigation †

Robert Deans, Alejandro O. Cuello, Trent H. Galow, Matthias Ober and Vincent M. Rotello *

Department of Chemistry, University of Massachusetts, Amherst, MA 01003, USA

Received (in Cambridge, UK) 7th December 1999, Accepted 13th April 2000
Published on the Web 1st June 2000

We have synthesized a family of conjugated diaminotriazine-functionalized receptors. Variation of distal functionality modulated the affinity of these receptors for flavin, demonstrating efficient electronic communication over a distance of 11 Å. The origin of this communication was explored using DFT methodology. These calculations demonstrate that modulation of recognition in these systems is derived from a complex push–pull type mechanism.

The communication of stimuli arising from molecular recognition events is of fundamental importance in biological systems[1,2] and synthetic sensors/devices.[3] Conversely, the modification of molecular recognition over extended distances is central to the regulation of biological processes and the creation of molecular devices.

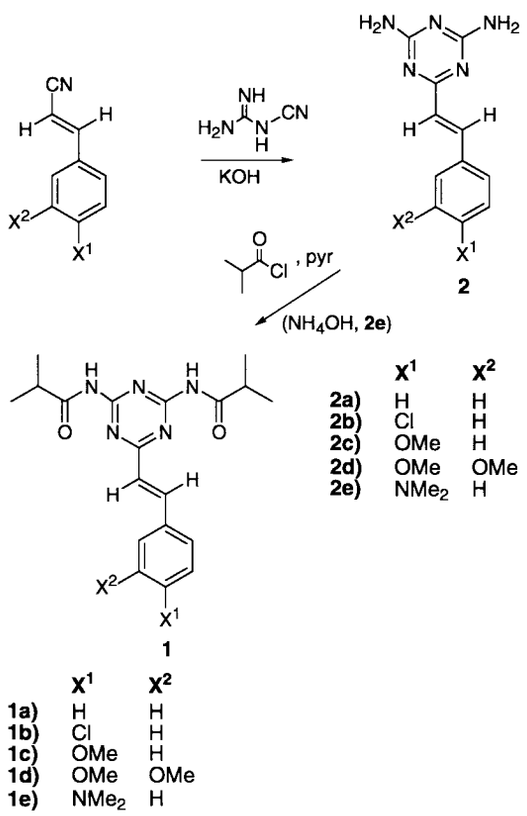
To gain a better understanding of these recognition events and their concomitant activities, we have designed a family of chemosensors for flavin[4] featuring extended conjugation. In these acyldiaminotriazine-based receptors[5] variation of spatially remote substituents modulates the electronic characteristics of the hydrogen bonding surface (11 Å away), and hence the efficiency of the recognition process. Concomitantly, the recognition event modulates the electronic properties of the distal substituents. As a result, these systems serve as both prototypes and subtle probes for the behavior of molecular wires, providing insight into their modes of action.[6]

Results and discussion

Receptors **1a**–**d** were readily prepared starting from the corresponding nitriles through reaction with dicyandiamide and potassium hydroxide to provide the diaminotriazines **2** (Scheme 1).[5a] Acylation of the amino groups with isobutyryl chloride then provided receptors **1a-d**. In the case of receptor **1e**, this procedure resulted in the formation of the triply-acylated product, which was converted to the diacyl receptor using ammonia (Scheme 1).

In our studies, receptor **1** dimerization[7] was quantified using ^{1}H NMR titration experiments (Fig. 1) in $CDCl_3$.[8] When the resulting titration curves were fitted to dimerization isotherms, the dimerization constants (K_{dim}) were obtained (Table 1).[9] Next, receptor **1**–flavin **3** complexation (Fig. 2) was quantified *via* ^{1}H NMR titration studies. The association constants (K_a) were obtained by fitting of the titration curves to 1 : 1 binding isotherms, with explicit compensation made for receptor **1** dimerization (Table 1).[10]

From Table 1, it is apparent that the observed strength of receptor **1**–flavin **3** recognition is directly related to the nature of the substituents present, with association constants ranging between 37–82 M^{-1}.[11] These changes are the result of alterations in the electrostatic potential/polarizability of the receptor's hydrogen bonding surface.



Scheme 1

The hydrogen bonding surface of receptor **1** is composed of two elements: the hydrogen bond donating amides and the hydrogen bond accepting triazine-N(3) position. Receptors featuring electron donating substituents enhance the negative potential/basicity of the triazine ring nitrogen, as shown by increased maximal shift values (δ_{max}) for the flavin H(3). Concurrently, the positive potential/acidity of the amide protons is diminished. The overall trend observed is a consequence of the enhanced strength of the single hydrogen bond acceptor being overcome by the diminished strength of the two hydrogen bond donors. A plot of association energies ($-\Delta G_a$) *versus* $\Sigma\sigma_{m,p}$ reveals a roughly linear relationship between the free energies of association and the donor/acceptor abilities of the substituents present (Fig. 3).[12] The slope of this line is approximately 1/3 that of our previously reported system, in which the phenyl ring was attached directly to the triazine residue.[5a]

† Titration graphs (dimerization and association) for receptors **1a**–**e**, NMR, IR and UV-Vis spectra of receptors **1a**–**e**, fluorescence spectra of receptors **1b** and **1e** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/a9/a909634e/

DOI: 10.1039/a909634e

Table 1 Binding constants, energetics and limiting shift values for receptor **1**–flavin **3** complexes

Host	K_{dim}/M^{-1} [a,b,c]	ΔG_{dim}/kcal mol^{-1} [c]	K_a/M^{-1} [a,c,d]	ΔG_a/kcal mol^{-1} [c]	δ_{max} (H(3))/ppm [a,d,e]
1a	70 ± 1	−2.50 ± 0.01	58 ± 2	−2.38 ± 0.02	13.2 ± 0.08
1b	71 ± 2	−2.50 ± 0.01	82 ± 3	−2.59 ± 0.02	12.8 ± 0.08
1c	69 ± 1	−2.49 ± 0.01	73 ± 1	−2.53 ± 0.02	12.6 ± 0.05
1d	54 ± 1	−2.34 ± 0.01	63 ± 2	−2.43 ± 0.02	13.3 ± 0.11
1e	78 ± 1	−2.56 ± 0.01	37 ± 1	−2.12 ± 0.02	14.0 ± 0.12

[a] $CDCl_3$, 23 °C. [b] Amide peak followed. [c] Errors represent the standard error of the data fit to the calculated isotherm. [d] H(3)-peak followed. [e] ppm downfield from TMS.

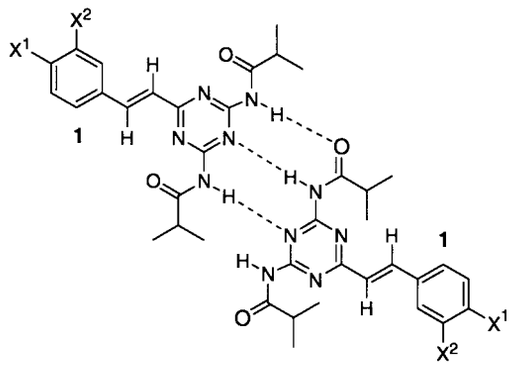


Fig. 1 Dimerization of receptor **1**.

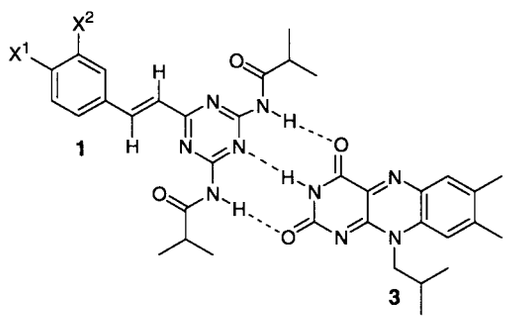


Fig. 2 Receptor **1**–flavin **3** complex.

Thus far, we have demonstrated that electronic variations within the receptor system alter the strength of the resultant host–guest complex. To study the converse effect of binding events on the electronics of the receptor system, we explored the application of computational methodology. In previous research,[13] *ab initio* techniques that do not take into account electron correlation interactions have been shown to lack the precision required to accurately describe electronic properties related to hydrogen bond formation. In contrast, hybrid density functional theory (DFT) methods,[14] for example B3LYP, require a fraction of the computational time of post Hartree–Fock calculations, while better describing the atomic characteristics. In recent studies, we have shown that wavefunctions generated through B3LYP methods accurately replicate key experimental parameters for systems featuring hydrogen bonding.[15]

To establish the validity of the B3LYP wavefunction to our host–guest systems, we calculated the enthalpy of interaction for hydrogen bond complex formation for the **1b·3** and **1e·3** complexes. B3LYP calculations accurately predict enhanced recognition by receptor **1e**, with the calculated difference of 0.83 kcal mol^{-1} obtained for the relative stability of these complexes agreeing quite well with the experimental value of 0.47 kcal mol^{-1}.[16]

The interplay of electronics and recognition at the hydrogen bonding surfaces of receptors **1b** and **1e** was examined through the use of atomic charges. When individual components of the hydrogen bonding surfaces of receptors **1b** and **1e** were studied,

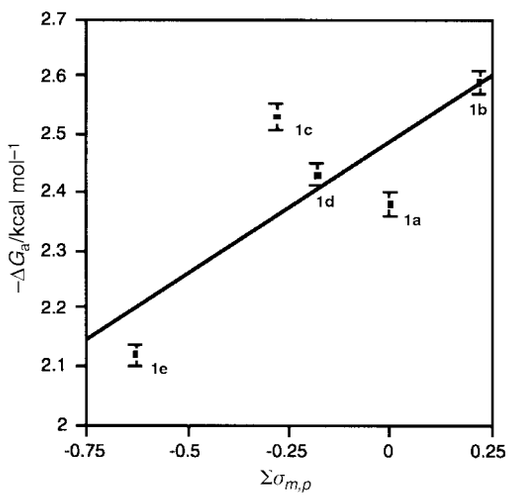


Fig. 3 Plot of association energies versus $\Sigma\sigma_{m,p}$ for receptor **1**–flavin **3** complexes.

we observed that the hydrogen bond accepting triazine-N(3) position of the dimethylamino-substituted receptor **1e** was more negative than that of **1b**. The changes in atomic charge upon binding are, however, the same. The enhanced basicity of **1e** (as experimentally established by the greater limiting shift value for the flavin imide for the receptor **1e**–flavin **3** complex) is thus an electrostatic effect. In contrast, the atomic charges for H(16) and H(17) at the hydrogen bonding surface are identical for receptors **1b** and **1e**. In the receptor **1b**–flavin **3** complex, however, there is a greater positive change in the potential of these protons upon binding. This indicates that polarizability dominates this aspect of the recognition process.

Further insight into electronic effects arising from host–guest interactions in the receptor **1**–flavin **3** systems can be obtained by comparing the atomic charges of the triazine receptor before and after complex formation (Table 2). For the chloro-receptor **1b**, dramatic increases in electron density are observed in the distal aromatic ring upon binding to **3**. These increases arise from the electron-releasing effect of hydrogen bonding to the amide H(16/17) protons. In strong contrast, there is little change observed in the atomic charges of **1e** upon bonding to flavin **3**. For this system, the dimethylamino substituent in **1e** behaves as an "electron buffer", maintaining essentially equal atomic charges throughout the structure. This arises from the electron-releasing nature of the dimethylamino substituent, providing electrons "on demand" to the electron-deficient triazine nucleus.

Further understanding of the "push–pull" modulation observed with receptor **1e** can be obtained from surface electrostatic potentials (Fig. 4). The changes observed in the surface potentials of the receptors **1b** and **1e** upon binding are almost identical. This arises from the greater sensitivity of the surface potential to the more diffuse π electron density. As a result, the σ-withdrawing chlorine atom has a lesser effect on the surface electrostatic potential, while the π-donating amino group has a greater effect.

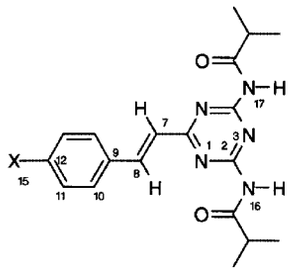


Table 2 Atomic charges on triazine receptor (selected atoms)

Atomic center	**1b**	**1b**·**3**	Δq	**1e**	**1e**·**3**	Δq
C(7)	−0.37	−0.35	0.02	−0.38	−0.37	0.01
C(8)	0.75	0.73	−0.02	0.73	0.71	−0.02
C(9)	0.16	0.24	0.08	0.14	0.14	0.00
C(10/14)[a]	−0.22	−0.28	−0.06	−0.19	−0.18	0.01
C(11/13)[a]	−0.12	−0.28	−0.17	−0.28	−0.28	0.00
C(12)	0.06	0.00	−0.06	0.24	0.21	−0.03
H(16/17)[a]	0.39	0.46	0.07	0.39	0.44	0.05
N(3)	−0.90	−0.93	−0.03	−0.92	−0.95	−0.03
N(15) or Cl(15)	−0.11	−0.10	0.01	−0.12	−0.09	0.03

[a] For these atoms, the value reported is the average of the two calculated.

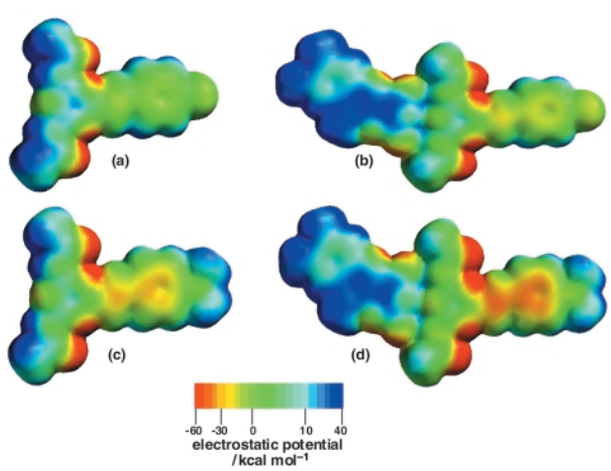


Fig. 4 Electrostatic potential maps projected over the electron density surfaces for (a) receptor **1b** only; (b) receptor **1b**–flavin **3** complex; (c) receptor **1e** only; (d) receptor **1e**–flavin **3** complex.

In conclusion, we have developed a family of model chemosensors for flavins. These receptors demonstrated significant modulation of recognition arising from functionality over 11 Å distance from the hydrogen bonding surface. This electronic communication was explored using the B3LYP hybrid density function, allowing the interdependence of electronic and recognition effects to be explored. Future research will build upon these fundamental insights, and will be reported in due course.

Experimental

General methods

Chemicals were purchased from Aldrich and Fisher and used as received. Thin layer chromatography (TLC) and column chromatography were carried out on glass pre-coated TLC plates with silica gel 60 and silica gel 60 (230–400 mesh), respectively. All reactions were performed under an argon atmosphere. Microanalyses were performed by the University of Massachusetts (Amherst) Microanalysis Service. Infrared spectra were measured on a Perkin-Elmer Model 783 Spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker/IBM AC200 (200 MHz) spectrometer. All spectra were recorded using either $CDCl_3$ or DMSO-d_6 as solvent.

Synthesis of diaminotriazines 2a–e

To a solution of potassium hydroxide (337 mg, 6 mmol) in pentan-1-ol (20 mL), dicyandiamide (3.03 g, 36 mmol) and the starting nitrile (30 mmol) were added. This was then stirred for 24 h at 140 °C. After cooling, the resulting solid was suspended in boiling water, filtered and dried. Diaminotriazines **2a**–**e** thus obtained exhibited satisfactory NMR spectra in DMSO-d_6 and were therefore used without further purification. The yields obtained were as follows: **2a** (46%); **2b** (32%); **2c** (31%); **2d** (57%); **2e** (63%).

Synthesis of acylated diaminotriazines 1a–d

To a suspension of the diaminotriazine (4 mmol) in pyridine (10 mL), isobutyryl chloride (2.10 mL, 20 mmol) was added at room temperature. This was then stirred at 75 °C for 24 h before removal of the pyridine (under a stream of air). The resulting solid was dissolved in CH_2Cl_2 (20 mL), washed with a saturated solution of $NaHCO_3$ (20 mL) followed by H_2O (20 mL), dried (Na_2SO_4) and the CH_2Cl_2 evaporated under reduced pressure. The resulting solid was purified by column chromatography on silica gel with 5:1 hexanes–ethyl acetate and recrystallized from MeOH. **1a** (13%): mp 184–184.5 °C; IR (KBr) 3260, 3180, 2980, 1740, 1685, 1640, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (12H, d, J = 6.9 Hz), 3.34 (2H, septet, J = 6.9 Hz), 7.04 (1H, d, J = 15.9 Hz), 7.40–7.45 (3H, m), 7.61–7.66 (2H, m), 8.13 (1H, d, J = 15.9 Hz), 9.15 (2H, br s). Anal. Calcd. for $C_{19}H_{23}N_5O_2$: C, 64.57; H, 6.56; N, 19.82. Found: C, 64.59; H, 6.47; N, 19.96%. **1b** (27%): mp 203.5–204 °C; IR (KBr) 3250, 3180, 2970, 1745, 1670, 1640, 990, 825 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (12H, d, J = 6.9 Hz), 3.33 (2H, septet, J = 6.9 Hz), 7.01 (1H, d, J = 15.9 Hz), 7.39 (2H, d, J = 8.7 Hz), 7.56 (2H, d, J = 8.7 Hz), 8.08 (1H, d, J = 15.9 Hz), 9.28 (2H, br s). Anal. Calcd. for $C_{19}H_{22}N_5O_2Cl$: C, 58.84; H, 5.72; N, 18.06. Found: C, 58.80; H, 5.63; N, 18.01%. **1c** (14%): mp 212–213 °C; IR (KBr) 3250, 3180, 2970, 2870, 1735, 1675, 985 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (12H, d, J = 6.9 Hz), 3.29 (2H, septet, J = 6.9 Hz), 3.86 (3H, s), 6.89 (1H, d, J = 15.9 Hz), 6.94 (2H, d, J = 8.7 Hz), 7.58 (2H, d, J = 8.7 Hz), 8.09 (1H, d, J = 15.9 Hz), 8.88 (2H, br s). Anal. Calcd. for $C_{20}H_{25}N_5O_3$: C, 62.65; H, 6.57; N, 18.26. Found: C, 62.70; H, 6.69; N, 18.37%. **1d** (24%): mp 219.5–220 °C; IR (KBr) 3250, 3170, 2970, 1735, 1685, 1635, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (12H, d, J = 6.5 Hz), 3.25 (2H, septet, J = 6.5 Hz), 3.93 (3H, s), 3.94 (3H, s), 6.91 (1H, d, J = 15.5 Hz), 6.92 (1H, s), 7.17–7.20 (2H, m), 8.08 (1H, d, J = 15.5 Hz), 8.91 (2H, br s). Anal. Calcd. for $C_{21}H_{27}N_5O_4$: C, 61.00; H, 6.58; N, 16.94. Found: C, 60.78; H, 6.44; N, 16.86%.

Synthesis of acylated diaminotriazine 1e

To a suspension of diaminotriazine **2e** (235 mg, 0.9 mmol) in pyridine (1 mL), isobutyryl chloride (0.48 mL, 4.6 mmol) was added at room temperature. The reaction mixture was then stirred at 75 °C for 24 h before removal of the pyridine (under a stream of air). The resulting solid was dissolved in CH_2Cl_2 (10 mL), washed with a saturated solution of $NaHCO_3$ (10 mL) followed by H_2O (10 mL), dried (Na_2SO_4) and the CH_2Cl_2 evaporated under reduced pressure. The crude triply-acylated product thus obtained was then re-dissolved in CH_2Cl_2, 5 drops of concentrated NH_4OH added and stirred at room temperature for 6 h. The reaction mixture was then washed with a saturated solution of $NaHCO_3$ (10 mL) followed by H_2O (10 mL), dried (Na_2SO_4) and the CH_2Cl_2 evaporated under reduced pressure. The resulting solid was purified by column chromatography on silica gel with 5:1 hexanes–ethyl acetate and recrystallized from MeOH. **1e** (14%): mp 238–239 °C; IR (KBr) 3240, 2965, 1730, 1675, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29

(12H, d, J = 6.9 Hz), 3.05 (6H, s), 3.22 (2H, septet, J = 6.9 Hz), 6.70 (2H, d, J = 9.0 Hz), 6.78 (1H, d, J = 15.5 Hz), 7.52 (2H, d, J = 9.0 Hz), 8.07 (1H, d, J = 15.9 Hz), 8.39 (2H, br s). Anal. Calcd. for $C_{21}H_{28}N_6O_2$: C, 63.62; H, 7.12; N, 21.20. Found: C, 63.59; H, 7.22; N, 21.00%.

^{1}H NMR titrations

NMR complexation studies were performed in $CDCl_3$, a non-competitive solvent, to allow the observation of specific hydrogen bonds. Association constants were determined through non-linear least-squares curve fitting.

Dimerization of receptor 1

Dimerization constants (K_{dim}) were obtained *via* NMR concentration studies using previously described protocols. In the case of receptors **1b** and **1d**, a 0.1 M receptor solution was used (initial concentration = 0.00196 M; final concentration = 0.075 M). For receptors **1a** and **1c**, a 0.05 M receptor solution was used (initial concentration = 0.00098 M; final concentration = 0.0375 M). Finally, for receptor **1e**, a 0.0275 M receptor solution was used (initial concentration = 0.00054 M; final concentration = 0.021 M).

Receptor 1–flavin 3 binding

Association constants (K_a) were obtained *via* NMR studies using previously described protocols. In the case of receptors **1a**–**d**, a 0.005 M flavin **3** host solution and 0.05 M receptor solution were used (final concentrations: $[Guest]_{total}$ = 0.025 M; $[Host]_{total}$ = 0.0025 M). For receptor **1e**, a 0.005 M flavin **3** host solution and 0.0275 M receptor solution were used instead, due to solubility problems (final concentrations: $[Guest]_{total}$ = 0.0157 M; $[Host]_{total}$ = 0.0021 M).

Computer modeling studies

The calculations were run on a 100 MHz R4000 Iris Silicon Graphics using Gaussian 94.[17] All geometries were initially optimized at the HF/3-21G* level, followed by a B3LYP/3-21G* single point calculation. The electrostatic potential energies mapped onto the electronic density surfaces were generated by running the single point calculation mentioned using Spartan 4.1[18] as a graphical interface for Gaussian 94.

Acknowledgements

This research was supported by the National Science Foundation (CHE 9905492 to V. M. R.), V. M. R. acknowledges the Petroleum Research Fund of the ACS, the Alfred P. Sloan Foundation, Research Corporation, and the Camille and Henry Dreyfus Foundation.

References

1 (*a*) A. Fersht, *Enzyme Structure and Mechanism*, 2nd edn., Freeman, New York, 1985; (*b*) G. Jeffrey and W. Saenger, *Hydrogen Bonding in Biological Structures*, Springer Verlag, Berlin, 1991.

2 For recent biomimetic model systems see: (*a*) E. A. Gallo and S. H. Gellman, *J. Am. Chem. Soc.*, 1993, **115**, 9774; (*b*) J. S. Nowick, J. S. Chen and G. Noronha, *J. Am. Chem. Soc.*, 1993, **115**, 7636; (*c*) S. C. Zimmerman and T. J. Murray, *Tetrahedron Lett.*, 1994, **35**, 4077; (*d*) A. D. Hamilton, N. Pant and A. Muehldorf, *Pure Appl. Chem.*, 1988, **60**, 533; (*e*) A. Aggeli, M. Bell, N. Boden, J. N. Keen, P. F. Knowles, T. C. B. McLeish, M. Pitkeathly and S. E. Radford, *Nature*, 1997, **386**, 259.

3 For overviews of sensors/devices see: (*a*) J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 89; (*b*) D. Goldhaber-Gordon, M. S. Montemerlo, J. C. Love, G. J. Opiteck and J. C. Ellenbogen, *Proc. IEEE*, 1997, **85**, 521; (*c*) A. Aviram, *J. Am. Chem. Soc.*, 1988, **110**, 5687.

4 For further examples of flavin binding receptors see: (*a*) E. Breinlinger and V. M. Rotello, *J. Am. Chem. Soc.*, 1997, **119**, 1165; (*b*) E. Breinlinger, A. Niemz and V. M. Rotello, *J. Am. Chem. Soc.*, 1995, **117**, 5379; (*c*) N. Tamura, K. Mitsui, T. Nabeshima and Y. Yano, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2229; (*d*) S. Shinkai, G.-X. He, T. Matsuda, A. D. Hamilton and H. S. Rosenzweig, *Tetrahedron Lett.*, 1989, **30**, 5895.

5 For examples of triazine-based receptors see: (*a*) R. Deans, G. Cooke and V. M. Rotello, *J. Org. Chem.*, 1997, **62**, 836; (*b*) R. Deans and V. M. Rotello, *J. Org. Chem.*, 1997, **62**, 4529; (*c*) F. H. Beijer, H. Kooijman, A. L. Spek, R. P. Sijbesma and E. W. Meijer, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 75; (*d*) Y. Honda, K. Kurihara and T. Kunitake, *Chem. Lett.*, 1991, 681; (*e*) I. Willner, J. Rosengaus and S. Biali, *Tetrahedron Lett.*, 1992, **33**, 3805.

6 For examples of molecular wires see: (*a*) Q. Zhou and T. M. Swager, *J. Am. Chem. Soc.*, 1995, **117**, 12593; (*b*) L. A. Bumm, J. J. Arnold, M. T. Cygan, T. D. Dunbar, T. P. Burgin, L. Jones II, D. L. Allara, J. M. Tour and P. S. Weiss, *Science*, 1996, **271**, 1705; (*c*) A. P. H. Schenning, R. E. Martin, M. Ito, F. Diederich, C. Boudon, J.-P. Gisselbrecht and M. Gross, *Chem. Commun.*, 1998, 1013; (*d*) I. Jestin, P. Frere, P. Blanchard and J. Roncali, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 942; (*e*) M. Magoga and C. Joachim, *Phys. Rev. B*, 1997, **56**, 4722; (*f*) L. M. Tolbert, X. Zhao, Y. Ding and L. A. Bottomley, *J. Am. Chem. Soc.*, 1995, **117**, 12891; (*g*) T. M. Swager, *Acc. Chem. Res.*, 1998, **31**, 201.

7 F. H. Beijer, R. P. Sijbesma, J. A. J. M. Vekemans, E. W. Meijer, H. Kooijman and A. L. Spek, *J. Org. Chem.*, 1996, **61**, 6371.

8 K. A. Connors, *Binding Constants. The Measurement of Molecular Complex Stability*, Wiley and Sons, New York, 1987.

9 To provide K_{dim}, the data were fitted to the equation:

$$\delta_{obs} = \delta_m + \left(\frac{\delta_d - \delta_m}{[H]}\right)\left(\left([H] + \frac{1}{4K_{dim}}\right) - \left(\left([H] + \frac{1}{4K_{dim}}\right)^2 - [H]^2\right)^{1/2}\right)$$

where the experimentally determined parameters are as follows: [H], the total concentration of analyte and δ_{obs}, the observed shift. Parameters obtained through fitting are δ_m, the shift of the monomer, δ_d, the shift of the dimer and K_{dim}, the dimerization constant.

10 To provide K_a and δ_{HG}, the data were fitted to the equation:

$$[G]_t = [H]_t\left(\frac{\delta_{obs} - \delta_H}{\delta_{HG} - \delta_H}\right)^3 + \left(\frac{2K_{dim}}{K_a^2} - [G]_t - 2[H]_t - \frac{1}{K_a}\right)\left(\frac{\delta_{obs} - \delta_H}{\delta_{HG} - \delta_H}\right)^2 + \left(2[G]_t + [H]_t + \frac{1}{K_a}\right)\left(\frac{\delta_{obs} - \delta_H}{\delta_{HG} - \delta_H}\right)$$

where the experimentally determined parameters are as follows: $[G]_t$ and $[H]_t$, the total guest and host concentrations, respectively, δ_{obs} the observed shift, δ_H, the shift of the host in the absence of guest and K_{dim}, the guest dimerization constant. Parameters determined through fitting are K_a, the host–guest association constant and δ_{HG}, the chemical shift of the host–guest complex.

11 For a purely electrostatic approach to predicting hydrogen bonding see: C. S. Wilcox, E. Kim, D. Romano, L. H. Kuo, A. L. Burt and D. P. Curran, *Tetrahedron*, 1995, **51**, 621.

12 O. Exner, *Correlation Analysis of Chemical Data*, Plenum, New York, 1988.

13 For discussions and considerations on molecular calculations related to hydrogen bonds see, for example: (*a*) M. S. Gordon and J. H. Jensen, *Acc. Chem. Res.*, 1996, **29**, 536; (*b*) D. A. Smith, *Modeling the Hydrogen Bond*, *ACS Symposium Series*, ACS, Washington D.C., 1994; (*c*) S. Scheiner, *Hydrogen Bonding: A Theoretical Perspective*, Oxford University Press, New York, 1997; (*d*) K. Kim and R. A. Friesner, *J. Am. Chem. Soc.*, 1997, **119**, 12952.

14 (*a*) W. Khon and L. J. Sham, *Phys. Rev.*, 1965, **140**, A1133; (*b*) R. G. Parr and W. Yang, *Density Functional Theory of Atoms and Molecules*, Oxford University Press, Oxford, 1989; (*c*) J. P. Perdew and W. Yang, *Phys. Rev.*, 1992, **B 45**, 1324; (*d*) J. K. Labanowsky, *Density Functional Theory Methods in Chemistry*, Springer-Verlag, New York, 1991.

15 A. Niemz and V. M. Rotello, *J. Am. Chem. Soc.*, 1997, **119**, 6833.

16 Although our calculations provide ΔH and the experimental results measure ΔG, we have assumed that $\Delta S_{(1b + 3 \rightarrow 1b \cdot 3)} = \Delta S_{(1e + 3 \rightarrow 1e \cdot 3)}$, since both complexes under study are quite similar with only minor structural differences. The small discrepancy between the calculated

and experimental energetics can be attributed to lack of solvent correction in the computational model.
17 Gaussian 94, Revision E.3, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1995.
18 Spartan Version 4.1.2, Wavefunc Inc., 18401 Von Karman Ave., #370, Irvine, CA 92715.