Model Systems for Flavoenzyme Activity. Regulation of Flavin Recognition via Modulation of Receptor Hydrogen-Bond Donor−Acceptor Properties

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We have synthesized a new family of receptors for flavins based on 6-aryl-2,4-(acyldiamino)-*s*-triazines. In these synthetic hosts, systematic variation of the spatially remote substituents on the 6-aryl ring alters the hydrogen-bond-donating abilities of the amide functionality and the hydrogen-bond-accepting properties of the triazine N(3). This variation results in a strong modulation of the efficiency of flavin binding, with association constants for the receptor flavin complexes ranging over an 8-fold range.

An important feature of biomolecular catalysts is their ability to modulate the energetics of the binding event.[1] Modeling of this ability provides us with insight into the origin and nature of intermolecular forces. Additionally, improving our control over the recognition event allows us to more effectively model biological systems where recognition and function are directly correlated.[2,3] Finally, our ability to modulate the recognition process allows us to control the mechanical properties of materials and tune the reactivity of catalysts.

In previous research,[2,4] we have established the recognition of flavins by diacyldiaminopyridines through hydrogen bonding.[5] While binding energies in these systems could be regulated to a certain extent through choice of acyl group,[2] the individual steric and electronic causes for this modulation could not be individually determined.

To provide enhanced versatility in the design of recognition-based sensors and devices, and gain a better understanding of the factors that govern hydrogen-bonding processes, we have designed a system where the effects of hydrogen-bond-donor and -acceptor capabilities are decoupled from steric considerations. These receptors are based on the diaminotriazine nucleus[6] and utilize three-point hydrogen bonding between receptors **1** and flavin **3** (Figure 1).[7] In these receptors, variation of the spatially distant aryl substituent modulates the electronic properties of the triazine nucleus. Since the sterics of the binding surface of these receptors are identical, the electronic effects of the substituents can be determined independently.

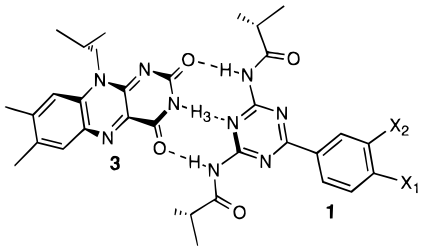

Figure 1. Receptor **1**−flavin **3** complex, as predicted by the AMBER forcefield.[8]

Results

Receptors **1a**−**h** were synthesized from the corresponding nitriles via reaction with dicyandiamide and potassium hydroxide[9] to provide the sparingly soluble (in $CDCl_3$) diaminotriazines **2a**−**h** (Scheme 1). Acylation with isobutyryl chloride then provided receptors **1a**−**h**, which were readily soluble in $CDCl_3$.

Dimerization of Receptors 1. The ^{1}H chemical shifts of the amide protons of receptors **1a**−**h** in $CDCl_3$ show a strong concentration dependence. ^{1}H NMR titrations of these receptors show a steady downfield shift of the amide protons, indicative of formation of a hydrogen-bound complex (Figure 2). The curves obtained from these titrations were fitted to dimerization isotherms to obtain dimerization constants (K_{dim}) (Table 1).[10] The energies of dimerization of these systems shows a general dependence on the electronic properties of the substituents, with electron-withdrawing groups diminishing recognition and electron-releasing groups enhancing binding. Due to the complexity of the system, a direct linear

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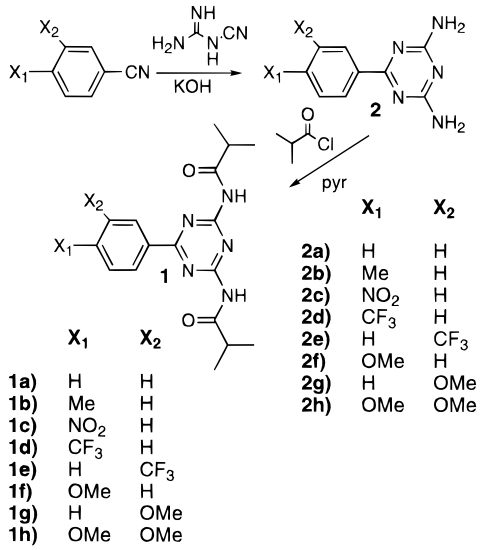
Scheme 1



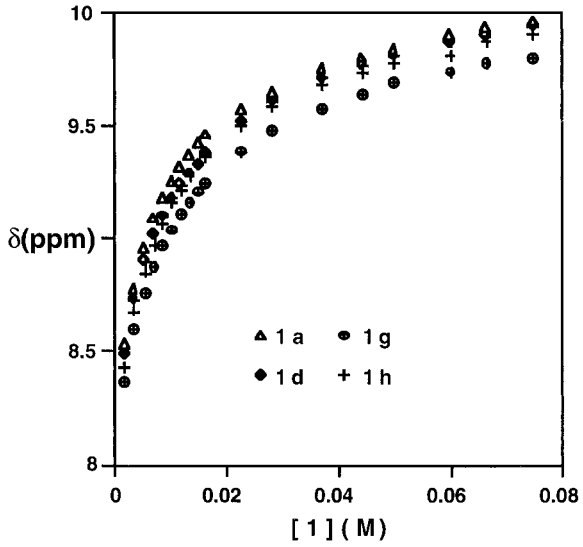


Figure 2. Plot of the chemical shifts of the amide protons of **1a**, **1d**, **1g**, and **1h** as a function of concentration.

Table 1. Binding Constants, Energetics, and Limiting Shift Values for Receptor 1−Flavin 3 Complexes

host	K_{dim}[a−c] (M^{-1})	ΔG_{dim}[c] (kcal/mol)	K_a[a,c,d] (M^{-1})	ΔG_a[c] (kcal/mol)	δ_{max}[a,d,e] (H(3))(ppm)
1a	95 ± 3	−2.68 ± 0.02	24 ± 4	−1.87 ± 0.09	16.4 ± 1.0
1b	75 ± 2	−2.54 ± 0.02	53 ± 10	−2.34 ± 0.03	12.2 ± 0.04
1c	41 ± 2	−2.18 ± 0.05	97 ± 4	−2.69 ± 0.02	13.3 ± 0.1
1d	63 ± 2	−2.44 ± 0.02	63 ± 5	−2.44 ± 0.04	12.9 ± 0.2
1e	50 ± 3	−2.27 ± 0.03	58 ± 3	−2.36 ± 0.03	11.9 ± 0.2
1f	88 ± 2	−2.63 ± 0.02	44 ± 3	−2.23 ± 0.04	13.1 ± 0.3
1g	60 ± 2	−2.41 ± 0.02	20 ± 2	−1.76 ± 0.06	14.8 ± 0.6
1h	80 ± 3	−2.58 ± 0.02	12 ± 4	−1.46 ± 0.16	19.8 ± 2.0

[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.

relationship between free energy and electron donor/acceptor strengths would not be expected. A plot of dimerization energies ($-\Delta G_{dim}$) versus $\Sigma\sigma_{m,p}$ (Figure 3)[11] shows a strong correlation between the free energy of dimerization and substituent donor/acceptor values, with receptors **1a** and **1d** as the only significant outlying points.

Recognition of Flavin 3 by Receptors 1. Addition of receptors **1a**−**h** to solutions of flavin **3** in $CDCl_3$ resulted in a smooth downfield shift in the resonance of H(3) of flavin **3** (Figure 4). The resulting curve was fitted to a 1:1 binding isotherm, with explicit compensation made for the reduction in free receptor **1** due to dimerization of **1** (Table 1).[12] From this fit, both the association constants and limiting shift values for the receptors **1a**−**h**−flavin **3** complexes were determined (Table 1). These association constants ranged from 12 to 97 M^{-1}, in contrast to a recent study using alkyl(diacylamino)-triazines that had association constants of approximately 6 M^{-1}.[13] It was proposed that these low observed binding constants were due to the acyl groups of the triazine

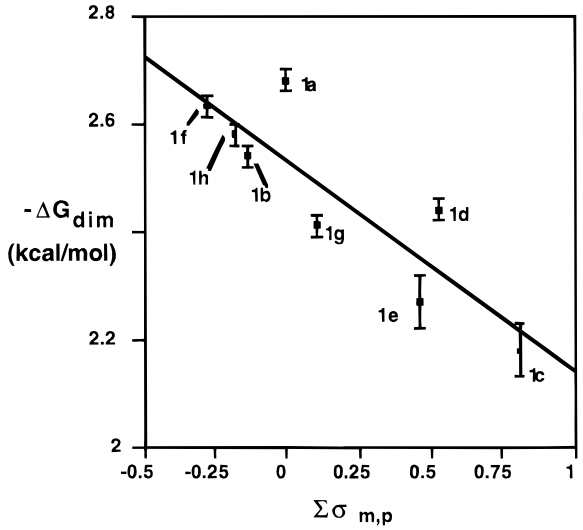


Figure 3. Plot of dimerization energy versus $\Sigma\sigma_{m,p}$.

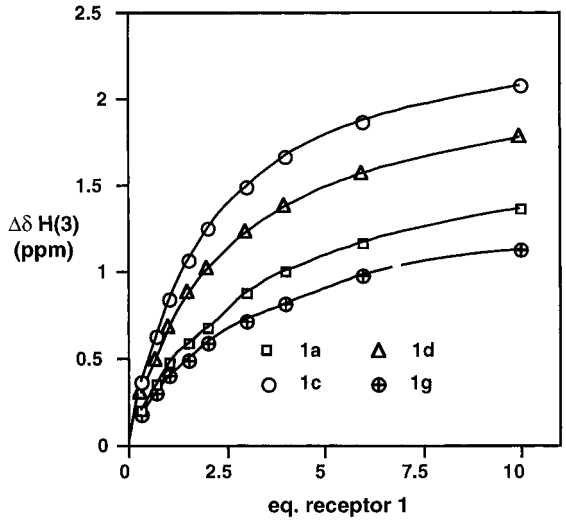


Figure 4. Chemical shift changes of flavin **3** H(3) upon addition of selected receptors **1**.

(10) Dimerization constants (K_d) for receptors **1a**−**h** were obtained via NMR titration, with the shift of the amide proton followed as a function of concentration. Conners, K. *Binding Constants*; Wiley and Sons: New York, 1987. To provide K_d, the data were fitted to the equation

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

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_d, the dimerization constant.

(11) Chapman, N.; Shorter, J. *Correlation Analysis in Chemistry*; Plenum: New York, 1978.

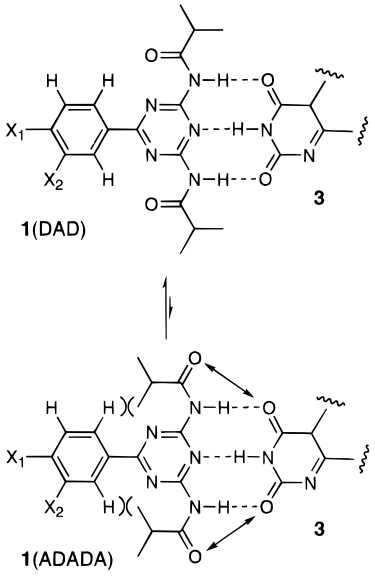


Figure 5. Representation of the two predicted conformations adopted by the acyl groups in the triazine **1**−flavin **3** complex.

adopting a cis configuration (ADADA), creating additional repulsive interactions during the binding event. The enhanced binding observed in our system is most likely caused by unfavorable steric interactions between the aryl group and the side chains of the acyl groups in the cis configuration, resulting in the preferred DAD configuration required for complexation (Figure 5).

As shown in Table 1, variation of the substituents on the aromatic ring of receptors **1a**−**h** markedly influences the efficiency of flavin **3** recognition. Since receptors **1a**−**h** present sterically identical hydrogen bonding surfaces for the recognition of flavin **3**, all changes in binding energies in receptor−flavin complexes can be directly attributed to changes in the electrostatic potentials and polarizability of the receptor hydrogen bonding surface. Consequently, the efficiencies of binding in the receptor **1**−flavin **3** complexes are determined directly by the nature of the substituents on the phenyl ring: electron-withdrawing substituents enhance binding and electron-donating groups diminish binding efficiency. The correlation between recognition and the electron-donating/-withdrawing properties of the substituents is not direct: a plot of binding energy ($-\Delta G_a$) versus $\Sigma\sigma_{m,p}$ (Figure 6) indicates a generally linear correlation for the bulk of the systems studied, with strong deviations

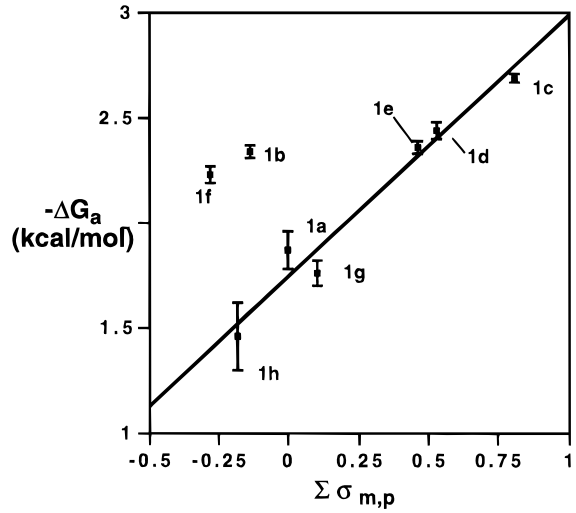


Figure 6. Plot of the binding energies vs $\Sigma\sigma_{m,p}$ for the complexes of receptor **1**−flavin **3**.

observed for **1f** and **1b**, the two receptors with electron-releasing substituents *para* to the triazine ring.[14]

The observed relationship between binding efficiency and electron-donor/-acceptor properties of the aromatic substituents can be attributed to concomitant changes in the electrostatic potential and polarizabilites of the hydrogen-bonding surface.[15] The hydrogen-bonding surface of receptors **1** can be divided into two components: the hydrogen-bond-donating amides and the hydrogen-bond-accepting N(3) position of the triazine. Changing the electron density of the triazine nucleus affects both of these recognition elements. As the electron-withdrawing abilities of the substituents on the aromatic ring increase, electron density in the triazine ring of receptors **1** decreases, increasing the positive electrostatic potential of the amide protons. This increases the hydrogen-bond-donating ability of the host, enhancing recognition.[16] Concurrently, decreased electron density enhances the negative potential and, hence, basicity of the triazine ring nitrogen. This is shown in the decrease in the maximal shift values (δ_{max}) for the flavin **3** H(3) observed with receptors featuring electron-withdrawing substituents. While this decrease in basicity should result in energetically less favorable hydrogen bonding,[17] the diminished strength of the single hydrogen bond acceptor is overcome by the enhancement of the two other hydrogen-bond donors, providing the overall trend observed.

In summary, we have developed a family of diaminotriazine-based receptors for flavin derivatives. These receptors modulate the recognition of flavin derivatives through variation of the electronic characteristics of the hydrogen bonding surface. These receptors show a direct correlation between the electronic properties of the receptor and the efficiency of recognition, allowing fine

(12) Explicit solution of the simultaneous equilibria for host−guest and guest−guest binding leads to a cubic expression. To provide K_a and δ_{HG}, the data were fitted to the equation

$$[G_t] = [H_t]\left(\frac{\delta_{obs}-\delta_H}{\delta_{HG}-\delta_H}\right)^3 + \left(\frac{2K_d}{K_a^2} - [G_t] - 2[H_t] - \frac{1}{K_a}\right)\left(\frac{\delta_{obs}-\delta_H}{\delta_{HG}-\delta_H}\right)^2 + \left(2[G_t] + [H_t] + \frac{1}{K_a}\right)\left(\frac{\delta_{obs}-\delta_H}{\delta_{HG}-\delta_H}\right)$$

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_d, 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.

(13) Beijer, F. H.; Sijbesma, R. P.; Vekemans, J. A. J. M.; Meijer, E. W.; Kooijiman, H.; Spek, A. L. *J. Org. Chem.* **1996**, *61*, 6371−6380. Also useful are: Park, T. K.; Feng, Q.; Rebek, J. *J. Am. Chem. Soc.* **1992**, *114*, 4529−4532. Willner, I; Rosengaus, J; Biali, S. *Tetrahedron Lett.* **1992**, 3805−3808. Simanek, E. E.; Wazeer, M. I. M.; Mathias, J. P.; Whitesides, G. M. *J. Org. Chem.* **1994**, *59*, 4904−4909.

(14) The large difference in binding constants between the *p*-methoxy receptor **1f** and the *m*-methoxy receptor **1g** indicate a substantial resonance contribution to the modulation of flavin recognition in these receptors. Due to the complex additivity of the various effects, further analysis was not performed.

(15) For a study on the effects of electron-donating and -accepting groups in urea and thiourea binding of sulfonic acids see: Wilcox, C.; Kim, E.; Romano, D.; Kuo, L.; Burt, A.; Curran, D. *Tetrahedron* **1995**, 621−634.

(16) Tsai, R. S.; Fan, W.; Tayar, N.; Carrupt, P. A.; Testa, B.; Kier, L. *J. Am. Chem. Soc.* **1993**, *115*, 9632−9639. Chen, C. T.; Siegel, J. *J. Am. Chem. Soc.* **1994**, *116*, 5959−5960.

(17) Neder, K.; Whitlock, H. *J. Am. Chem. Soc.* **1990**, *112*, 9412−9413.

tuning of the binding event. Applications of these receptors for the modulation of flavin reactivity are underway and will be reported in due course.

Experimental Section

General Methods. Chemicals were purchased from Acros Organics, Aldrich, Eastman Organic Chemicals, and EM Science and used as received. Thin layer chromatography (TLC) and column chromatography were carried out on glass precoated 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. Fourier transform infrared spectra (FTIR) were measured on a Perkin-Elmer Model 1600 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker/IBM AC200 (200MHz) spectrometer. All spectra were recorded using either $CDCl_3$ or DMSO-d_6 as solvent.

General Procedure for the Preparation of the Diaminotriazines 2a−h. To a solution of potassium hydroxide (168 mg, 3 mmol) in 1-pentanol (10 mL) were added dicyandiamide (1.51 g, 18 mmol) and the starting nitrile (15 mmol). The reaction mixture was then stirred for 24 h at 140 °C. After cooling, the resulting solid was suspended in boiling water, filtered, and dried. The diaminotriazines **2a**−**h** thus obtained were found to be sparingly soluble in $CDCl_3$ but showed satisfactory NMR spectra in DMSO-d_6 and were thus used without further purification. The yields obtained for the various diaminotriazines were as follows: **2a** (78%); **2b** (75%); **2c** (95%); **2d** (77%); **2e** (53%); **2f** (97%); **2g** (99%); **2h** (99%).

General Procedure for the Preparation of the Acylated Diaminotriazines 1a−h. To a suspension of the triazine (5 mmol) in pyridine (10 mL) was added dropwise isobutyryl chloride (2.62 mL, 25 mmol) at room temperature. The reaction mixture was then stirred at 100 °C for 24 h, after which time the pyridine was removed under a stream of air. The resulting solid was dissolved in CH_2Cl_2 (25 mL), washed with a saturated aqueous solution of $NaHCO_3$ (25 mL) and then H_2O (25 mL), and 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** (83%): mp 211.5−212.5 °C; FT-IR (KBr) 3256, 3185, 2964, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (12H, d, J = 6.9 Hz), 3.44 (2H, septet, J = 6.9 Hz), 7.47−7.64 (3H, m), 8.47 (2H, app dt, J = 6.9, 1.5 Hz), 9.33 (2H, br s). Anal. Calcd for $C_{17}H_{21}N_5O_2$: C, 62.35; H, 6.47; N, 21.4. Found: C, 62.31; H, 6.36; N, 21.09. **1b** (53%): mp 213−213.5 °C; FT-IR (KBr) 3246, 3185, 2969, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (12H, d, J = 6.9 Hz), 2.49 (3H, s), 3.44 (2H, septet, J = 6.9 Hz), 7.31 (2H, d, J = 7.9 Hz), 8.36 (2H, d, J = 8.3 Hz), 9.47 (2H, br s). Anal. Calcd for $C_{18}H_{23}N_5O_2$: C, 63.31; H, 6.79; N, 20.52. Found: C, 63.09; H, 6.72; N, 20.72. **1c** (71%): mp 238−239 °C; FT-IR (KBr) 3246, 3185, 2969, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (12H, d, J = 6.9 Hz), 3.23 (2H, septet, J = 6.9 Hz), 8.35 (2H, d, J = 8.7 Hz), 8.65 (2H, d, J = 8.7 Hz), 9.02 (2H, br s). Anal. Calcd for $C_{17}H_{20}N_6O_4$: C, 54.82; H, 5.42; N, 22.58. Found: C, 54.74; H, 5.83; N, 18.50.[18] **1d** (92%): mp 210.5−211.5 °C; FT-IR (KBr) 3256, 3185, 2969, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (12H, d, J = 6.9 Hz), 3.27 (2H, septet, J = 6.9 Hz), 7.77 (2H, d, J = 8.3 Hz), 8.57 (2H, d, J = 7.9 Hz), 8.81 (2H, br s). Anal. Calcd for $C_{18}H_{20}N_5O_2F_3$: C, 54.66; H, 5.1; N, 17.72. Found: C, 54.77; H, 5.14; N, 17.52. **1e** (33%): mp 235.5−236 °C; FT-IR (KBr) 3256, 3185, 2969, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (12H, d, J = 6.9 Hz), 3.36 (2H, septet, J = 6.9 Hz), 7.66 (1H, t, J = 7.9 Hz), 7.85 (1H, d, J = 7.2 Hz), 8.69 (1H, s), 8.71 (1H, d, J = 6.5 Hz), 9.31 (2H, br s). Anal. Calcd for $C_{18}H_{20}N_5O_2F_3$: C, 54.66; H, 5.1; N, 17.72. Found: C, 54.73; H, 5.24; N, 17.92. **1f** (26%): mp 224.5−225 °C; FT-IR (KBr) 3256, 3174, 2969, 2836, 1679 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (12H, d, J = 6.9 Hz), 3.41 (2H, septet, J = 6.9 Hz), 3.90 (3H, s), 6.99 (2H, d, J = 9.0 Hz), 8.42 (2H, d, J = 9.0 Hz), 9.24 (2H, br s). Anal. Calcd for $C_{18}H_{23}N_5O_3$: C, 60.47; H, 6.49; N, 19.6. Found: C, 60.25; H, 6.37; N, 19.60. **1g** (21%): mp 209−210 °C; FT-IR (KBr) 3246, 3174, 2826, 1679 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (12H, d, J = 6.9 Hz), 3.47 (2H, septet, J = 6.9 Hz), 3.91 (3H, s), 7.15 (1H, ddd, J = 7.9, 2.5, 1.1 Hz), 7.42 (1H, t, J = 7.9 Hz), 7.98 (1H, app dd, J = 2.5, 1.1 Hz), 8.09 (1H, app dt, J = 7.9, 1.1 Hz), 9.47 (2H, br s). Anal. Calcd for $C_{18}H_{23}N_5O_3$: C, 60.47; H, 6.49; N, 19.6. Found: C, 60.18; H, 6.38; N, 19.79. **1h** (82%): mp 232−233 °C; FT-IR (KBr) 3226, 2969, 2826, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (12H, d, J = 6.9 Hz), 3.41 (2H, septet, J = 6.9 Hz), 3.98 (3H, s), 4.01 (3H, s), 6.97 (1H, d, J = 8.7 Hz), 7.99 (1H, d, J = 1.8 Hz), 8.14 (1H, dd, J = 8.7, 1.8 Hz), 9.04 (2H, br s). Anal. Calcd for $C_{19}H_{25}N_5O_4$: C, 58.89; H, 6.51; N, 18.08. Found: C, 58.94; H, 6.45; N, 17.69.

^{1}H NMR Titrations. Dimerization of Receptor 1. Complexation studies were performed in $CDCl_3$, a noncompetitive solvent, to allow the observation of specific hydrogen bonds. The dimerization constants (K_d) were obtained by means of NMR concentration studies, carried out on the receptors **1a**−**h**. With the exception of receptors **1b**, **1e**, and **1f**, this involved addition of aliquots of 0.1 M receptor solution to an NMR tube containing $CDCl_3$. The receptor concentration ranged from 0.001 96 M (initially) to 0.075 M (finally). For receptors **1b**, **1e**, and **1f**, due to solubility problems, aliquots of 0.05 M receptor solution were added. The receptor concentration ranged from 0.000 98 M (initially) to 0.0375 M (finally).

Receptor 1-Flavin 3 Binding. To a host solution of flavin **3** (5×10^{-3} M) were added aliquots of receptor guest solution **1a**−**h** (5×10^{-2} M). This resulted in a smooth downfield shift in the resonance of H(3) of flavin **3**. Final concentrations: $[Guest]_{total} = 0.025$ M; $[Host]_{total} = 0.0025$ M. Nonlinear least-squares curve fitting was performed, with the resulting curve providing a good fit to a 1:1 binding isotherm, when compensation had been made for the dimerization of the receptor **1a**−**h**. From this curve fit it was possible to determine both the association constant (K_a) and the limiting shift value (δ_{max}H(3)) for the various receptor **1a**−**h**−flavin **3** complexes.

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Supporting Information Available: Titration graphs (dimerization and association) for receptors **1a**−**h**. NMR spectra of diaminotriazines **2a**−**h** and **1a**−**h** and IR spectra of receptors **1a**−**h** (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(18) The elemental analysis results for receptor **1c** always showed low nitrogen content. This was attributed to the fact that one of the nitrogen atoms had directly attached oxygens.