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Control of host dimerization and flavin recognition via intramolecular receptor self-assembly

Eunhee Jeoung,[a] Hugues Augier de Cremiers,[a,b] Robert Deans,[a] Graeme Cooke,[b] Sarah L. Heath,[c] Petra E. Vanderstraeten[b] and Vincent M. Rotello[a,*]

[a]*Department of Chemistry, University of Massachusetts, Amherst MA 01003, USA*
[b]*Centre for Biomimetic Design & Synthesis, Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, Scotland, UK*
[c]*Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK*

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Abstract—We have synthesized a family of receptors for flavins based on 6-aryl-2,4-acyldiamino-*s*-triazines. In these synthetic hosts, systematic variation of the position and functionalization of a hydrogen bond-donating amide moiety on the 6-aryl ring modulates dimerization over a 17-fold range, and flavin recognition over a 7-fold range.

Control of host–host and host–guest interactions is a central goal in the field of supramolecular chemistry. Efficient command of these binding events is essential for catalysis,[1] the creation of devices such as sensors[2] and switches,[3] as well as for the formation of structural units such as polymers,[4] capsules,[5] and other assemblies. In recent studies, intramolecular self-assembly has been shown to be a useful tool for the control of supramolecular processes. These studies have focused on two main approaches: host preorganization[6] and cooperative polarization.[7] In the course of our research, we have explored the role of electronic effects on hydrogen bond-mediated recognition. In these studies we have found that this recognition can be controlled through substituent effects transmitted through conjugated systems.[8] We report here a highly effective strategy in which simultaneous control of conjugation[9] and receptor structure through intramolecular hydrogen bonding regulates both host dimerization and host–guest interactions.

To provide a system where host structure could be readily controlled, we synthesized diaminotriazine-based receptors **1**–**3** (Fig. 1).[†] X-Ray crystallography analysis of receptors **1** and **3** (Fig. 2a and b) show the dimeric structure of receptors **1**,[‡] featuring the expected 4-point hydrogen bonding.[§,10] In these receptors, conjugation between the two aromatic rings is structurally controlled: in receptor **1**, the intramolecular hydrogen bonding (N···H distance 1.902 Å and O···H distance 2.456 Å) enforces coplanarity on the molecular backbone (interaromatic dihedral = 0.3°), enforcing conjugation throughout the molecule. In contrast, receptor **3**

* Corresponding author. Fax: (413) 545-4490; e-mail: rotello@chem.umass.edu

† The synthesis was based on Ref. 8. For receptor **1**, isobutyric anhydride was used instead of isobutyryl chloride as the acylation reagent, providing better yields and efficient separation. For receptor **2**, the amine of 4-aminobenzonitrile was acylated before triazine synthesis, followed by acylation of the diaminotriazine with isobutyryl chloride using DMAP as a base. For receptor **3**, anthranilonitrile was acylated with isobutyric anhydride and the amide methylated with sodium bis(trimethylsilyl)amide and CH_3I before formation and acylation of the triazine. Compound **1**: $P\bar{1}$; a = 8.6129(6), b = 9.1348(5), c = 14.8810(8) Å; α = 82.131(3), β = 85.795(4), γ = 71.319(4)ß; Z = 2; V = 1098.10(10) Å^3; R = 0.097. Compound **3**: $P\bar{1}$; a = 8.8256(4), b = 11.7575(6), c = 12.1161(7) Å; α = 90.569(4), β = 108.244(4), γ = 96.867(4)ß; Z = 2; V = 1184.00(10) Å^3; R = 0.085. Crystals of receptor **1** and **3**, were obtained by slow evaporation of the solvent from dichloromethane (DCM) solutions and 10 % ethyl acetate/DCM solutions, respectively.

‡ For receptor **1**, N–H···O = 2.803 Å, N–H···N = 3.256 Å, intramolecular hydrogen bonding site N–H···N = 2.710 Å and N–H···O = 3.282 Å.

§ Receptor **3** possessed an entirely different packing motif presumably due to the non-coplanar rings.

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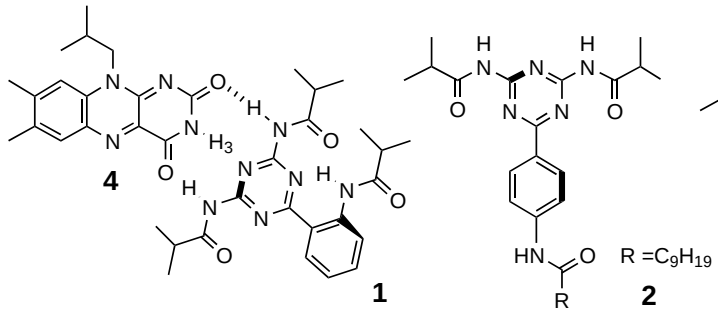

	1	2	3
K_{dim}	2248 M^{-1}	427 M^{-1}	129 M^{-1}
K_a	744 M^{-1}	181 M^{-1}	104 M^{-1}

Figure 1. Receptor **1**-flavin **4** complex and receptors **2** and **3**, with dimerization constants (K_{dim}) of receptors and association constants (K_a) with flavin **4** in $CDCl_3$.

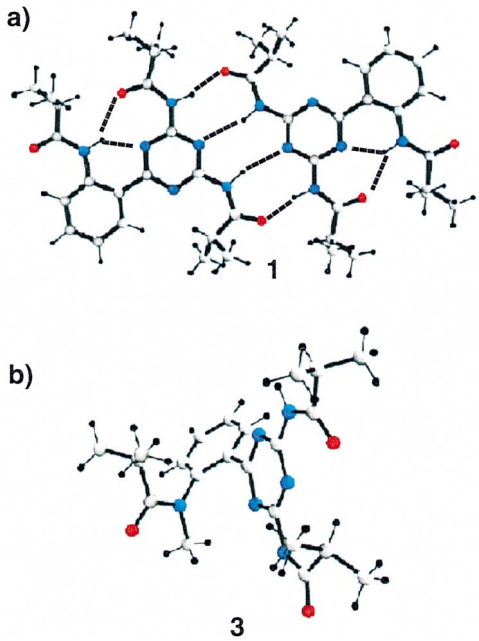

Figure 2. Crystal structures of receptors, showing the dimeric structure of **1** and receptor **3**.

cannot achieve planarity due to the bulky *N*-methyl substituent on the acylaniline ring (interaromatic dihedral = 49.3°). Receptor **2** presents an intermediate case: this system can achieve planarity. In solution, however, it is expected to freely rotate around the aryl–aryl bond

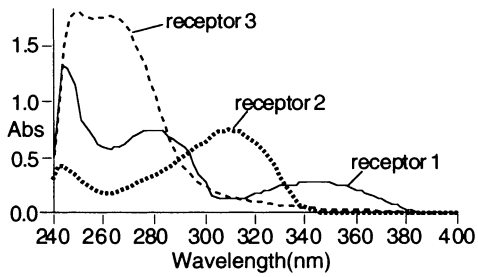

Figure 3. UV–vis spectra of receptors **1**–**3** in $CHCl_3$ solutions at 25°C.

UV–vis spectroscopy experiments verify the structural control of conjugation for receptors **1**–**3** (Fig. 3). As shown in Fig. 3, receptor **3**, has little absorption at λ>290 nm. Receptor **1**, in contrast, possesses a λ_{max} at 344 nm, consistent with the predicted extended conjugation. As expected from its ability to rotate around the aryl–aryl bond, receptor **2** possesses behavior intermediate between that of **1** and **3**, with a λ_{max} at 310 nm.

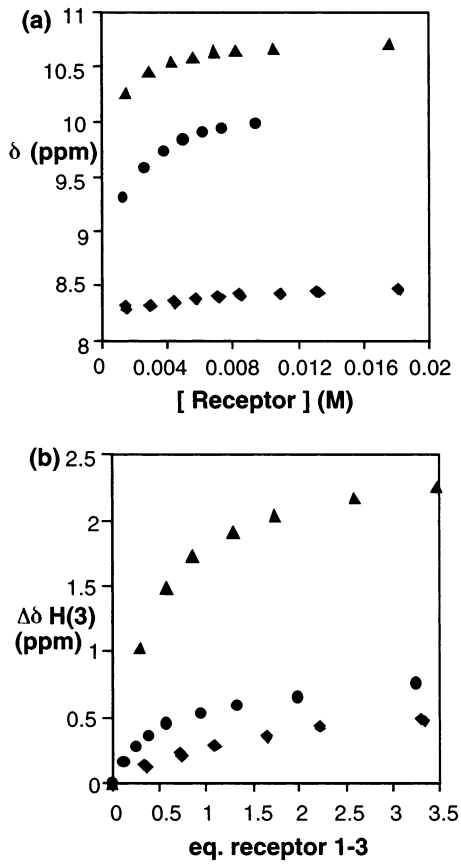

Figure 4. (a) Plot of the chemical shifts of the amide protons of **1** (▲), **2** (●) and **3** (◆) as a function of concentration; (b) chemical shift changes of flavin **4** H(3) upon addition of receptors **1** (▲), **2** (●) and **3** (◆)in $CDCl_3$ at 23°C.

The role of receptor structure on recognition properties was determined quantitatively using ^{1}H NMR titration. The ^{1}H NMR chemical shifts of the triazine amide protons of receptors **1**–**3** in $CDCl_3$ are concentration-dependent: a steady downfield shift in all receptors is observed upon increase of receptor concentration (Fig. 4a). The curves obtained from these titrations were fitted to dimerization isotherms to obtain dimerization constants (K_{dim}, Fig. 1). From these titrations, we observe that increasing conjugation increases the efficiency of dimerization: freely rotating receptor **2** dimerizes 3.3-fold more efficiently than non-coplanar receptor **3**, despite the similar electronics of the acylaniline moiety. Receptor **1** has the highest dimerization constant (17-fold greater than **3**). This enhanced interaction arises from increased conjugation of the aromatic systems coupled with intramolecular hydrogen bond-enforced favorable geometry and dipolar cooperativity of the amide at the binding surface.

Guest recognition by receptors **1**–**3** was likewise controlled through receptor structure. Titrations of flavin **4** with receptors **1**–**3** result in smooth downfield shifts in the resonance of H(3) of flavin (Fig. 4b). After explicit compensation was made for the reduction in free receptor **1**–**3** due to dimerization,[8] the association constants and complex-induced shifts were obtained by fitting the resulting curve to a 1:1 binding isotherm. Inspection of the association constants (Fig. 1) reveals that once again the most efficient recognition was observed for the 'locked' coplanar system **1**, and the least efficient binding was observed for the non-coplanar receptor **3**.

In conclusion, we have developed a family of receptors where binding efficiency is controlled through intramolecular assembly and communication. This system provides another tool for the control of supramolecular processes that can be applied to the creation of electronic devices such as sensors and switches, an area we are currently exploring.

Supplementary material

^{1}H NMR, IR, mp and elemental analyses for compounds **1**–**3**.

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