Molecular Recognition with Convergent Functional Groups. 6. Synthetic and Structural Studies with a Model Receptor for Nucleic Acid Components

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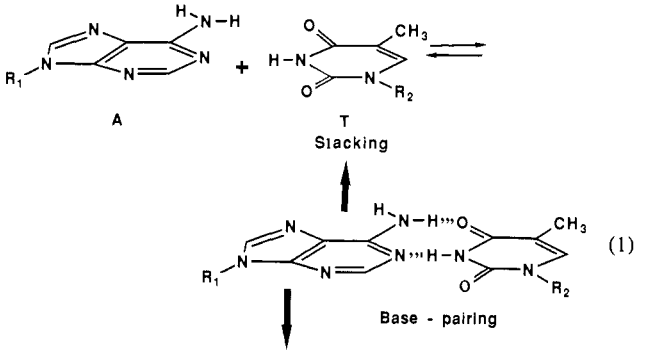
Abstract: Experimental details are given for the synthesis and characterization of a new class of model receptors for adenine derivatives. The molecules feature an imide function and a suitably placed aromatic surface that permit simultaneous base pairing and aryl stacking interactions. The structures are built from the Kemp tricarboxylic acid **3** and suitable spacers with aromatic surfaces attached via ester or amide linkages. The general features of complexation with 9-ethyladenine in $CDCl_3$ are established by NMR techniques involving chemical shift changes and NOE experiments. These establish that Watson–Crick, Hoogsteen, and bifurcated hydrogen bonds are present in the complexes. Aryl stacking interactions are controlled by the size of the aromatic surface and its pendant functionality. Model receptors bearing two imide functions act as molecular chelating agents for adenine and its derivatives. The highly organized hydrogen-bonding surfaces presented by these systems permit extraction of adenine derivatives from aqueous solution into $CDCl_3$.

Molecular recognition lies at the heart of most biochemical phenomena. In the recent past terms such as host–guest chemistry, inclusion complexes, and clathrates were used as substitutes for the original lock and key notions envisioned by Emil Fischer for enzyme–substrate specificity; molecular recognition is merely the most recent expression. In the chemistry of nucleic acids, Watson–Crick base pairing (eq 1) is the most classical example



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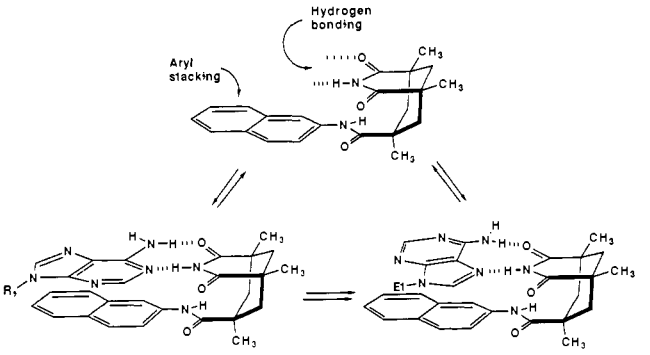
of this behavior. Recent communications[1-5] from this laboratory have described systems that can model the base-pairing process and, at the same time, incorporate the aromatic stacking interactions that also stabilize double-helical nuclei acids. These systems have led to the spectroscopic detection of Watson–Crick **1**, bifurcated, and Hoogsteen[6] **2** hydrogen bonding in $CDCl_3$ solution (eq 2).

Although these studies are inspired by the naturally occuring systems, the new models offer simplicity and interpretability—perhaps even naivete. After all, organic solvents such as $CDCl_3$ resemble the gas phase more than they do water. The spectroscopic techniques at high resolution that are easily brought to bear in the model systems are often difficult to apply in the original. Even so, the rules of intermolecular interactions hold in both



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systems. Moreover, a term like "recognition" bears no structural content, and its expression in synthetic systems requires choices concerning molecular shape, complementary functionality, surface type, and rigidity vs flexibility. The enterprise, then, offers a set of challenges and rewards quite outside of any resemblance to naturally occurring systems,

The most relevant precedent for base pairing in model systems is that of Rich,[7] using cyclohexyluracil binding to 9-ethyladenine in $CHCl_3$. Systematic structural modifications in both components were made in this study and revealed trends concerning steric effects and acid–base effects, At the same time these systems were used to examine the kinetics of the base-pairing event. Aromatic stacking interactions of simple bases were studied by Chan[8] in aqueous solutions, whereas Tinoco[9] et al. have developed a set of rules for the sequence-specific hydrogen bonding and stacking contributions of various base pairs to the stability of intact nucleic acids.

Our departure from previous model studies is made possible by the construction of a new molecular shape which permits both hydrogen bonding and aromatic stacking forces to act simultaneously. The structural developments are a consequence of the

(1) Rebek, J., Jr.; Askew, B.; Buhr, C.; Jones, S.; Nemeth, D.; Williams, K.; Ballester, P. *J. Am. Chem. Soc.* **1987**, *109*, 5033–5035.
(2) Rebek, J., Jr.; Askew, B.; Ballester, P.; Buhr, C.; Costero, A.; Jones, S.; Williams, K. *J. Am. Chem. Soc.* **1987**, *109*, 6866–6867.
(3) Rebek, J., Jr.; Williams, K.; Parris, K.; Ballester, P.; Jeong, K.-S. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1244–1245.
(4) Rebek, J., Jr. *Science (Washington, D.C.)* **1987**, *235*, 1478–1483.
(5) Jeong, K. S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 3327–3328.
(6) Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, 1984; Chapter 6. Hoogsteen, K. *Acta Crystallogr.* **1963**, *16*, 907–916.
(7) Kyogoku, Y.; Lord, R. G.; Rich, A. *Proc. Natl. Acad. Sci. U.S.A.* **1967**, *57*, 250–257. Hammes, G. C.; Park, A. C. *J. Am. Chem. Soc.* **1968**, *90*, 4151–4157.
(8) Chan, S. I.; Schweitzer, M. P.; Tso, P. O. P.; Helmkamp, G. K. *J. Am. Chem. Soc.* **1964**, *86*, 4182. Schweitzer, M. P.; Chan, S. I.; Tso, P. O. P. *Ibid.* **1965**, *87*, 5241–5247. Iwahashi, H.; Kyogoku, Y. *Ibid.* **1977**, *99*, 7761–7765.
(9) Tinoco, I., Jr.; Borer, P. N.; Dengler, B.; Levine, M. D.; Uhlenbeck, O. C.; Crothers, D. M.; Gralla, J. *Nature, New Biol.* **1973**, *246*, 40–41. For a recent discussion see: Turner, D. H.; Sugimoto, N.; Kierzek, R.; Dreiker, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 3783–3785, and references cited therein.

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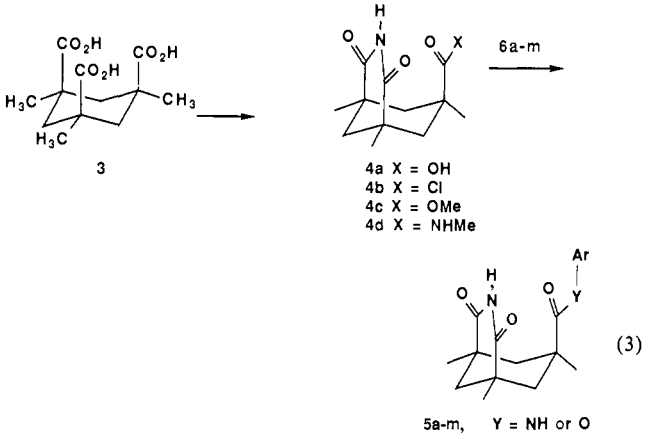
use of Kemp's[10] triacid **3**, in which a U-shaped (diaxial) relationship exists between any two carboxyl functions. Conversion of the triacid to the imide acid chloride **4b** gives an acylating agent that can be attached via amide or ester linkages to practically any available aromatic surface (eq 3).



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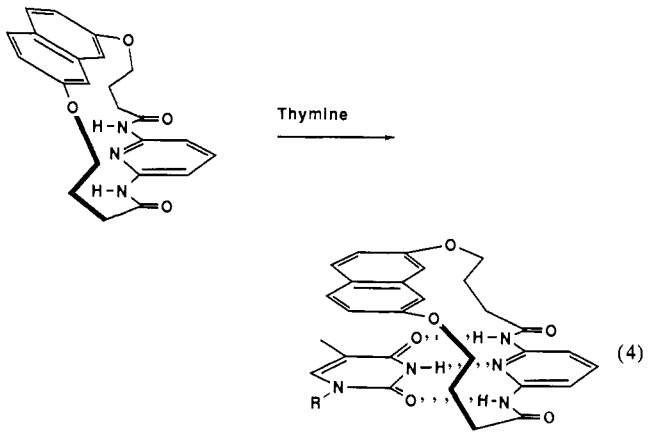
The resulting structure features an aromatic plane which can be roughly parallel to that of the atoms in the imide function; *hydrogen bonding and stacking forces converge from perpendicular directions to provide a microenvironment complimentary to adenine derivatives.* These same structural features are also present in a model for thymine and uracil recognition developed by Hamilton[11] (eq 4). Here we present full experimental details



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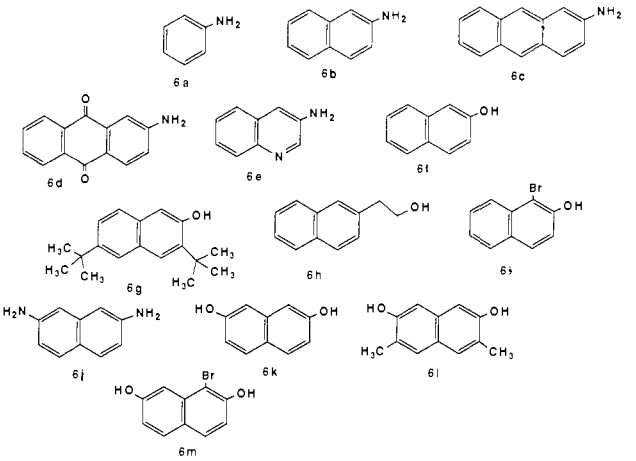
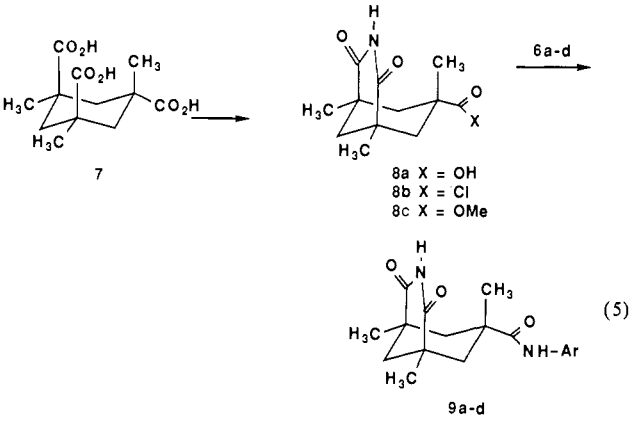
for the synthesis and structural characterization of our new adenine receptors. In the sequel, we explore the energetics of their binding interactions.

Synthesis. Our synthetic forays confirmed that virtually any available surface could be appended to **4a**. Below we list the structures of the various anilines **6** and naphthols **8** that could be acylated with the imide acid chloride **4b**.

Additionally, the synthesis was extended to diamine **6j** and diols **6k–6m**. In parallel experiments, the cis–trans isomer **7** (a by-product of the synthesis[12a] of **3**) was converted to the respective imide acid chloride **8b** and then acylated with representative **6a–6d** to give derivatives **9a–9d** aromatic amines (eq 5). This provided



structures in which the hydrogen-bonding "edge" and aromatic surfaces are at some distance from each other. Because such structures cannot express both binding forces simultaneously, they provide a realistic set of controls for the interpretation of phenomena involving the cis–cis isomers. The alkyl derivatives such as **4c,d** and **8c** were also prepared. These offer all of the hydrogen-bonding possibilities of their aromatic counterparts but lack the stacking interactions.



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Crystal Structures. Three of the compounds were obtained in suitable form for crystallographic investigations to be undertaken on them. The simple β-naphthyl ester **5f**, its di-*tert*-butyl derivative **5g**, and the β-phenethyl derivative **5h** were solved; the structures are reproduced in Figure 1.[13] For the esters **5f** and **5h**, intermolecular association is observed in the solid state involving imide dimerization with complementary hydrogen bonding with stacking interactions to a third molecule. The *tert*-butyl derivative **5g**, however, does not show such intermolecular interactions; the steric bulk of the substituents prevents close approach of the molecules.

The crystal structures also reveal that the planes of the ester and imide functions of **5f** and **5g** are at some angle with respect to the aromatic atoms. This is caused, in part, by repulsion between the ortho hydrogen (or other groups) and the carbonyl oxygen. This repulsion must be overcome to achieve a coplanar state. Estimates[14] of the magnitude of this effect for a ortho hydrogen are small and suggest that rapid rotation around the bond indicated may be expected in solution at room temperature. As a consequence, the unsubstituted structures feature at least two conformations in solution (eq 6). During base pairing even more isomers are possible due to reverse Watson–Crick and reverse Hoogsteen hydrogen bonding. Since some of the conformations are more appropriately arranged for aromatic stacking than are others,[3] the orientation of the aromatic surfaces can effect the preference for Watson–Crick vs Hoogsteen base pairing.

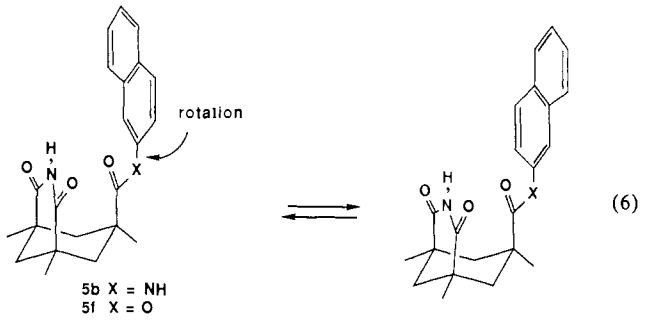
(10) Kemp, D. S.; Petrakis, K. S. *J. Org. Chem.* **1981**, *46*, 5140–5143. An improved synthesis is given in ref 12a.

(11) (a) Hamilton, A. D.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 5035–5036. (b) Constant, J. F.; Fahy, J.; Lhommey, J.; Anderson, J. E. *Tetrahedron Lett.* **1987**, 1777–1780. (c) Kim, M. S.; Gokel, G. W. *J. Chem. Soc., Chem. Commun.* **1987**, 1686–1688.

(12) (a) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426–2431. (b) Rebek, J., Jr. *Pure Appl. Chem.*, in press.

(13) Hydrogen atoms have been omitted for clarity; full details will be published elsewhere.

(14) Abraham, R. J.; Barnett, G. H.; Hawkes, G. G. E.; Smith, K. M. *Tetrahedron* **1966**, *32*, 2949.



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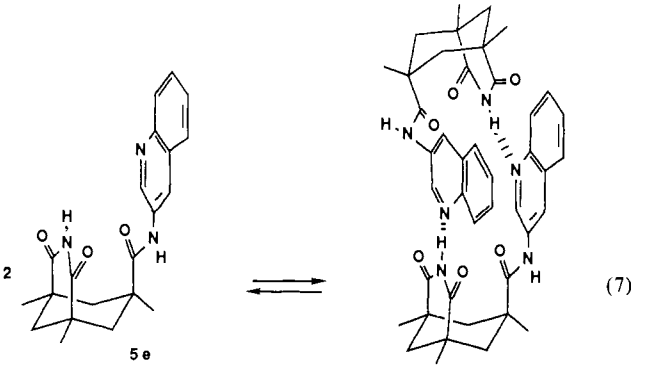
Spectroscopic Features. The new structures exhibited the anticipated NMR spectroscopic features, and only those characteristics used in subsequent binding studies are discussed here; the imide NH and the aromatic CH resonances. The 300-MHz spectrum of the β-naphthylamide **5b** is reproduced in Figure 2a. The signal for the imide NH is at 7.6 ppm, while the amide NH signal appears broadened at 7.31 ppm.

These chemical shifts were consistently observed in most of the structures **5a–5m**. Moreover, for almost all of the imides the chemical shift of the NH imide proton changed only slightly with changes in concentration. For example, a 5-fold dilution of the β-naphthylamide derivative **5b** caused only a 0.1 ppm shift in the signal. The most notable exception was the quinoline derivative **5o** in which dilutions shifted the signal considerably, i.e,, a 5-fold dilution caused a 1.0 ppm change. In addition, shifts were observed in some of the aromatic signals. This is indicative of strong self-association, presumably of the dimerization sort, involving binding of the one imide to the basic quinoline nitrogen of another (eq 7). In an unexpected way, this structure is *self-complementary*, and it is our intent to parlay this delightful feature into a system that is a primitive model for *self-replication*. Specifically, the covalent attachment of adenine to a receptor for adenine can lead to a molecule capable of acting as a template for its own formation,[12b] as shown in Scheme I. For the other imides, however, the constant chemical shifts observed as a function of concentration suggested that very little self-association occurred in the solution phase at NMR concentrations.



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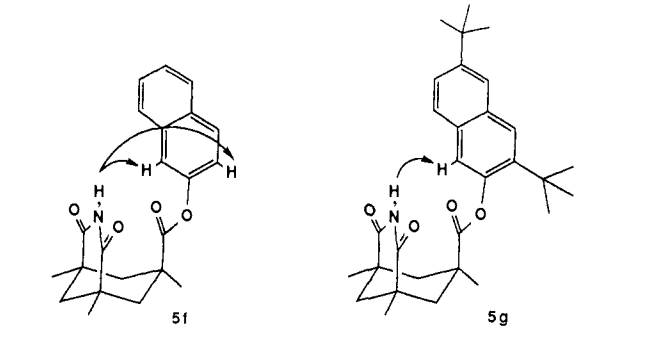
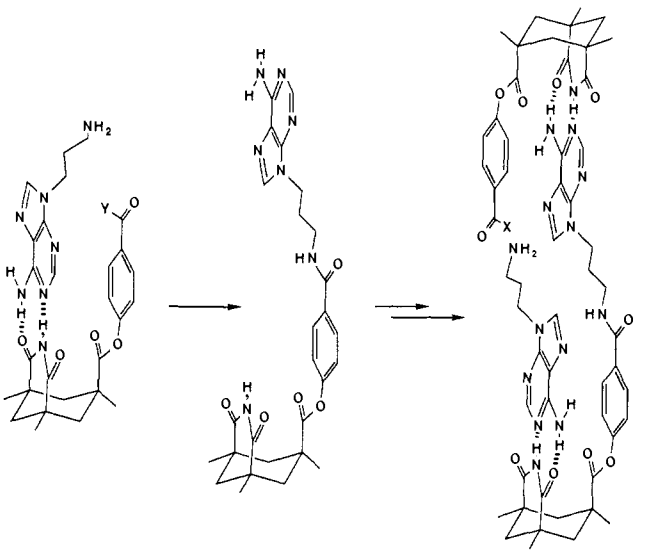
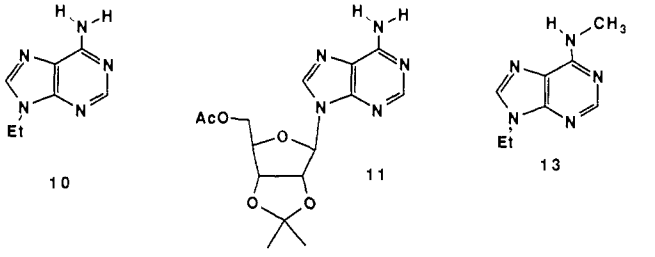
Studies involving nuclear Overhauser effects (NOEs) were undertaken to explore some of the conformational preferences. For example, irradiating the NH bond of the imide resulted in comparable enhancements of H_1 (1.2%) and H_3 (1.8%) in the aromatic protons of **5f**. A 2D-NOESY experiment was also performed in order to permit the assignment of the various proton signals for the more complicated systems. A similar study with the *tert*-butyl derivative **5g** showed a large enhancement (6% with H_1), indicating propinquity of the NH and CH bonds as suggested by the crystal structure; i.e., nearly perpendicular aromatic and imide ring planes exist in the lowest energy conformation of the molecule.



Scheme I



Structural Aspects of Complexation. The solubility of the molecules indicated the use of deuteriated solvents such as $CDCl_3$ or CD_3CN for binding studies. The low solubility in aqueous media prevented our experimentation in that most biologically relevant solvent, although mixtures of D_2O and CD_3OD could be used in some cases. When solutions of these receptors in $CDCl_3$ were treated with 9-ethyladenine (**10**) or the isopropylideneribose

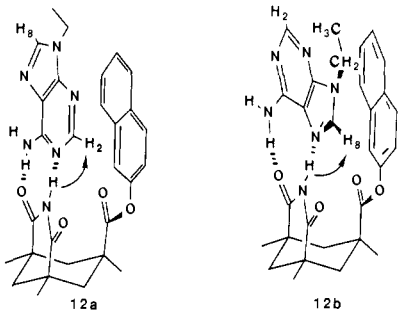


derivative **11**, large chemical shift changes were observed in the resulting NMR spectra. Figure 2b gives the trace with 5.00 equiv of 9-ethyladenine added; a sizable (4 ppm) downfield shift of the imide NH signal was observed and upfield shifts in the aromatic signals also occurred. These shifts tend to simplify the spectra toward first-order systems. With a large excess of adenine, the limiting shift observed for the imide was in the 13 ppm range. Much smaller amide NH shifts were observed; the limiting spectra for the aromatic resonances generally involved ~0.3 ppm upfield shifts.

These spectroscopic changes indicate that hydrogen bonding occurs between adenine and the NH of the imide; the upfield shifts in the aromatic portion indicate that the π bonds of the adenine system are in contact with the aromatic surfaces of the receptors, i.e., stacking occurs. The gross structural features anticipated for complexation are thereby confirmed by the NMR spectra,

(a) Watson–Crick vs Hoogsteen. The structural details involved in complexation could be mapped out with NOE methods. Two types of experiments were used to establish the existence of both Watson–Crick- and Hoogsteen-type base pairing. First, irradiation of the imide NH in the complex of **10** with **5f** caused enhancements of 1.9 and 2.1%, respectively, in H_2 and H_8 of the adenine (Table I). These are quite sizable for intermolecular effects, and they can only be accommodated by the presence of both Watson–Crick **12a** and Hoogsteen **12b** base pairing. While such data

Table I. Observed NOEs and Base-Pairing Preferences in Complexation Reactions



entry	receptor	adenine deriv	NOE obsd, % H_8 vs H_2 with imide NH	Hoogsteen of Watson–Crick (est)
1	**5b**	**10**	5.3:4.2	55:45
2		**13**	1.7:0.3	85:15
3	**5f**	**10**	2.1:1.9	55:45
4		**13**	3.3:0.6	85:15
5	**5g**	**10**	2.9:1.8	70:30
6		**13**	3.4:<0.5	>85:<15
7	**5c**	**10**	5.1:8.5	35:65
8		**13**	3.7:1.1	75:25

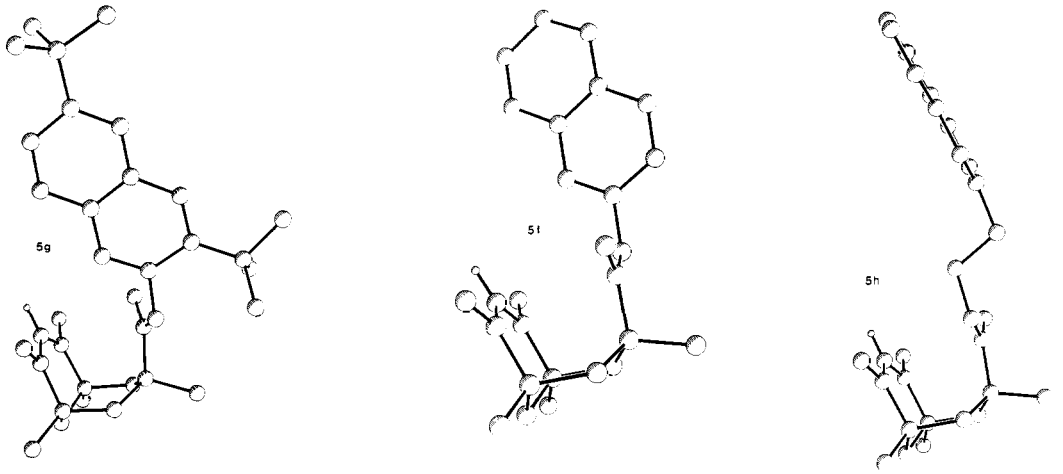


Figure 1. Crystal structures of three synthetic receptors for adenine derivatives. All hydrogens except those of the imide functions have been omitted for clarity.

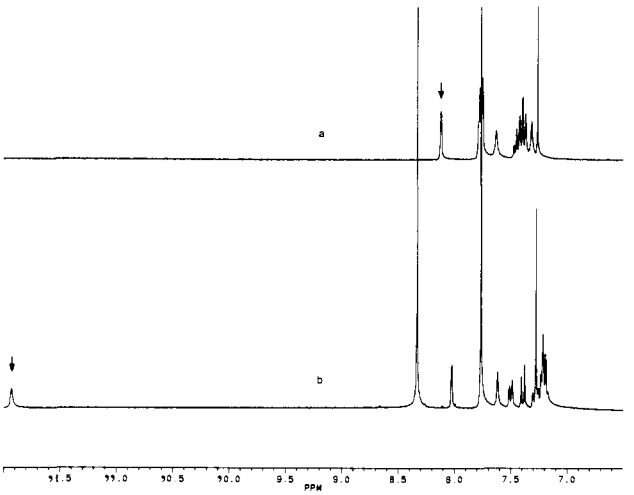


Figure 2. (a) Downfield region of the 300-MHz proton NMR spectrum of **5b** in $CDCl_3$: the imide N–H proton is indicated with the arrow. (b) Same as (a) but with 5 equiv **10** (9-ethyladenine) added.

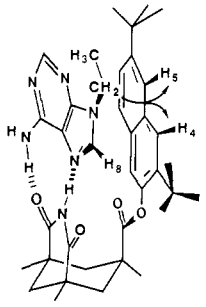
are difficult to place on a quantitative level, it appears that roughly equal amounts of the two types of binding are present. (For comparison with a more biorelevant adenine receptor, we examined Rich's system[7] of cyclohexyluracil with **10** under these conditions. Irradiations of H_2 and H_8 gave 1.4 and 0.9%, respectively, enhancements of the imide NH. Thus, both forms of base pairing are expressed in the A–U interaction.) Irradiation at the methylene group of **10** in the presence of **5c** also confirmed these structural conclusions. Enhancements in both the proximal and the distal ring of the anthracene derivative **5c** were observed.

Similar experiments were performed with the substituted N_6-methyladenine (**13**). In such a structure, as in other N_6 adenine derivatives, the alkyl group is directed *away* from N_7 with the result that Hoogsteen base pairing becomes favored.[15a] Indeed, during complexation with this derivative the imides continued to show the downfield shifts characteristic of hydrogen bonding, but NOE experiments gave evidence for mostly Hoogsteen base pairing. For example, irradiation of the imide proton now showed only enhancement with H_8 and complementary irradiations in the aromatic confirmed these interactions (Table I, entries 2, 4, 6, and 8 and Table II, entry 8).

The *tert*-butyl derivative **5g** interacting with 9-ethyladenine (**10**) produced an intermediate situation between these two extremes. The bulk of the distal *tert*-butyl group was expected to help direct and select for Hoogsteen vs Watson–Crick binding through steric

(15) (a) Dodin, G.; Dreyfus, M.; DuBois, J.-E. *J. Chem. Soc., Perkin Trans. 2*, **1979**, 439. (b) For bifurcated hydrogen bonds in binding of base pairs, see: Kopka, M. L.; Yoon, C.; Goodsell, D.; Pjura, P.; Dickerson, R. E. *J. Mol. Biol.* **1985**, *183*, 553–563. Wade, W. S.; Dervan, P. *J. Am. Chem. Soc.* **1987**, *109*, 1574–1575.

Table II. Intermolecular NOEs of the Receptors **5d**, **5f**, and **5g** in Contact with **10**



12c

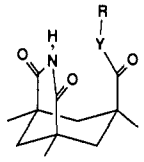
entry	receptor	irradiation	enhanced signal(s)	NOE, %
1	**5d**	CH_2 (**10**)	H_6, H_7 (**5d**)	2.7, 2.7
2	**5d**	CH_2 (**10**)	H_5, H_8 (**5d**)	1.1, 1.1
3	**5g**	CH_2 (**10**)	$H_{4,5,7,8}$ (**5g**)	1.0, 1.0, 1.2, 0.9
4	**5g**	H_2 (**10**)	H_7, H_8 (**5g**)	1.0, 1.0
5	**5g**	H_1 (**5g**)	H_2, H_8 (**10**)	0.9, 1.0
entry	receptor	irradiation	correlns obsd with **10**	
		2D-NOESY Experiments		
6	**5g**	imide NH	only H_8	
7	**5f**	imide NH	both H_2 and H_8	
8	**5g**	H_1	only H_8	
9	**5f**	H_1	both H_2 and H_8	
10	**5g**	H_5	only H_2	

Table III. Heteronuclear, Intermolecular NOEs between Model Receptors and Adenine Derivative **10**

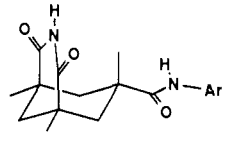
		^{13}C enhancement (%) obsd on irradiation of NH_2 ^1H signal of **10**	
entry	receptor	imide carbonyls	other carbonyl
1	**4c**	24	4 (ester)
2	**4d**	26	34 (amide)
3	**5d**	20	24 (amide)
4	**5f**	19	0 (ester)
5	**9c**	11	0 (amide)

interactions with the aromatic and ethyl side chains. The NOE experiments did result in the selective and larger enhancements shown (Tables I, entry 5 vs 3, and Table II, entries 6, 8, and 10) and confirmed that more Hoogsteen than Watson–Crick base pairing was occurring (e.g., **12c**), If the ratio of the enhancements is used as a measure, it can be estimated that ~70% of the binding of the *tert*-butyl derivative to **10** is in the Hoogsteen sense while 30% is in the Watson–Crick sense (Table I, entry 5). On the other end, the extended surface of the anthracene **5c** favors the Watson–Crick mode (Table I, entry 7) presumably because better stacking can be achieved.

(b) Bifurcated Hydrogen Bonds. Heteronuclear NOE experiments were performed with a number of these interacting systems. For the imide *amides* such as **5d** and **4d**, irradiation of the adenine



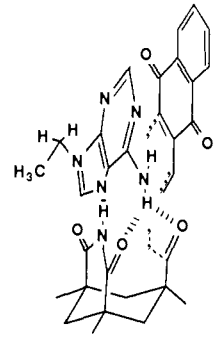
Y = NH or O



9c Ar = 2- Anthryl

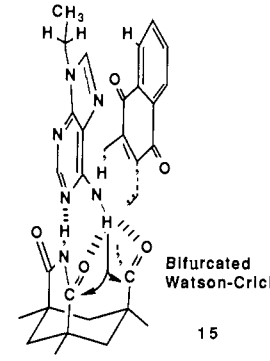
4c Y = O, R = Me
4d Y = NH, R = Me
5d Y = NH, R = 2- Anthraquinonyl
5f Y = O, R = 2- Naphthyl

NH signal at various stoichiometries was observed to cause enhancements in the ^{13}C signals, These are reported in Table III. Surprisingly, the enhancements are not limited to the imide carbonyl signals. The NOEs indicate that some contact exists between the adenine NH and the *amide* carbonyl as well (Table III, entries 2 and 3). Parallel experiments using the cis–trans isomer **9c** showed enhancements only at the *imide* carbonyls (but not at the amide). Thus, the enhancement is not merely due to rapid exchange in binding of the amine to the amide and imide in a series of simple hydrogen bonds. Nor can it be due to saturation transfer involving proton exchange between the NH and the hydrogens attached near the carbonyls. Instead, the most economical explanation involves simultaneous binding of the NH to both carbonyls, i.e., bifurcated hydrogen bonding. The magnitude of the NOEs in these types of studies is considerably enhanced by the inability of the carbonyl carbons to relax effectively without neighboring protons.



Bifurcated Hoogsteen

14

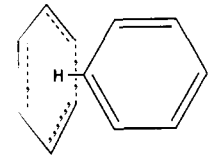


Bifurcated Watson-Crick

15

Identical studies with representative aryl esters, or **5f**, gave no evidence for such contacts between the ester carbonyl and the NH of the adenine, i.e., bifurcation does not appear to contribute to the binding in these compounds. Perhaps the reduced basicity of esters vs amides is the cause, although the methyl ester **4c** showed a small enhancement. The main features of complexation—aromatic stacking and imide hydrogen bonding—were expressed with both the ester and amide receptors, but it seems likely that bifurcated hydrogen bonds featured by the amides force the adenine closer to the aromatic surfaces of the amides than to those of the esters.[15b]

(c) Aryl Stacking Interactions. Considerable attention is being paid to π stacking interactions in bioorganic[16] and synthetic chemistry.[17] Such forces help align complementary structural features in receptor–guest or substrate–reagent contacts and provide an additional vehicle for selectivity. Recently, Petsko[18] discovered a phenomenon frequently expressed in enzyme interiors. Many interaromatic contacts are *edge-to-face* in geometry, i,e., the aryl CH bonds are directed toward neighboring π systems as in **16**. The crystal structures of both the *tert*-butyl derivative



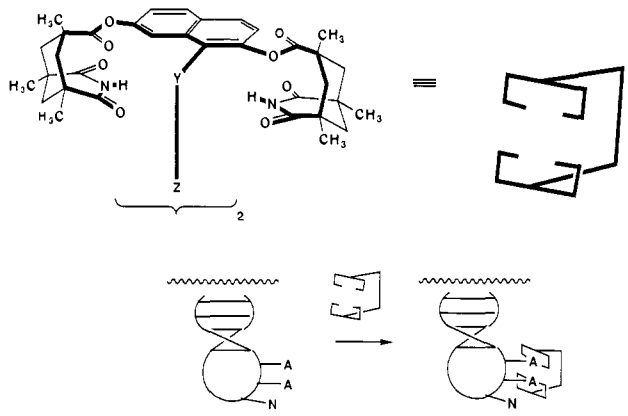
16

5g and its unsubstituted counterpart **5f** suggested an ideal arrangement (at least in the solid state) for their perpendicular interactions with adenine.

Accordingly, these systems were examined with an attempt to establish edge-to-face interactions by use of NMR experiments. Specifically, large upfield shifts of H_1 and H_8 of the naphthalene would be expected when contact is made by **5f** or **5g** with adenine

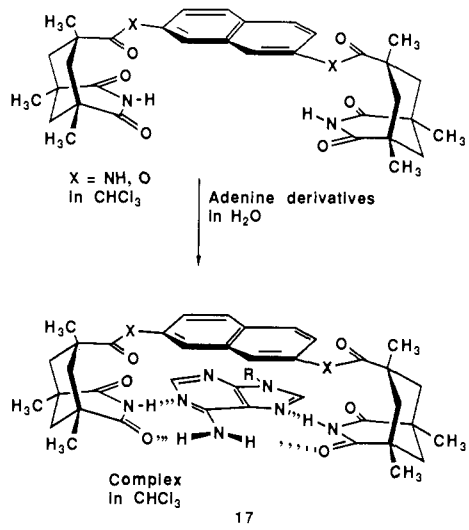
(16) Rebek, J., Jr.; Askew, B.; Nemeth, D.; Parris, K. *J. Am. Chem. Soc.* **1987**, *109*, 2432–2434. Rebek, J.; Askew, B.; Ballester, P.; Costero, A. *J. Am. Chem. Soc.* **1988**, *110*, 923–297.
(17) Evans, D. A.; Chapman, K. T.; Tan Hung, D.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184–1185.
(18) Burley, S. K.; Petsko, G. *Science*, (*Washington, D.C.*) **1985**, *229*, 23. Burley, S. K.; Petsko, G. *J. Am. Chem. Soc.* **1986**, *108*, 7995–8001.

Scheme II



derivatives. Irradiation of the CH_2 of 9-ethyladenine in contact with **5g** results in NOEs of these protons (Table II, entries 2 and 3), but at the same time, upfield shifts and enhancements in H_5 and H_4 are seen (see **12c**). Only the H_1 and H_8 enhancements can be accommodated by a perpendicular, edge-to-face arrangement, e.g., **16**, but all four observed enhancements and shifts are nicely accommodated by conventional, parallel π stacking interactions between the two aromatic surfaces. Accordingly, we conclude that the large dipole of adenine derivatives results in induced dipoles on the neighboring aromatic surface that are more stabilizing than the quadrupole interactions of the alternate edge-to-edge geometry.

(d) Molecular Chelation. Studies with the diimide **5j** and diester **5k** were in accord with the observations for the monoimides outlined above. However, sheer magnitude of binding, as described in the sequel, suggested that simultaneous Watson–Crick, Hoogsteen, and aryl stacking interactions were occurring with these model receptors as suggested in **17** (eq 8). A simple



(8)

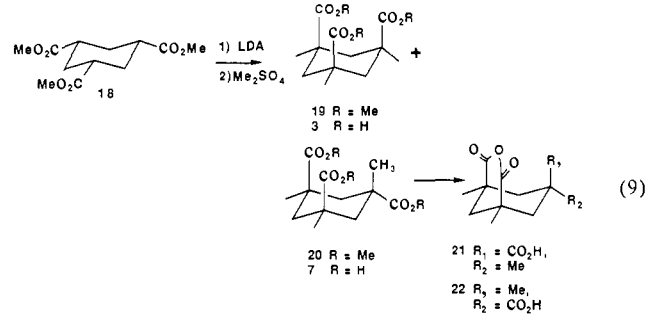
17

extraction experiment offered qualitative evidence concerning the extraordinary affinity of **5j** for adenine. Both **5j** and **5k** are capable of extracting 1 equiv of adenine from aqueous solutions into $CDCl_3$; simple monoimides fail in this regard. The structural details of adenine chelation by these multidentate systems are unknown, but **17** is in accord with the observations.

In summary, we have described the synthesis and structural characterization of new model receptors for adenine derivatives. Structural details of complexation, including Watson–Crick, Hoogsten, and bifurcated hydrogen bonding have been observed. Aromatic stacking effects have been established by NOE techniques. In the accompanying paper, we describe the quantitative aspects of binding and the thermodynamic parameters involved. Binding of these imides to adenosine derivatives can also be detected in aqueous methanol, an observation which suggests that the high degree of organization of hydrogen bond donors and acceptors in these structures permits competition with hydroxylic solvents. Preliminary experiments have also established the ability of these materials to transport adenosine and deoxyadenosine across organic liquid membranes. It should be possible to develop agents capable of specific recognition of single-stranded nucleic acids involving adenine by use of these models. One possibility involving a tRNA, is shown in Scheme II. We are progressing toward these goals.

Experimental Section

Cis–Cis Anhydride Acid 21. Trimethyl 1,3,5-cyclohexanetricarboxylate (**18**) was alkylated as previously described,[12] affording a mixture of cis–cis **19** and cis–trans triesters **20** (eq 9). Cis–cis triester



(9)

19 precipitates from the crude mixture and is collected by filtration. The remaining oil consisted of a 60/40 ratio of cis–cis/cis–trans triester. Cis–cis triester **19** (70.0 g, 0.233 mol) was hydrolyzed to the triacid **3** as previously described.[12] The damp product (60.2 g) was not carefully dried, but immediately converted to the anhydride acid **21** by the modifications described here. A mass of 60.2 g of damp triacid was suspended in 1200 mL of xylenes and heated under reflux for 17 h with a Dean–Stark trap under N_2. The resulting mixture was evaporated, and traces of remaining solvent were removed in a vacuum oven at 77 °C for 1 h. This procedure afforded 47.9 g of product (85.5% overall yield from solid triester). The anhydride acid **21** could also be prepared by sublimation of the triacid **3** at 190 °C (0.5 mmHg): mp 252–254 °C; IR 3200–2200, 1790, 1759, 1693, 1466, 1277, 1210, 1182, 1136, 1095, 1001 cm^{-1}; ^1H NMR (pyridine-d_5) δ 2.95 (d, 2 H, J = 14.1 Hz), 2.05 (d, 1 H, J = 13.2 Hz), 1.41–1.21 (m, 12 H, including 1.37 [s, 6 H] and 1.31 [s, 3 H]). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71; O, 33.30. Found: C, 60.12; H, 6.78; O, 33.10.

Imide Acid 4a. To a stirred solution of 1500 mL of concentrated aqueous ammonium hydroxide (NH_4OH) containing 4.79 g (0.0392 mol, 0.20 equiv) of 4-(dimethylamino)pyridine (DMAP) was added 47.9 g (0.199 mol) of solid anhydride acid **21** in several portions. The reaction was heated to 110 °C for 12 h and then carefully concentrated (vigorous bumping) to ca. 300 mL. The resulting mixture was cooled on an ice water bath, and the Ph of the mixture was adjusted to ca. 1.0 with concentrated HCl. After 20 min, the colorless solid was collected by filtration and thoroughly washed with water. The product was dried at 110 °C under vacuum for 3 h, affording 44.4 g of **4a** (93.3% yield): mp >300 °C (from MeOH); IR, 3300–2500, 3140, 3073, 2971, 1730, 1707, 1456, 1383, 1311, 1219, 1184 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.19 (s, 1 H, CO_2H), 10.36 (s, 1 H, NH), 2.36 (d, 2 H, J = 13.3 Hz), 1.88 (d, 1 H, J = 12.8 Hz), 1.38 (d, 1 H, J = 13.0 Hz), 1.18 (d, 2 H, J = 13.8 Hz), 1.11 (s, 3 H), 1.08 (s, 6 H); high-resolution mass spectral analysis for $C_{12}H_{17}NO_4$ calcd 239.1157, found 239.1156. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85; O, 26.75. Found: C, 60.08; H, 7.35; N, 5.80; O, 26.77.

Imide Acid Chloride 4b. The 44.4 g (0.185 mol) of imide acid **4a** described above was added to 667 mL of freshly distilled thionyl chloride in several portions as a solid. The stirred reaction was heated at reflux under a dry nitrogen atmosphere for 3 h. The solution was then carefully concentrated on a rotary evaporator to afford 47.3 g of **4b** (99.0% yield, 78.5% overall yield from cis–cis triester) as a pale yellow solid. A small sample was recrystallized from EtOAc and afforded colorless crystals: mp 181.5–183.5 °C; IR, 3200, 3094, 2987, 1780, 1721, 1696, 1462, 1385, 1205, 924, 897, 833 cm^{-1}; ^1H NMR δ 7.77 (s, 1 H, NH), 2.78 (d, 2 H, J = 14.0 Hz), 2.04 (d, 1 H, J = 13.4 Hz), 1.45–1.25 (m, 12 H including 1.32 [s, 3 H] and 1.29 [s, 6 H]); high-resolution mass spectral analysis for $C_{12}H_{16}NO_3Cl$ calcd 257.0819, found 257.0820.

Imide Methyl Ester 4c. To 60 mL of anhydrous methanol (MeOH), which was stirred at room temperature under a dry nitrogen atmosphere, was added 2.50 g (9.70 mmol) of imide acid chloride **4b** in one solid portion. After being stirred for 10 h at room temperature, the reaction

was concentrated affording crude product. The crude product was taken up in 100 mL of $CHCl_3$, washed with 2 × 50 mL of saturated aqueous sodium bicarbonate ($NaHCO_3$) and once with 50 mL of saturated brine solution, then dried ($MgSO_4$), filtered, and concentrated. The resulting solid was purified by flash chromatography[19] on a 32-mm column using 30% EtOAc in $CHCl_3$ and afforded 1.70 g (69.1% yield) as a colorless solid: mp 212–213.5 °C from (MeOH); IR, 3194, 3094, 2965, 1721, 1698, 1464, 1379, 1325, 1209, 1176 cm^{-1}; ^1H NMR δ 7,65 (s, 1 H, N*H*), 3.61 (s, 3 H), 2.70 (d, 2 H, J = 13.2 Hz), 1.98 (d, 1 H, J = 13.4 Hz), 1.37 (d, 1 H, J = 13.3 Hz), 1.26 (s, 6 H), 1.22 (s, 3 H), 1.18 (d, 2 H, J = 14.4 Hz); high-resolution mass spectral analysis for $C_{13}H_{19}NO_4$ calcd 253.1314, found 253.1314.

Imide *N*-Methylamide 4d. A solution of 1.0 g of **4b** in 90 mL of dry THF containing a catalytic amount of DMAP was treated with a slow stream of gaseous CH_3NH_2 with vigorous stirring at room temperature for 1 h. After being stirred for an additional hour, the solution was evaporated and the residue was subjected to flash chromatography using EtOAc. This gave 65% yield of **4d**: mp 260–261 °C; NMR ($CDCl_3$) δ 7.59 (s, 1 H), 5.52 (s, 1 H), 2.72 (d, 3 H, J = 4.8 Hz), 2.55 (d, 2 H, 13.3 Hz), 1.63 (d, 1 H, J = 13.3 Hz), 1.38 (d, 2 H, J = 13.3 Hz), 1.27 (s, 6 H), 1.25 (d, 1 H, J = 13.3 Hz), 1.21 (s, 3 H); IR ($CHCl_3$) 3306, 3194, 3094, 1699, 1684, 1522, 1506, 1373 cm^{-1}.

Naphthalene Imide 5b. A solution of 3.60 g (0.0140 mol) of imide acid chloride **4b** in 20 mL of $CHCl_3$ was added to a stirred solution of 0.34 g of DMAP (2.78 mmol, 0.20 equiv) in 110 mL of dry pyridine at room temperature. The reaction was heated to 90 °C and stirred under a dry nitrogen atmosphere for 12 h. The reaction was concentrated to a crude solid which was taken up in ca. 600 mL of $CHCl_3$. The solution was washed with 2 × 200 mL of 10% aqueous HCl and 1 × 200 mL of saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography as follows. The crude product was loaded onto a 41-mm column in ca. 800 mL of CH_2Cl_2 and then eluted with 20% EtOAc in CH_2Cl_2. This procedure afforded 3.13 g (61.5% yield) of product as a colorless solid: mp 281–282 °C from (EtOAc); IR, 3486, 3366, 3200, 3092, 2963, 1719, 1690, 1547, 1470, 1385, 1363, 1210 cm^{-1}; ^1H NMR δ 8.12 (s, 1 H), 7.81–7.69 (m, 3 H), 7.66 (s, 1 H, imide NH), 7.49–7.25 (m, 4 H), 2.70 (d, 2 H, J = 14.1 Hz), 1.96 (d, 1 H, J = 13.2 Hz), 1.42–1.19 (m, 12 H, including 1.36 (s, 3 H) and 1.30 (s, 6 H)); high-resolution mass spectral analysis for $C_{22}H_{24}N_2O_3$ calcd 364.1787, found 364.1788. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69; O, 13.17. Found: C, 72.50; H, 6.57; N, 7.73; O, 13.20.

Anthracene Imide 5c. The preparation of **5c** is the same as that described for **5b** except that 2.97 g (0.0154 mol, 1.1 equiv) of 2-aminoanthracene was used instead of 9-aminonaphthalene. Technical-grade 2-aminoanthracene was purified by sequential sublimation. The crude solid was taken up in ca. 1500 mL of $CHCl_3$ and the solution washed with 3 × 500 mL of 6 N HCl and 1 × 500 mL of saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography on a 41-mm column using 15% EtOAc in CH_2Cl_2 as eluent. This procedure was afforded 3.77 g (65.1% yield) of product as a tan solid. A small sample was recrystallized from EtOAc and afforded colorless crystals: mp 280–281 °C; IR, 3368, 3194, 3052, 2965, 1696, 1541, 1522, 1462, 1429, 1381, 1360, 1312, 1213 cm^{-1}; ^1H NMR δ 8.36–8.28 (m, 3 H), 8.00–7.91 (m, 3 h), 7.62 (s, 1 H, imide NH), 7.50–7.39 (m, 2 H), 7.36–7.30 (m, 2 H), 2.73 (d, 2 H, J = 13.8 Hz), 2.01 (d, 1 H, J = 13.3 Hz), 1.48–1.20 (m, 12 H including 1.38 (s, 3 H) and 1.32 (s, 6 H); high-resolution mass spectral analysis for $C_{26}H_{26}N_2O_3$ calcd 414.1943, found 414.1943.

Anthraquinone Imide 5d. Technical-grade 2-aminoanthraquinone (Aldrich) was purified by two sublimations [195 °C (0.5 mmHg)]. A solution of 300 mg of imide acid chloride **4b** (1.16 mmol) in 5 mL of dry pyridine was added to a stirred solution of 319 mg (1.43 mmol, 1.2 equiv) of purified 2-aminoanthraquinone and a catalytic of DMAP in 10.0 mL of dry pyridine. The reaction was heated under reflux for 18 h under a nitrogen atmosphere and then allowed to cool to room temperature. The solution was then poured onto 100 mL of Et_2O, washed with 2 × 50 mL of 10% HCl and 1 × 50 mL of saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography on a 32-mm column using 40% EtOAc in $CHCl_3$ as eluent. This procedure afforded 98.0 mg (19.0% yield) as a yellow solid: mp >280 °C; IR, 3355, 3243, 2967, 1700, 1672, 1589, 1524, 1466, 1329, 1291, 1182 cm^{-1}; ^1H NMR δ 8.82 (s, 1 H, imide NH), 8.27–8.18 (m, 3 H), 8.05 (s, 1 H), 8.00 (d, 1 H, J = 2.0 Hz), 7.82–7.72 (m, 3 H), 2.88 (d, 2 H, J = 14.4 Hz), 2.12 (d, 1 H, J = 13.3 Hz), 1.51 (d, 1 H, J = 13.3 Hz), 1.45–1.32 (m, 11 H including 1.39 (s, 9 H); high-resolution mass spectral analysis for $C_{26}H_{24}N_2O_5$ calcd 444.1685, found 444.1684.

Quinoline Imide 5e. A solution of 300 mg of imide acid chloride **4a** (1.16 mmol) in 3.0 mL of $CHCl_3$ was added, at room temperature, to a stirred solution of 168 mg (1.16 mmol, 1.0 equiv) of 3-aminoquinoline (that was previously dried for 8 h at 77 °C under vacuum) and 30 mg (0.246 mmol, 0.21 equiv) of DMAP in 8.0 mL of dry pyridine. The reaction was then heated under reflux beneath a dry nitrogen atmosphere for 8 h. The reaction was then concentrated. The residue was taken up in $CHCl_3$, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography on a 32-mm column using 20% $CHCl_3$ in EtOAc. This procedure afforded 266 mg (62.7% yield) of product as a colorless solid after drying under vacuum for 4 h at 110 °C: mp 300–302 °C (as the monohydrate, from MeOH); IR, 3370, 2967, 1693, 1536, 1489, 1466, 1364, 1211 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.47 (s, 1 H), 9.67 (s, 1 H), 8.90 (d, 1 H, J = 2.3 Hz), 8.44 (d, 1 H, J = 2.0 Hz), 8.00–7.87 (m, 2 H), 7.70–7.52 (m, 2 H), 2.72 (d, 2 H, J = 13.9 Hz), 1.93 (d, 1 H, J = 12.8 Hz), 1.43 (d, 1 H, J = 12.9 Hz), 1.30 (d, 2 H, J = 14.1 Hz), 1.24 (s, 3 H), 1.15 (s, 6 H); high-resolution mass spectral analysis for $C_{21}H_{23}N_3O_3$ calcd 365.1739, found 365.1738. Anal. Calcd for $C_{21}H_{23}N_3O_3 \cdot H_2O$: C 65.78; H, 6.57; N, 10.96: O, 16.69. Found: C, 65.99; H, 6.62; N, 10.88; O, 16.51.

2-Naphthyl Ester Imide 5f. To a magnetically stirred, ice cold solution of 73 mg (0.506 mmol) of 2-naphthol in 15 mL of dry THF was added 18 mg (1.5 equiv) of sodium hydride (NaH) as a 50% oil dispersion. The reaction was stirred under N_2 for 20 min, and then a solution of 129 mg (0.500 mmol, 10 equiv) of imide acid chloride **4b** in 15 mL of dry THF was added dropwise over 10 min. After the addition was complete, the ice batch was removed. Stirring was continued for 2 h, and then the reaction was quenched with 15 mL of water. The reaction was then concentrated, and the resulting solid was taken up in CH_2Cl_2 and washed sequentially with water, saturated aqueous $NaHCO_3$, saturated brine, and water. The organic portion was then dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography on a 19-mm column using hexanes/EtOAc (2/1) affording 153 mg (84% yield) of **5f** as a colorless solid: mp 214–216 °C; IR, 3208, 3096, 2968, 1750, 1697, 1205, 1105 cm^{-1}; ^1H NMR δ 7.81 (m, 3 H), 7.62 (s, 1 H, NH), 7.50 (d, 1 H, J = 2 Hz), 7.47 (m, 2 H), 7.16 (dd, 1 H, J_1 = 9 Hz, J_2 = 2 Hz), 2.88 (d, 2 H, J = 14 Hz), 2.07 (d, 1 H, J = 13 Hz), 1.49 (s, 3 H), 1.46 (d, J = 13 Hz, 1 H), 1.33 (s, 6 H), 1.33 (d, 2 H, J = 13 Hz); high-resolution mass spectral analysis for $C_{22}H_{23}NO_4$ calcd 365.1627, found 365.1627.

Di-*tert*-butylnaphthyl Ester Imide 5g. To a magnetically stirred, ice cold solution of 536 mg (2.08 mmol) of 3,6-di-*tert*-butyl-2-naphthol[20] in 50 mL of dry THF was added 2.00 mL of 0.992 M *n*-butyllithium (1.98 mmol, 0.95 equiv) dropwise, under a nitrogen atmosphere. After the resultant mixture was stirred for 20 min, a solution of 537 mg (2.08 mmol, 1.0 equiv) of imide acid chloride **4b** in 10 mL of dry THF was added dropwise over 10 min. The ice bath was then removed, and the stirring was continued for an additional 2 h. The reaction was then quenched with 5.0 mL of water and then concentrated. The residue was taken up in 100 mL of diethyl ether, washed with 2 × 50 mL of 1 N NaOH and 2 × 50 mL of saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography on a 25-mm column using 40% EtOAc in hexanes as eluent. This procedure afforded 795 mg (80.0% yield) of **5g** as a colorless solid: mp 260–262 °C; IR, 3250, 2900, 1750, 1695, 1200, 1100, 1000–1050 cm^{-1}; ^1H NMR δ 7.74 (s, 1 H), 7.74 (d, 1 H, J = 1 Hz), 7.70 (d, 1 H, 7 Hz), 7.52 (dd, 1 H, J_1 = 7 Hz, J_2 = 1 Hz), 7.40 (s, 1 H), 2.91 (d, 2 H, 14 Hz), 2.06 (d, 1 H, 14 Hz), 1.55 (s, 18 H), 1.39 (s, 6 H), 1.33 (s, 3 H); high-resolution mass spectral analysis for $C_{30}H_{39}NO_4$ calcd 477.2879, found 477.2879.

2-(2-Naphthyl)ethyl Ester Imide 5h. To a stirred solution of 0.500 g (2.90 mmol) of 2-(2-naphthalene)ethanol in 20 mL of CH_2Cl_2 containing 1.0 mL of dry pyridine and a catalytic amount of DMAP was added 0.820 g (3.18 mmol, 1.1 equiv) of **4b**. The reaction was heated at reflux under a nitrogen atmosphere for 5 h. The solution was allowed to cool to room temperature, washed with 2 × 10 mL of 3 N HCl, 1 × 10 mL of H_2O, 2 × 10 mL of saturated aqueous $NaHCO_3$, 1 × 10 mL of brine, and 1 × 10 mL of H_2O, dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography on a 19-cm column using hexanes/Et_2O (201) and afforded 0.990 g (86.8% yield) of **5h** as a colorless solid: mp 192–194 °C; IR, 3219, 3094, 2967, 2932, 1728, 1695, 1508, 1462, 1381, 1238, 1205, 1178, 1093, 1601, 820 cm^{-1}; ^1H NMR δ 7.79 (m, 3 H), 7.66 (d, 1 H, J = 2 Hz), 7.53 (s, 1 H, N*H*), 7.45 (m, 2 H), 7.34 (dd, 1 H, J_1 = 8 Hz, J_2 = 2 Hz), 4.30 (t, 2 H, J = 7 Hz), 3.08 (t, 2 H, J = 7 Hz), 2.68 (d, 2 H, J = 14 Hz)8, 1.98 (d, 1 H, J = 13 Hz), 1.36 (d, 1 H, J = 14 Hz), 1.26 (s, 6 H), 1.14 (d, 2 H, J = 14 Hz), 1.10

(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(20) 3,6-Di-*tert*-butyl-2-naphthol was a gift from Dr. D. Chasar. See: Chasar, D. W. *J. Org. Chem.* **1984**, *49*, 4302–4303.

(s, 3 H); high-resolution mass spectral analysis for $C_{24}H_{27}NO_4$ calcd 393.1940, found 393.1940.

1-Bromo-2-naphthyl Ester Imide 5i. The procedure used in the preparation of **5f** was used except that 112 mg of 1-bromo-2-naphthol (0.502 mmol, 1.0 equiv) was used in the preparation of **5i**. Purification of the product by flash chromatography on a 19-mm column using hexanes/EtOAc (2/1) afforded 156 mg (70.3% yield) of **5i** as a colorless solid: mp 267–269 °C; IR, 3198, 3088, 2974, 2914, 1757, 1722, 1698, 1595, 1502, 1462, 1385, 1205, 1130, 1074, 808 cm^{-1}; ^1H NMR δ 8.17 (d, 1 H, J = 8 Hz), 7.84 (dd, 1 H, J_1 = 8 Hz, J_2 = 1 Hz), 7.82 (d, 1 H, J = 8 Hz), 7.68 (s, 1 H, N*H*), 7.59 (t, 1 H, J = 8 Hz, further 1 Hz splitting), 7.51 (t, 1 H, J = 8 Hz, further 1 Hz splitting), 7.28 (d, 1 H, J = 8 Hz), 2.91 (d, 2 H, J = 13 Hz), 2.09 (d, 1 H, J = 13 Hz, further 1 Hz splitting), 1.56 (s, 3 H), 1.47 (d, 1 H, J = 13 Hz), 1.36 (d, 2 H, J = 13 Hz), 1.33 (s, 6 H); high-resolution mass spectral analysis for $C_{22}H_{22}{}^{81}BrNO_4$ calcd 445.0712, found 445.0713.

Naphthalene Diimide 5j. A solution of 326 mg (1.26 mmol, 2.0 equiv) of imide acide chloride **4b** in 3.0 mL of CH_2Cl_2 was added to a stirred solution of 100 mg of 2,7-diaminonaphthalene[21] (0.632 mmol) and a catalytic amount of DMAP in 8.0 mL of dry pyridine. The reaction was stirred at room temperature under N_2 for 10 h and then concentrated. The residue was taken up in 300 mL of 1-butanol, washed with 2 × 100 mL of 10% aqueous HCl and 1 × 100 mL of saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography on a 32-mm column using 5% MeOH in $CHCl_3$. This procedure afforded 79.4 mg of product (20.9% yield) as a dull orange solid: mp >300 °C; IR, 3390, 3196, 2965, 1721, 1692, 1636, 1559, 1508, 1466, 1400, 1289, 1210 cm^{-1}; 1 H NMR (DMSO-d_6) δ 10.44 (s, 1 H), 9.34 (s, 1 H), 7.93 (s, 1 H), 7.73 (d, 1 H, J = 8.7 Hz), 7.45 (d, 1 H, J = 8.9 Hz), 2.72 (d, 2 H, J = 13.9 Hz), 1.91 (d, 1 H, J = 12.9 Hz), 1.43 (d, 1 H, J = 12.8 Hz), 1.31–0.90 (m, 11 H including 1.22 (s, 3 H) and 1.14 (s, 6 H)); high-resolution mass spectral analysis for $C_{34}H_{40}N_4O_3$ calcd 600.2948, found 600.2947.

2,7-Dihydroxy Ester Diimide 5k. To a magnetically stirred, ice cold solution of 80.0 mg (0.499 mmol) of 2,7-naphthalenediol in 12.0 mL of dry THF was added 0.99 mL (0.998 mmol, 2.0 equiv) of 0.992 M *n*-butyllithium under a dry nitrogen atmosphere. After the resultant mixture was stirred for 20 min., a solution of 258 mg (1.00 mmol, 2.0 equiv) of imide acid chloride **4b** in 3.0 mL of dry THF was added dropwise over 10 min. After the addition was complete, the ice bath was removed, and stirring was continued for an additional 2 h. The reaction was then quenched with 5.0 mL of water and concentrated. The residue was taken up in 100 mL of Et_2O, washed with 2 × 50 mL of 1 N NaOH and 2 × 50 mL of saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography on a 25-mm column using hexanes/EtOAc (10/1) as eluent. This procedure afforded 224 mg (74.4% yield) of **5a** a colorless solid: mp > 300 °C; IR, 3300, 3100, 2900, 1750, 1695, 1220, 1150 cm^{-1}; ^1H NMR 7.79 (dd, 2 H, J_1 = 7 Hz, J_2 = 1 Hz), 7.68 (s, 2 H), 7.49 (d, 2 H, J = 1 Hz), 7.19 (d, 2 H, J = 1 Hz), 2.86 (d, 4 H, J = 14 Hz), 2.05 (d, 2 H, J = 14 Hz); 1.43 (s, 6 H), 1.32 (s, 12 H), 1.29 (m, 6 H); high-resolution mass spectral analysis for $C_{34}H_{38}N_2O_8$ calcd 602.2628, found 602.2628.

3,6-Dimethyl-2,7-dihydroxy Ester Diimide 5l. The procedure used for the preparation of **5k** was used except that 94.1 mg (0.500 mmol) of 3,6-dimethyl-2,7-naphthalenediol was used in the preparation of **5l**. The crude product was purified by flash chromatography on a 25-mm column using hexanes/EtOAc (1/1) and afforded 223 mg (70.8%) yield) of **5l** as a colorless solid: mp >300 °C; IR, 3200, 2980, 1730, 1695, 1490, 1350, 1250 cm^{-1}; ^1H NMR δ 9.47 (s, 2 H), 8.13 (s, 2 H) 2.93 (d, 4 H, J = 14 Hz), 1.78 (d, 2 H, J = 14 Hz), 1.15 (s, 6 H), 1.26 (m, 6 H) 1.12 (s, 12 H); high-resolution mass spectral analysis for $C_{36}H_{42}N_2O_8$ calcd 630.2941, found 630.2941.

1-Bromo-2,7-dihydroxyl Ester Diimide 5m. The procedure used in the preparation of **5f** was used except that 2-naphthol (1.0 equiv) was replaced with 59.8 mg (0.250 mmol 0.50 equiv) of 1-bromo-2,7-naphthalenediol[22] for the preparation of **5m**. The crude product was purified by flash chromatography on a 19-mm column using hexanes/EtOAc (2/1) and afforded 170 mg (52.3% yield) of **5m** as a colorless solid: mp >260 °C; IR, 3206, 3086, 2924, 1759, 1726, 1693, 1651, 1504, 1454, 1383, 1199, 1134, 1070, 746 cm^{-1}; ^1H NMR δ 7.91 (d, 1 H, J = 2 Hz), 7.82 (d, 1 H, J = 8 Hz), 7.80 (d, 1 H, J = 8 Hz), 7.69 (s, 1 H, N*H*), 7.64 (s, 1 H, N*H*), 7.25 (d, 1 H, J = 8 Hz), 7.21 (dd, 1 H, J_1 = 8 Hz, J_2 = 2 Hz), 2.91 (d, 2 H, J = 13 Hz), 2.87 (d, 2 H, J = 13 Hz), 2.09 (d, 2 H, J = 13 Hz), 1.49–1.33 (m, 24 H); high-resolution mass spectral analysis for $C_{34}H_{37}{}^{79}BrN_2O_8$ calcd 680.1733, found 680.1735.

***cis–trans*-1,3,5-Trimethyl-1,3,5-cyclohexanetricarboxylic Acid (7).** A solution of 100 g of the 60/40 mixture of cis–cis/cis–trans triesters (from above) in 50 mL of MeOH was added to a solution of 66.0 g of NaOH in 500 mL of H_2O. The mixture was heated at reflux for 6 h. After the solution was allowed to cool to room temperature, cis–cis triacid **3** (ca. 5 g) precipitated as the sodium salt and was removed by filtration. The filtrate was concentrated to ca. 250 mL and then acidified to pH 1.0 with concentrated aqueous HCl. The resulting 58/42 mixture of cis–cis/cis–trans triacid solids was collected by filtration. The mixture of triacids was added to 500 mL of Et_2O, stirred rapidly for 0.5 h, and then filtered again. The cis–trans triacid **7** was dissolved. The ether was concentrated, and more (ca. 50 g) cis–cis triacid **3** precipitated. After removal of **3**, the concentration, precipitation, and filtration sequence was repeated (ca. three times) until no more precipitate **3** formed (combined yield of 60 g of **3**). The remaining mother liquors were then concentrated to a solid. Acetone–soluble impurities were removed by trituration of the solid with acetone, leaving 15.0 g of cis–trans triacid **7** as a colorless solid: mp 241–245 °C (from EtOH) dec; IR, 3200–2200, 1690, 1466, 1406, 1290, 1182 cm^{-1}; ^1H NMR (pyridine-d_5) δ 11.110.6 (br s, 3 H, CO_2H), 3.32 (d, 1 H, J = 14.2 Hz), 2.72 (d, 2 H, J = 14.2 Hz), 2.57 (d, 2 H, J = 14.2 Hz), 1.80–1.61 (m, 10 H, including 1.73 (s, 3 H) and 1.66 (s, 6 H)). Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02; O, 37.17. Found: C, 55.68; H, 7.22; O, 37.10.

Cis–Trans Anhydride Acid 22. A mixture of 100 g (0.387 mol) of triacid **7** and a catalytic amount of *p*-toluenesulfonic acid (ca. 1 mg) in 700 mL of xylenes was heated at reflux, under N_2, for 12 h, while a Dean–Stark trap was used, and then allowed to cool to room temperature. To this solution was added 1000 mL of Et_2O, and **22** precipitated as a colorless powder (90.2 g, 97.0% yield): mp 270–280 °C (sublimed) dec; IR, 3200–2400, 1794, 1771, 1696, 1456, 1294, 1140, 1009 cm^{-1}; ^1H NMR (pyridine-d_5) δ 2.25 (d, 2 H, J = 14 Hz), 2.17 (d, 2 H, J = 14 Hz), 2.02 (d, 1 H, J = 14 Hz), 1.49 (s, 3 H), 1.35 (s, 6 H); high-resolution mass spectral analysis for $C_{12}H_{16}O_5$ calcd 240.0998, found 240.0999. Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71; O, 33.30. Found: C, 60.70; H, 7.09; O, 32.21.

Cis-Trans Imide Acid 8a. A solution of 500 mg (2.08 mmol) of anhydride acid **22** in 50 mL of dry pyridine was saturated with anhydrous ammonia. The mixture was then stirred for 2 h at room temperature and concentrated. The resulting solid was dissolved in 50 mL of trifluoroacetic anhydride, stirred for 2 h under N_2, and then poured onto 100 mL of cold H_2O. Colorless **8a** precipitated and was collected by filtration. After drying at 110 °C under vacuum, **8a** was obtained (423 mg, 84.9% yield) and used without further purification: mp >300 °C: IR, 3500–2500, 1763, 1693, 1385 cm^{-1}; ^1H NMR (pyridine-d_5) δ 12.5 (s, 1 H), 2.20 (d, 2 H, J = 13 Hz), 2.10 (d, 2 H, J = 13 Hz), 2.05 (d, 1 H, J = 13 Hz), 1.36 (s, 6 H), 1.34 (s, 3 H), 1.31 (d, 2 H, J = 13 Hz); high-resolution mass spectral analysis for $C_{12}H_{17}NO_4$ calcd 239.1157, found 239.1156.

Cis–Trans Imide Acid Chloride 8b. A 400-mg (1.67 mmol) sample of **8a** in 0.6 mL of $SOCl_2$ (8.35 mmol, 5.0 equiv) was heated at reflux for 2 h under N_2. The reaction was then concentrated. The resulting yellow solid was taken up in hot $CHCl_3$ and precipitated with hexanes as a colorless solid (370 mg, 85.8% yield): mp 170–175 °C; IR, 3350, 2970, 1730, 1690, 1200 cm^{-1}; ^1H NMR δ 7.79 (s, 1 H), 2.12 (d, 2 H, J = 14 Hz), 2.10 (d, 1 H, J = 14 Hz), 1.85 (d, 2 H, J = 14 Hz), 1.39 (s, 3 H), 1.3 (s, 6 H), 1.25 (d, 1 H, J = 14 Hz); high-resolution mass spectral analysis for $C_{12}H_{16}NO_3Cl$ calcd 257.0819, found 257.0820.

Cis–Trans Imide Methyl Ester 8c. To 50 mL of anhydrous MeOH was added 106 mg (0.411 mmol) of **8b**. The solution was stirred for 3 h under N_2 at room temperature and then concentrated. The product was purified by flash chromatography on a 19-mm column using 30% EtOAc in hexanes as eluent. This procedure afforded 72.9 mg (70.1% yield) of product as a solid: mp 135–136 °C; IR, 3188, 2952, 1718, 1685, 1439 cm^{-1}; ^1H NMR (pyridine-d_5) δ 12.5 (s, 1 H), 3.60 (s, 3 H) 2.12 (d, 2 H, J = 14 Hz), 1.92 (d, 1 H, J = 14 Hz), 1.80 (d, 2 H, J = 14 Hz), 1.80 (s, 3 H), 1.30 (s, 6 H), 1.25 (d, 2 H, J = 14 Hz); high-resolution mass spectral analysis for $C_{13}H_{19}NO_4$ calcd 253.1314, found 253.1315.

Cis–Trans Imide Amide Aniline 9a. A solution of 300 mg of **8b** (1.16 mmol) in 2.0 mL of CH_2Cl_2 was added to a stirred solution of 0.30 mL of aniline (3.29 mmol, 2.8 equiv) and a catalytic amount of DMAP in 8.0 mL of CH_2Cl_2. The reaction was stirred at room temperature, under N_2, for 8 h. The solution was diluted with CH_2Cl_2, washed with 10% aqueous HCl and saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The crude solid was purified by flash chromatography on a 19-mm column using 25% EtOAc in hexanes as eluent. This procedure afforded 292 mg (79.8% yield) as a colorless solid: mp 200–201 °C; IR, 3364, 3196, 3086, 2970, 1695 cm^{-1}; ^1H NMR δ 7.54 (dd, 2 H, J_1 = 7 Hz, J_2 = 1 Hz), 7.46 (dd, 1 H, J_1 = 7 Hz, J_2 = 1 Hz), 7.31 (s, 1 H), 7.30 (t, 2 H, J = 1 Hz), 2.19 (d, 1 H, J = 14 Hz), 2.06 (q, 4 H,

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J = 14 Hz), 1.50 (s, 3 H), 1.39 (s, 6 H), 1.20 (d, 1 H, J = 14 Hz); high-resolution mass spectral analysis for $C_{18}H_{22}N_2O_3$ calcd 314.1630, found 314.1630.

Cis-Trans Imide Amide Naphthalene 9b. A solution of 75.0 mg (0.291 mmol) of **8b** in 2.0 mL of CH_2Cl_2 was added to an ice cold solution of 129 mg (0.901 mmol, 3.1 equiv) of 2-aminonaphthalene in 2.0 mL of CH_2Cl_2, 1.25 mL of dry pyridine, and a catalytic amount of DMAP under N_2. After 1 h, the ice bath was removed and stirring continued for an additional 8 h. After workup and flash chromatography (described in **9a**), 79.7 mg of product **9b** (75.2% yield) was obtained as a colorless solid: mp 255-256 °C; IR, 3368, 3300, 1699, 1678, 1555, 1500 cm^{-1}; ^1H NMR δ 8.21 (s, 1 H), 7.88 (d, 1 H, J = 7 Hz), 7.79 (d, 1 H, J = 7 Hz), 7.45 (m, 3 H), 7.30 (s, 1 H), 2.15 (d, 1 H, J = 14 Hz), 2.05 (dd, 2 H, J = 7 Hz), 1.50 (m, 3 H), 1.45 (s, 3 H), 1.25 (ns, 6 H); high-resolution mass spectral analysis for $C_{22}H_{24}N_2O_3$ calcd 364.1787, found 364.1787.

Cis-Trans Imide Amide Anthracene 9c. A solution of 125 mg (0.485 mmol) of **8b** in 3.0 mL of $CHCl_3$ was added to a stirred solution of 103 mg (0.533 mmol, 1.1 equiv) of purified 2-aminoanthracene and a catalytic amount of DMAP in 8.0 mL of dry pyridine at room temperature. The reaction was stirred under N_2 for 10 h and then diluted with CH_2Cl_2. The solution was washed with 10% aqueous HCl and saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. Purification of the product by flash chromatography on a 19-mm column using 25% EtOAc in hexanes afforded 149 mg (74.1% yield) as a slightly yellow solid: mp > 300 °C; IR, 3337, 3244, 3100, 2924, 1670, 1550, 1377 cm^{-1}; ^1H NMR δ 8.37 (d, 2 H, J = 7 Hz), 8.36 (d, 2 H, J = 7 Hz), 7.97 (dd, 2 H, J_1 = 7 Hz, J_2 = 1 Hz), 7.26 (s, 1 H), 2.70 (d, 1 H, J = 14 Hz), 2.04 (q, 4 H, J = 7 Hz), 1.45 (s, 3 H), 1.36 (s, 6 H), 1.35 (m, 3 H); high-resolution mass spectral analysis for $C_{26}H_{26}N_2O_3$ calcd 414.1943, found 414.1945.

Cis-Trans Imide Amide Anthraquinone 9d. A solution of 96.8 mg (0.376 mmol) of imide acid chloride **8b** was added to an ice cold, magnetically stirred solution of 122 mg (0.546 mmol, 1.5 equiv) of purified 2-aminoanthraquinone and a catalytic amount of DMAP in 10.0 mL of dry pyridine under N_2. After 1 h, the ice bath was removed. Stirring was continued for 8 h, and then the reaction was diluted with CH_2Cl_2. The solution was washed with 10% aqueous HCl and saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. Purification of the product by flash chromatography on a 19-mm column using 25% EtOAc in hexanes as eluent afforded 128 mg (76.6% yield) of **9d** as a slightly yellow solid: mp > 300 °C; IR, 3350, 3200, 2950, 1772, 1716, 1695 cm^{-1}; ^1H NMR δ 8.31 (m, 5 H), 8.22 (d, 1 H, J = 1 Hz), 7.83 (s, 1 H), 7.81 (m, 2 H), 7.58 (s, 1 H), 2.32 (d, 2 H, J = 14 Hz), 2.15 (d, 2 H, J = 14 Hz), 2.02 (d, 2 H, J = 14 Hz), 1.58 (s, 6 H), 1.45 (s, 3 H), 1.30 (d, 1 H, J = 14 Hz); high-resolution mass spectral analysis for $C_{26}H_{24}N_2O_5$ calcd 444.1685, found 444.1685.

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Molecular Recognition with Convergent Functional Groups. 7. Energetics of Adenine Binding with Model Receptors

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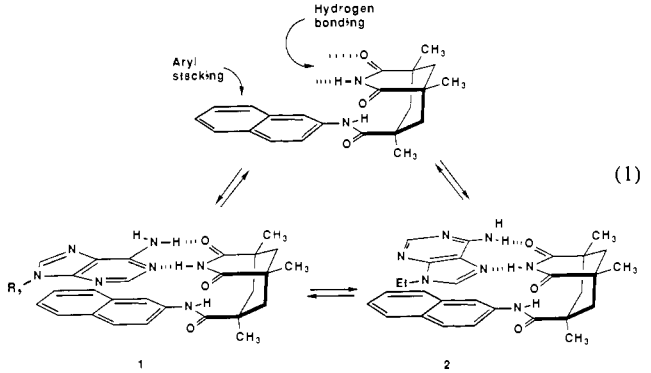
Abstract: The energetics of complexation for model receptors and adenine derivatives are reported. The new systems feature Watson-Crick, Hoogsteen, and bifurcated hydrogen bonding as well as aryl stacking interactions. These factors can act simultaneously on adenine derivatives because the model receptors present cleftlike shapes which are complementary to the surface of adenine. The association constants vary from 50 to 10^4 M^{-1} in solvents such as $CDCl_3$ that compete poorly for hydrogen bonds. The energetics of binding are explored as a function of receptor and guest structure, solvent, and temperature.

In the preceding paper we introduced a new type of receptor for adenine derivatives (eq 1) and gave evidence for structural features involved in its complexes,[1] The new systems are based



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on the U-shaped relationship between functional groups provided by Kemp's[2] triacid **3**, a feature that permits simultaneous binding through base pairing and aromatic stacking interactions. These forces converge from perpendicular directions and provide an ideal microenvironment for adenine derivatives. In this paper we explore the energetics of the binding event as a function of structure, solvent, temperature, and substrate.

Table I. Association Constants and Degree of Saturation Observed for the Binding of **10** to the Model Receptors ($CDCl_3$, 24 °C)

entry	receptor	K_a, M^{-1}	satrn, %
1	**4c**	50	65
2	**4d**	50	69
3	**5a**	101	79
4	**5b**	220	86
5	**5c**	440	96
6	**5d**	210[a]	96
7	**5e**	120[a]	98
8	**5f**	90	79
9	**5g**	125	76
10	**5h**	79	78
11	**5i**	64	77
12	**5j**	11000	96
13	**5k**	2500	~100
14	**5l**	2300	~100
15	**5m**	206	74
16	**8c**	50	65
17	**9a**	66	70
18	**9b**	54	69
19	**9c**	59	70

[a] Uncorrected for the presence of dimer.

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