Passive Template Effects and Active Acid–Base Involvement in Catalysis of Organic Reactions

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Abstract: A series of receptors were prepared all containing two adenine binding sites linked by various spacers. Their ability to act as templates in the coupling of two adenine derivatives, an active ester and an amine, in $CHCl_3$ was evaluated. The accelerations varied from none to 700-fold. Binding studies of the coupling product with these templates confirmed involvement of both binding sites. When the spacer was a 1,10-phenanthroline unit, an efficient hydrolysis reaction of the active ester was observed. Another series of receptors were prepared containing one adenine receptor and various polar functional groups. The molecules were evaluated as catalysts in the coupling of an adenine-derived active ester and *n*-butylamine. The orientation as well as the nature of the functional group greatly influenced the coupling rate. A carboxylate group was most effective, accelerating the intracomplex reaction 250-fold.

Keywords
adenine · catalysis · molecular recognition · template effects · transition states

Introduction

Bioorganic chemistry continues to be inspired by Nature's ability to catalyze reactions. For many bimolecular reactions gathering of substrates inside an enzyme's active site reduces large entropic barriers that are paid for by the binding energy of the substrates.[1] Reactions can be enhanced by this phenomenon alone, that is, by complementary surfaces orienting reactants favorably for reaction. Any catalyst of this sort is a template, and several synthetic model systems using various intermolecular forces for binding and recognition are available.[2] The increased rate with these catalysts is due to the reduction of *activation entropy* ($\Delta S^{\neq}$). Another feature of enzyme catalysis involves selective stabilization of the highest-energy transition state.[3] This reduces the *activation enthalpy* ($\Delta H^{\neq}$) of the reaction of bound substrates. Model systems that exhibit this feature are rarer, but the promise of model systems[4] is their capacity to isolate catalytic parameters ($\Delta H^{\neq}$, $\Delta S^{\neq}$), which can then be studied independently.

Advances in the field of molecular recognition have yielded many synthetic host–guest systems, but combining recognition with catalysis has proven especially challenging.[5] Receptors with high binding affinities are now available,[6] in which multiple additive interactions often lead to a well-defined geometry of the complex. Such a complex is a good starting point for the design of catalysts, since catalysis is very dependent on the three-dimensional positioning of functionality.[7] Hydrogen bonds are particular useful in molecular recognition, since their modestly directional nature is likely to produce predictable binding geometries. High affinities, however, require organic solvents since hydrogen bonds are weak in aqueous solutions. For catalytic purposes this is not a disadvantage. Poor solvation of polar functionality in organic solvents (as in some enzyme active sites) raises their chemical potential. Here we describe our efforts to explore separately the passive template effects and more active polar transition state stabilization by acids and bases as observed in covalent coupling reactions of amines and active esters as well as hydrolysis reactions.[8]

We rely on the molecular recognition of adenine for substrate binding, a system that has served us well in the past. The recognition event involves the chelation of the purine nucleus of adenosines by synthetic receptors based on Kemp's triacid and a carbazole spacer element.[9] High affinities of these receptors for adenine in nonpolar solvents result from the additive incremental effects of hydrogen bonding and aromatic stacking. Chelation of the purine nucleus between the imide functions results in an unambiguous geometry of the complex, allowing the position of catalytic groups or a reaction partner to be predicted with some confidence.

Results and Discussion

Template Catalysis in Bisubstrate Systems: The reaction we chose to study involves the aminolysis of an unusually reactive *p*-nitrophenyl (PNP) ester **2** by aminoadenosine **1** in $CHCl_3$ (Scheme 1). The ester **2** is about 10^3 times more reactive than *p*-nitrophenyl acetate under the same conditions. It is possible that intramolecular stabilization of the tetrahedral intermediate **3** by hydrogen bonding to the purine N3 nitrogen is the cause (see below).

A series of carbazole derivatives **5a–h** bearing two receptor sites separated by various spacers were prepared (Fig. 1). Two distinct synthetic pathways were used (Scheme 2). The first in-

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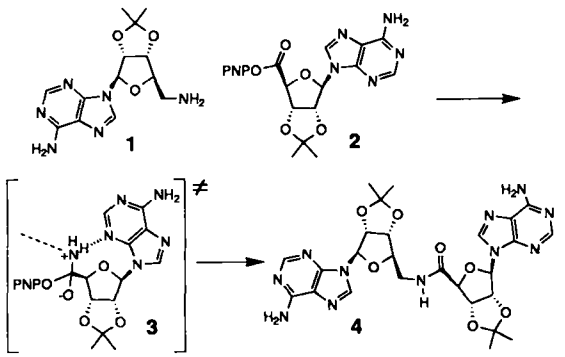


Scheme 1. Covalent coupling reaction used for the template studies.

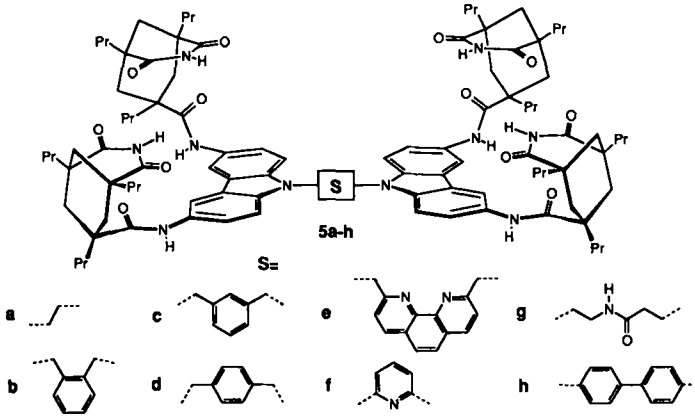
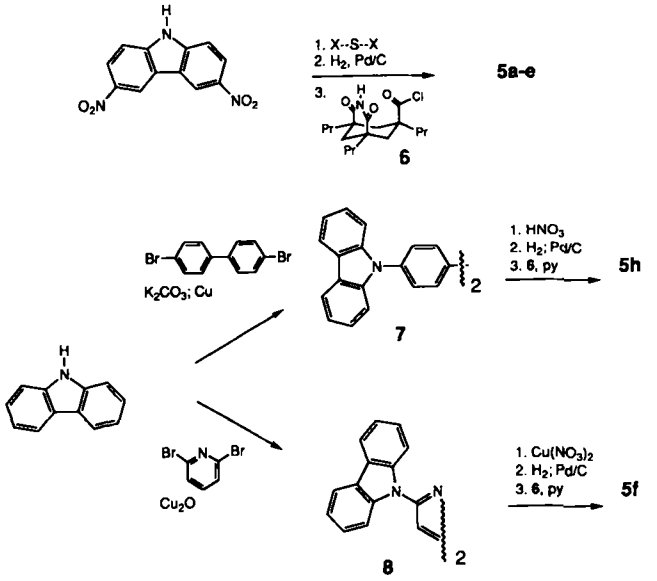


Fig. 1. Structures of the bis-receptors used as molecular templates.



Scheme 2. Synthesis of the bis-receptors.

volves alkylation of 3,6-dinitrocarbazole, followed by hydrogenation of the resulting tetranitro compound and coupling of the tetraamine with the Kemp's imide acid chloride **6**. The other uses an Ullmann coupling of aryl bromides to give a carbazole, followed by nitration to yield the tetranitro compounds. The only unsymmetrical template **5g** was obtained by a coupling of two different moieties as described earlier.[20]

The effect of these molecules (1 equiv) on the coupling rate of **1** and **2** (both at 0.05 mM concentrations) varied considerably

Table 1. Ratio (r) of the initial coupling rates of **1** + **2** (both at 0.05 mM) in the presence and absence of 1 equiv of potential templates (observed acceleration) and 4 mM NEt_3 at 25 °C in $CHCl_3$.

Entry	Template	r	Entry	Template	r
1	**5h**	1	5	**5b**	116
2	**5d**	1.2	6	**5f**	160
3	**5c**	5.4	7	**5a**	31
4	**5g**	10			

from no effect to a 160-fold acceleration (Table 1). Reactions were run in $CHCl_3$ at 25 °C in the presence of 4 mM NEt_3. Within experimental error, compounds **5h** and **5d** had no or little effect on the reaction rate. Significant catalytic activity was observed for **5c** and **5g**. The distance between the receptor sites for both these templates does not differ much from **5h**, but they are more flexible (their spacers have fewer bonds fixed in a coplanar arrangement), and more conformations can be accommodated. Rate accelerations of over 100-fold were observed with **5b** and **5f**. The spacers of these two templates are slightly shorter than the previous ones, and the bound reagents are likely to be held in closer proximity. They are also more rigid. While this feature was a drawback for the longer spacers, it becomes an advantage when the distance and shape are appropriate for a productive complexation. The rigidity of **5f** is obvious: it has only two rotatable bonds. The poor flexibility of **5b** arises from restricted and coupled rotations of its four single bonds. Finally, the shortest spacer of **5a** did not lead to a larger acceleration. Here, negative cooperativity between the two binding events may be the cause. The very short distance between the receptor sites may accommodate the two substrates only when the backbone is in an S-shaped conformation, that is, the reactive functions diverge, rather than converge, and inhibition of the reaction is expected.

The template activity of **5f** was studied in further detail. The 160-fold acceleration was reduced to 10-fold when 10 equiv of competitive binder 9-ethyladenine was added. Similarly, addition of 1 equiv of the coupling product reduced the initial rate acceleration to 7-fold, a feature that precludes efficient turnover in this system. Support for the presence of a termolecular complex **1**·**2**·**5f** that is responsible for the observed accelerations was obtained in experiments where more than 1 equiv of **5f** was added. For concentrations of **5f** beyond 1 equiv, the reaction rate *decreases*; the reagents are then separated on different template molecules (Fig. 2). This decrease is characteristic of the

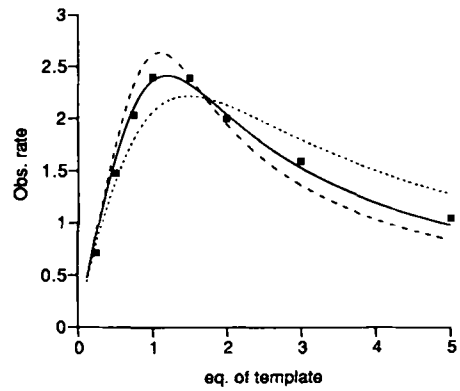


Fig. 2. Observed initial rate (10^{-6} M min^{-1}) of **1** + **2** vs. the amount of template **5f** (■). Calculated concentrations of productive complex **1**·**2**·**5f** using different binding affinities: ΔG = 6.6 kcal mol^{-1} (solid line), 5.9 kcal mol^{-1} (dotted line), and 7.2 kcal mol^{-1} (dashed line). Note that no vertical scale is represented for the calculated data as the scale is different for each line.

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termolecular mechanism, and should be expected in all such systems at high template concentrations.

Binding Studies: For templates to be effective they must be able to accommodate all the species they encounter along the reaction coordinate.[2a] One frequently observed phenomenon is that they are highly complementary to the product, causing—as is the case for our system—product inhibition and no turnover. In order to evaluate if there was a correlation between rate acceleration and binding to the product, we conducted the appropriate binding studies. Since the product of the coupling reaction **4** has a structure similar to the tetrahedral intermediate **3** and the corresponding transition state of its decomposition is rate determining,[15b] such a correlation seemed likely. Besides the similarity, the intermediate **3** differs from **4**, because its tetrahedral carbon orients the two purines differently, a feature which might be reflected in the binding affinity to the templates.

The binding constants of the molecules involved are very high, and we needed to employ UV spectroscopy for our affinity studies. The single adenine–receptor interactions have been previously determined by ^{1}H NMR titrations.[9a] This is not an ideal method because the high affinities (6–7 kcal mol^{-1}) require low host concentrations in order to obtain reliable data.[10] With ^{1}H NMR, relatively high concentrations are required for data collection whereas with UV spectroscopy the relevant data can be conveniently obtained at lower concentrations. On the other hand, UV does not give the structural information that ^{1}H NMR does. However, in the case at hand, this information was already available from previous work.[9] Stacking interactions of the aromatic moieties of our host and guest with our receptors is well established, and changes in the UV spectra on complexation were anticipated. Binding of an adenine derivative to the receptor resulted in a bathochromic shift of the carbazole absorption bands, and the largest absorbance increase was observed at 312 nm. Three adenine derivatives **10**, **11**, and **12** were selected, and their binding constants with the single receptor **9** were determined (Fig. 3). Next

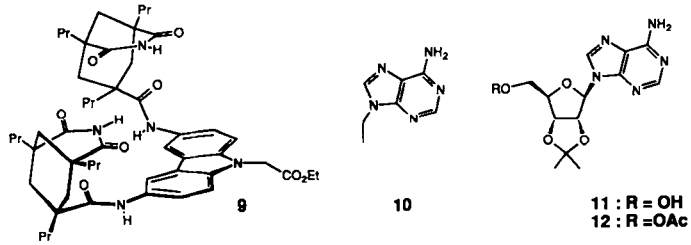

Fig. 3. Structures of molecules used in the binding studies.

the three templates **5b**, **5d**, and **5g** were titrated with **4**. They all had very different catalytic activity. Template **5b** was an effective catalysts accelerating the aminolysis 116-fold; **5d** was a moderate catalysts (10-fold acceleration), whereas **5g** was basically not a catalyst. All three systems contain the methylene bridge between spacer and carbazole, and therefore the same isolated carbazole chromophore (in contrast to, e.g., **5f**). The binding affinities are shown in Table 2. At 330 nm, the wavelength at which the aminolysis kinetics were measured, no absorbance changes due to enhanced binding occurred. The increases in absorbance at 312 nm when titrating the bis-receptors with **4** (entries 4–6) were roughly twice those found in the single adenine–receptor interaction (entries 1–3). This suggests that

Table 2. Association energy of bis- and mono-receptors as obtained from UV titrations in $CHCl_3$.

Entry	Receptor	Guest	$-\Delta G^{298}$ (kcal mol^{-1})
1	**9**	**10**	6.0
2	**9**	**11**	6.9
3	**9**	**12**	6.6
4	**5b**	**4**	9.8
5	**5d**	**4**	8.0
6	**5g**	**4**	8.3

both receptors are involved in the binding process (see Fig. 4). This notion is supported by the magnitude of the binding constants. The free energy of binding of adenine derivatives to receptor **9** is about 6 to 7 kcal mol^{-1}. The ribose-containing **11** and **12** both bind a little stronger than 9-ethyladenine **10**; the

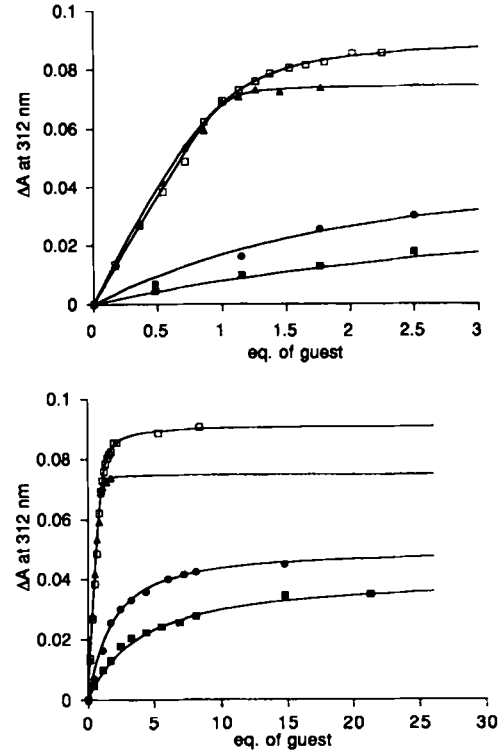

Fig. 4. Titration data and calculated lines of the following four titrations displayed with two different [guest] scales: **5g** + **4** (□), **5b** + **4** (▲), **9** + **12** (●), **9** + **10** (■). The concentration of all hosts was 1×10^{-5} M.

former might perhaps be benefitting from more van der Waals contacts. Binding of **4** by the bis-receptors is much stronger, in fact almost too strong to be accurately measured with these techniques. It was clear, however, that **5b** was the best receptor by over an order of magnitude. Since it was also the best catalyst in the aminolysis reaction, there does indeed seem to be a correlation between product binding and catalytic efficiency in this system. On the other hand, the correlation is not perfect; the binding constants for templates **5d** and **5g** are very similar, yet **5d** is basically not a catalyst, whereas **5g** is capable of accelerating the coupling reaction 10-fold.

Conformational Preferences in the Templates: The conformation of the adenine receptors is mostly determined by intramolecular hydrogen bonding between the two imides on a given carbazole.

This actually forms a small energetic barrier for the adenine binding. The conformation is deduced from the ^{1}H NMR spectrum of the bis-imides in $CDCl_3$, where the signal of the imide hydrogen appears at $\delta = 10.8$. This can be compared to $\delta = 7.6$ for a typical "free" imide in this solvent.[9a] Addition of adenines results in a downfield shift of this signal to $\delta \geq 13$. Most spectra of the adenine receptors show only broad signals, probably owing to additional intermolecular aggregation.[29]

The bis-receptor **5c** formed a notable exception to this usual pattern. The ^{1}H NMR spectrum of the free receptor is extremely sharp with an imide signal at $\delta = 7.6$. The receptor apparently folds itself into a sandwich conformation in which the carbazoles are stacked (Fig. 5). Two of the three different hydrogens

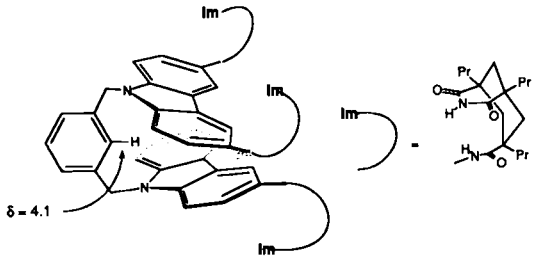

Fig. 5. Preferred conformation of template **1c**.

on the benzene ring can be found at a typical chemical shift ($\delta = 7.2$ and 7.3), whereas the aromatic hydrogen which is *in between* the carbazoles is shifted about 3 ppm *upfield* to $\delta = 4.1$. Its presence near the shielding faces of the aromatics is likely to be the cause of this shift. The signals of carbazole H1 and H4 are found at about 0.5 ppm upfield from the signals in comparable carbazole compounds, and in the UV spectrum of **5c** the main absorption band of carbazole appears at 293 nm compared to 286 nm for **5b** and **5d**. Both observations are consistent with some degree of intramolecular aromatic stacking. The sandwich conformation does not allow the intramolecular imide contacts. Surprisingly, the stacking apparently provides enough stabilization to prevent imide–imide contacts, since the unbound imide chemical shift is found at $\delta = 7.6$. It can not be excluded, however, that the amide bonds to the Kemp's imide units are hydrogen bonded to each other and provide additional stability to the conformation shown. Adenine binding is still possible because the imide signal moves to $\delta = 13$, as usual, with the addition of adenines. The template **5c** is only a modest catalyst for the coupling reaction. It is unlikely that the template can accommodate the compact tetrahedral intermediate **3** in the seemingly preorganized sandwich conformation. Rather, it may be advantageous for a different reaction.

Template Catalysis: A template-catalyzed reaction can be summarized as follows: 1) The template is able to bind the substrates, 2) it has a higher binding affinty for the highest transition state than the starting materials, and 3) it is complementary to all intermediates and other transition states along the reaction coordinate (otherwise new kinetic barriers are created). A template either accelerates a reaction or changes its normal (uncatalyzed) course in favor of a different product. In the present system a 160-fold rate enhancement has been achieved in an aminolysis reaction with a stoichiometric amount of template. No functional groups are present to stabilize the zwitterionic components of the tetrahedral intermediate.[11] The template possibly prevents the dissociation of the tetrahedral intermediate back to its free components by binding to the adenine units. If the breakdown of the tetrahedral intermediate to product is indeed rate-determing, as commonly assumed[15] for aminolysis reactions in organic solvents, then that means that a breakdown to starting materials is more favorable than to product. Another interpretation of the role of the template may then be that it is increasing the partitioning of the tetrahedral intermediate and thus increasing the odds of product formation. This could also be the case in self-replicating systems based on adenine recognition.[2m]

No matter what the provenance of the effects, the net result is that an otherwise bimolecular reaction is promoted to a unimolecular (intracomplex) one. Bringing two reagents in close proximity is not enough. This is shown by the lack of activity of **5d** and **5h**, which do not fulfill all three of the above-mentioned criteria. The geometrical factors of a template are of crucial importance in satisfying these conditions. The variable elements in the series of potential templates **5a–h** are: 1) the relative orientation of the two receptor sites induced by the spacer and the overall *shape* of the molecule; 2) the *distance* between the receptor sites associated with this shape; and 3) the *rigidity* of the molecule, or its propensity to retain a particular conformation corresponding to a particular shape and distance between sites.

Molecular modeling suggests that **5a–h** can all accommodate the tetrahedral intermediate in their cavities, but with conformations of the purines at the anomeric carbon that do not all allow the intramolecular stabilization of the ammonium ion by the purine N3. Thus, the ineffective templates prevent the reaction from proceeding along the most favorable reaction coordinate; they cause a new kinetic barrier. Only a few of the conformations of the tetrahedral intermediate result in a fast reaction, and only the templates complementary to these conformations can substantially accelerate the reaction. In other words, only templates that obey all three criteria will be catalysts. Our binding studies support this conclusion. Similar binding constants to the reaction product for **5d** and **5g** are not paralleled by similar catalytic activity. The relatively flexible **5g** is capable of accommodating not only the product, but also the reactive intermediates and transition states along the reaction coordinate. A consequence of this flexibility is also that **5g** is only a modest catalyst. With **5d** one must conclude that its ability to bind the product is accidental and not accompanied by a similar ability to bind the crucial intermediates and transition states.

The observed initial rates with various amounts of **5f** correlated well with the calculated concentration of termolecular complex **1·2·5f** (Fig. 2).[12] The fit was optimum for an association energy of 6.6 kcal mol^{-1}, consistent with the binding studies of the adenine–receptor interaction. At concentrations of 0.05 mM for each substrate, the receptor sites are not fully saturated with guests. With this binding energy, the calculated initial value of [**1·2·5f**] is 1.15×10^{-5} M for 1 equiv of **5f**, which leads to a corrected accelerating factor for the template-mediated reaction of 700-fold. An alternative description is based on effective molarity. At 1 equiv of template the initial rate is 2.4×10^{-6} M min^{-1}, and a termolecular complex concentration of 1.15×10^{-5} M can be calculated as before, which gives a "k_{cat}" of 0.21 min^{-1}. The background initial rate of 1.5×10^{-8} M min^{-1} and the initial concentrations of the reactants give $k_{uncat} = 6.0\,M^{-1}\,min^{-1}$. The ratio of k_{cat}/k_{uncat} gives an effective concentration of 35 mM, which can be compared to the 0.05 mM reactant concentration (a 700-fold increase in concentration).

Catalyzed Hydrolysis in $CHCl_3$: In our studies of the template effects we continually determined if the observed spectrophotometric increase (release of *p*-nitrophenolate) was due to aminol-

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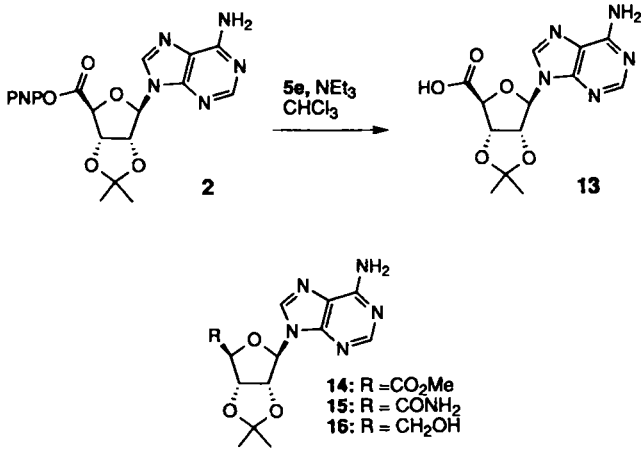
ysis rather than hydrolysis. This was accomplished by running the reactions with and without amine **1**. We observed no catalyzed hydrolysis except with **5e**, where almost the entire observed reaction was due to hydrolysis (Scheme 3). The catalyzed hydrolysis was about 100 times faster than the very slow background hydrolysis. When the water content of the $CHCl_3$ was increased to about 15–20 mM (by using a 1:1 ratio of "wet" and "dry" $CHCl_3$ as defined by Wilcox et al[13]) the observed rates increased about a factor of four, but the rate acceleration due to **5e** remained the same.



Scheme 3. Hydrolysis reaction catalyzed by **5e** and structure of additives.

The fact that binding was involved in the hydrolysis is supported by several observations: 1) No catalyzed hydrolysis was observed by 2,9-dimethyl-1,10-phenathroline (neocuproine); 2) competitive inhibition was observed with adenine derivatives containing nonprotic functional groups; and 3) a plot of rate acceleration vs. [**5e**] curves downward (i.e., exhibits saturation behavior). We propose that the catalytic effect of **5e** is due to the ability of the phenanthroline nitrogens to bind water and due to their basicity. They possibly also assist the water molecule in the attack. This type of binding is well established[14] and also reflected by the fact that neocuproine is sold only as the hydrate.

Intrigued by the fact that only one of the two binding sites was being used, we undertook experiments to evaluate the effect of other adenine derivatives as cocatalysts. The results are summarized in Table 3. Addition of 2 equiv of ester **14** resulted in a reduction of the acceleration to 80-fold, presumably due to competitive binding. However, when **15** and **16** (proton or hydrogen-bond donors) were added, accelerations were observed, overriding the competitive inhibition. The carboxylic acid **13**, which in the presence of excess NEt_3 is likely to be an ammonium carboxylate ion pair, slows the hydrolysis reaction by 10-fold. Part of this is due to nonspecific changes in solvation, since the same amount of benzoic acid also slows down the reaction by a factor of two. Since the substituents that were varied are constrained to converge on to the reaction center, it is tempting to ascribe their impact to transition state stabilization. The rate-limiting step in the hydrolysis is likely to be the attack by H_2O, which results in a build-up of negative charge in the transition state. The fact that proton sources, which can stabilize such a charge, are accelerating, while the repulsive negative charge of the carboxylate is counter-productive, is consistent with this picture.

Table 3. Rate accelerations (r) observed in the hydrolysis of **2** (0.05 mM) in the presence of several additives (2 equiv) and 4 mM NEt_3, in $CHCl_3$ containing 15–20 mM H_2O at 25 °C.

Entry	Equiv **5e**	Additive	r
1	–	–	1
2	1	–	100
3	1	**14**	80
4	1	**15**	200
5	1	**13**	10
6	1	**16**	130

Catalysis by Functional Groups: As previously stated, an alternative approach to template catalysis is the selective polar (or apolar) stabilization of the highest transition state by an array of complementary functional groups. In order to achieve this the position and orientation of the reaction center must be known and subject to control. We used the adenine receptor to position one purine-containing reactant, an electrophile, for reaction with an external reactant, an amine. Several derivatives of the receptors were synthesized, which position a functional group in various orientations, and we evaluated their effects on the reaction rates. It is well established for aminolysis reactions of active esters that molecules that can stabilize the ammonium group of the tetrahedral intermediate (hydrogen-bond donors) or help its deprotonation (bases, tautomeric catalysts) accelerate these reactions in organic solvents.[15] That is, the breakdown rather than the formation of the tetrahedral intermediate is rate-determining. If the ammonium portion of the zwitterionic intermediates loses a proton, expulsion of the negatively charged leaving group will lead to a neutral amide, rather than a high-energy protonated one.

The receptors **17a–i** used in this study and control compounds **18a–c** (Fig. 6) were synthesized according to Scheme 4. The specific reaction studied was the formation of amide **22** from *p*-nitrophenyl (PNP) adenosine ester **2** (0.05 mM) and *n*-butylamine (5 mM) in $CHCl_3$ (Scheme 5). Reactions were run under pseudo first-order conditions in the presence of excess amine and also NEt_3 (4 mM). It was established that k_{obs} only contains a first-order term in amine, that is, no second-order term in amine or first-order term in NEt_3 was observed. A plot

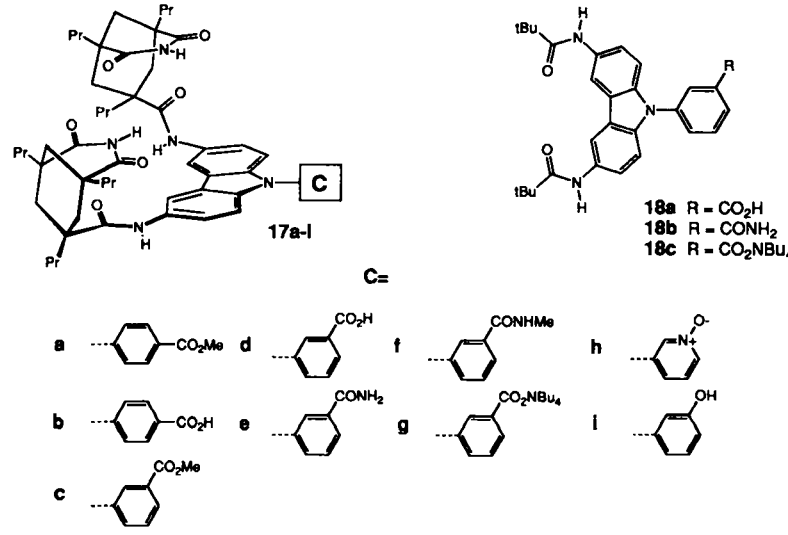
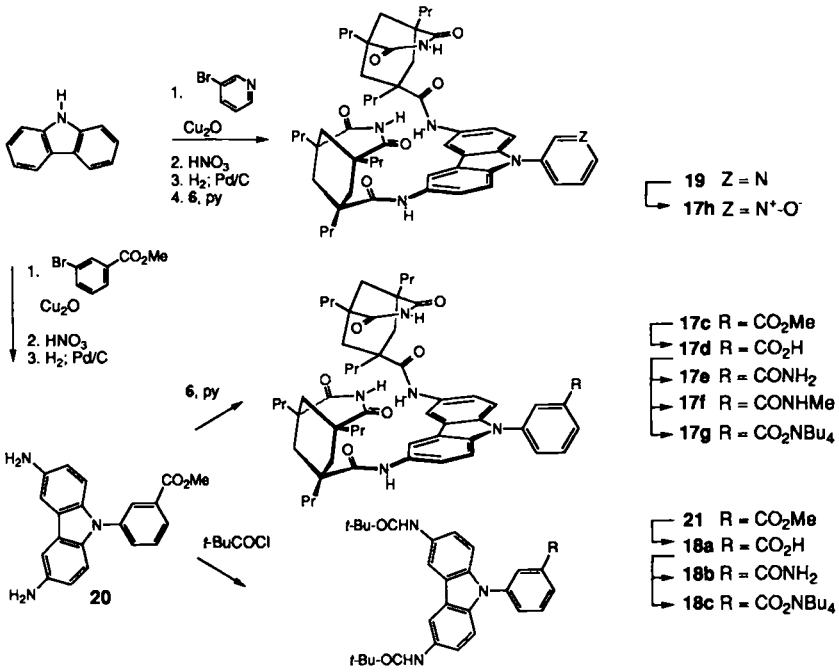
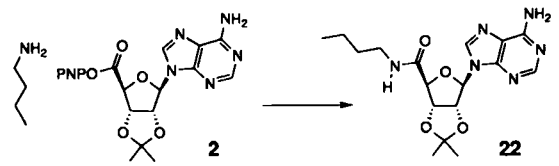


Fig. 6. Structures of the molecules used as catalysts and control compounds in the reaction of $BuNH_2$ and **2**.



Scheme 4. Synthesis of receptors and control compounds.



Scheme 5. Covalent coupling reaction used for the studies with the catalytic receptors.

of [amine] vs. k_{obs} gave a straight line, and no rate-dependency was seen on [NEt_3]. The system can be described by Equations (1) and (2):

$$\text{rate} = k_{obs}[\text{ester}] \quad (1)$$

$$k_{obs} = k_2[\text{amine}] \quad (2)$$

In presence of the receptors (1 equiv), accelerations of up to 100-fold were observed (see Table 4). Functional groups were placed on attached phenyl groups with orientation both *meta* and *para* to the carbazole. The *meta* substituents produced an increase in rates (entries 1–4). In entries 3–9 the functional groups are all in the *meta* position, and, since all the molecular complexes are expected to have practically the same geometry, the different activities of the carbonyl derivatives **17c–g** reflect their intrinsic catalytic ability in assisting in the breakdown of the tetrahedral intermediate.

Table 4. Ratio (r) of the initial rates for the butylaminolysis of **2** in the presence and absence of 0.05 mM (1 equiv) of various catalysts (observed acceleration) and NEt_3 (4 mM), at 25 °C in $CHCl_3$.

Entry	Catalyst	r	Entry	Catalyst	r
1	**17a**	1.2	6	**17f**	5
2	**17b**	2	7	**17g**	95
3	**17c**	3	7	**17h**	12
4	**17d**	8	9	**17i**	4
5	**17e**	5			

Ester carbonyls have weak hydrogen-bonding ability in chlorinated solvents,[16] and their effect on the rate was, accordingly, negligible. The more basic amides[17] show slightly higher activities. The *primary* amide **17e** is not measurably more active than the *trans secondary* amide **17f**; therefore, concerted or tautomeric catalysis by **17e** is unlikely, that is, either the carbonyl or the *anti* NH is involved, but not both.

The high activity of the carboxylate **17g** probably arises from its enhanced basicity. (The catalytic activity observed for the corresponding acid **17d** may be due to its partial deprotonation by the large amount of base present.) The well known acylation catalyst DMAP (4-dimethylaminopyridine) had no effect on the reaction rate as an external additive under our conditions.

The following results support the associative nature of the mechanism: 1) Control derivatives **18a–c** (1 equiv), which lack the recognition elements, had no effect on the reaction rate. 2) The presence of 100 equiv of benzamide did not result in a rate enhancement; this shows that the effective concentration of the amide group of **17e** in the complex is considerably higher than 100 times its actual concentration. This in contrast to generalized claims of acylation catalysis by amides.[18] 3) Lower reaction rates were observed in the presence of 9-ethyladenine **10**, as expected for a competitive inhibitor. For example, in the case of **17g**, the presence of 0.5 mM of **10** reduced the acceleration by an order of magnitude.

Polar Transition State Stabilization: The observed rate accelerations in this series can be traced to a single functional group. The most effective catalyst **17g** contains a carboxylate group.[19] In order to predict the most stable structure for the complex between **17g** and the reaction intermediate, molecular modeling was carried out. A 1000-step MacroModel/SUMM[20] conformational search using AMBER*[21] and GB/SA[22] $CHCl_3$ was undertaken. The most stable structure found allows for the simultaneous accommodation of two hydrogen bonds to the ammonium group, namely, an intramolecular bond from the N3 of the purine and an intracomplex bond from the carboxylate (see Fig. 7).

As stated earlier, the k_{obs} term contains a first-order term in amine. This is in contrast to earlier studies of the butylaminoly-

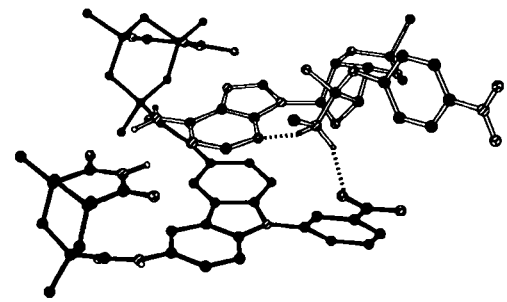


Fig. 7. Predicted structure of the complex between **17g** and the reaction intermediate. Carbon-bound hydrogens are not represented. The Monte-Carlo conformational search was carried out with methyl groups instead of propyl and butyl groups. The stereoconfiguration at the C5′ carbon of the adenosine was arbitrarily chosen. No counterion was used for the carboxylate.

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sis of *p*-nitrophenylacetate in chlorobenzene,[15a] which put forward the rate expression given in Equation (3):

$$k_{obs} = k_2[\text{amine}] + k_3[\text{amine}]^2 + k'_3[\text{amine}][\text{cat}] \quad (3)$$

where [cat] is a term for the concentration of added bases or hydrogen-bond acceptors. In that study the k_2 term was only observable at high temperatures or with secondary amines. The ester **2** is about 1000 times more reactive than *p*-nitrophenylacetate. This precludes a direct kinetic comparison under the same dilute conditions in $CHCl_3$. We have attributed this high reactivity to a stabilizing intramolecular contact of one of the ammonium hydrogens of the tetrahedral intermediate with N3 of the adenine. Simply stated, the purine N3 provides an intramolecular pathway for (partial) removal of the ammonium hydrogen thus avoiding the high-energy protonated amide product. This role is normally played by either a molecule of amine or by a catalyst, hence the higher order terms in the kinetics. The molecular modeling studies support a role for the purine N3. On the other hand, acylation reactions of the adenosine amine **1** show no special enhancement relative to butylamine, even though N3 could act in the same role, albeit in different conformational costumes.

The system follows simple second-order kinetics in both the catalyzed and the uncatalyzed reactions. In the uncatalyzed reaction, butylamine couples directly to the ester; in the catalyzed reaction, butylamine reacts with the ester–receptor complex. This allows a more direct analysis of electronic effects in the catalysis—in most model systems entropy effects dominate.[23]

The binding energy of the substrate can be measured independently. Titration of adenosine derivative **14** with receptor **17d** can be regarded as a model for all the *meta* carboxylic acid derivatives **17**. The binding energy was measured to be 5.9 kcal mol^{-1}, which means that 38% of the receptor sites are occupied by active ester under the reaction conditions. With this information a "corrected" intracomplex acceleration of 250-fold for **17g**, corresponding to an energy advantage of 3.3 kcal mol^{-1}, is estimated. This can be attributed entirely to the carboxylate–tetrahedral intermediate interaction[24] or, more precisely, the carboxylate–ammonium interaction, since only one functional group was varied. Similar calculations give 1.2 kcal mol^{-1} for the ester–ammonium interaction (using **17c**), 1.5 kcal mol^{-1} for the amide–ammonium interaction (using **17e** and **17f**), and 2.0 kcal mol^{-1} for the pyridine-*N*-oxide–ammonium interaction (using **17h**). Rate accelerations, however, do not reflect the interactions of the functional groups with the tetrahedral intermediate, but rather with the transition state of its decomposition. The structure of this transition state is not known, but is believed to be similar to the tetrahedral intermediate.[15a]

Conclusions

The aminolysis chemistry presented here shows two aspects of catalysis, which are both used by enzymes. The first involves overcoming entropic barriers and the second is based on transition-state stabilization. The synthetic templates described here promote a bimolecular reaction to a unimolecular (intracomplex) one. An increase in effective molarity of 700-fold has been achieved in the best case. Binding studies confirm the ability of both receptor sites to be involved in binding, and product binding is roughly paralleled by catalytic activity. Other bimolecular aminolysis reactions were accelerated by receptors containing several functional groups. The most effective group was a carboxylate, which is believed to interact by hydrogen bonding with the ammonium group of the collapsing tetrahedral intermediate. A 3.3 kcal mol^{-1} stabilization energy due to this interaction, as reflected in rate acceleration, was estimated.

With our present systems rate accelerations in aminolysis reactions of 700 and 250-fold have been achieved by template catalysis and transition-state stabilization, respectively. If these two features could be merged into one system, enzymatic reactivity, in a model system could be within reach. Desultory efforts towards this goal continue in our laboratories. In the meantime we note that if accelerations of the magnitude as described here can be achieved with enantioselective receptors[25] and racemic reactants, selective coupling reactions are to be expected.

Experimental Section

General: Infrared spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrophotometer. ^{1}H NMR spectra were measured with Bruker WM-250 (250 MHz), AC-250 (250 MHz), and Varian XL-300 (300 MHz), Unity 300 (300MHz). UV measurements were taken on a Perkin-Elmer Lambda 2 spectrophotometer. High-resolution mass spectra were obtained with a Finnegan Mat 8200 instrument. In the FAB mode (3-nitrobenzyl alcohol matrix) the molecular ion ($[M + H]^+$ or $[M]^+$) was almost invariably the most intense peak. Melting points were taken on a Electrothermal 9100 melting-point apparatus. Commercial-grade solvents were used without further purification with the exception of THF, which was distilled from Na/benzophenone ketyl, and $CHCl_3$ (J. T. Baker HPLC Reagent) was dried over molecular sieves unless stated otherwise. The following compounds were synthesized as previously published: **1**, **2**, and **4** [2o], **9** [9a] (methyl ester instead of ethyl ester), **17a,b** [26], **17i** [27], and **13** [28].

Ethyl bis-receptor 5a: To a suspension of 3,6-dinitrocarbazole (200 mg, 0.78 mmol) and 18-crown-6 (206 mg, 0.78 mmol) in anhydrous THF (10 mL) was added a solution of *t*BuOK in THF (1 M, 777 μL). The suspension turned to a deep red solution, and 1,2-dibromoethane (27 μL, 59 mg, 0.31 mmol) was added. The mixture was heated at reflux under Ar for 24 h. A precipitate formed, which was filtered, washed thoroughly with THF, and dried. It was identified by ^{1}H NMR as *N*,*N*′-ethylene-3,6,3′,6′-tetranitrodicarbazole. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.28 (s, 4H), 8.11 (d, J = 9.3 Hz, 4H), 7.31 (d, J = 9.1 Hz, 4H), 5.10 (s, 4H). This material (21 mg) and Pd/C (10%, 20 mg) were suspended in DMF (4 mL) and the mixture was stirred under balloon pressure of H_2 at 100 °C for 4 h at room temperature for 10 h. The catalyst was then filtered off and the filtrate was evaporated to dryness. The imide acid chloride **6** (60 mg, 4.5 equiv) was added, followed by pyridine (3 mL). The mixture was heated at reflux for 3 h, evaporated to dryness, and the residue was purified using column chromatography on silica gel eluting with MeOH/CH_2Cl_2. yielding 39 mg (8%) of a white solid: IR (KBr): $\tilde{\nu}$ = 3379, 3227, 2958, 2872, 1698, 1467, 1381, 1308, 1196, 802 cm^{-1}; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.42 (s, 4H), 9.12 (s, 4H), 7.97 (s, 4H), 7.25 (AB system, 8H), 4.80 (s, 4H), 2.69 (d, J = 13.4 Hz, 8H), 2.03 (d, J = 13.5 Hz, 4H), 1.79 (m, 8H), 1.60–1.00 (m, 52H), 0.88 (t, J = 6.7 Hz, 24H), 0.81 (t, J = 7.2 Hz, 12H); HRMS (FAB): *m/e* calcd for $C_{98}H_{133}N_{10}O_{12}$ (M + H): 1642.0104; found: 1642.0151.

***o*-Xylene bis-receptor 5b**: 3,6-Dinitrocarbazole (300 mg, 1.17 mmol), α,α′-dibromo-*o*-xylene (103 mg, 0.388 mmol), and K_2CO_3 (1.612 g, 11.67 mmol) were mixed in DMF (8 mL). The mixture was heated at 110 °C for 2 h. After cooling, the precipitate was filtered off and washed with cold DMF, H_2O, EtOH, and hexanes. The yellow tetranitrodicarbazole (198 mg, 83%) was obtained: ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.64 (s, 4H), 8.49 (d, J = 8.9 Hz, 4H), 7.98 (d, J = 9.1 Hz, 4H), 6.93 (brs, 2H), 6.25 (s, 4H), 6.03 (brs, 2H). Of this material 100 mg (0.16 mmol) was hydrogenated in DMF (60 mL) with Pd/C catalyst (10%, 175 mg) at room temperature for 14 h with a balloon of H_2. After removal of the catalyst and the solvent, the tetraamine was suspended in hexanes and filtered off (57 mg). All of this material was dissolved in pyridine (10 mL), after which imide acid chloride **6** (196 mg, 0.574 mmol, 5 equiv) and a catalytic amount of DMAP were added. The mixture was heated at reflux for 3 h. The solvent was then removed, and the residue chromatographed over silica gel using up to 4% MeOH in CH_2Cl_2. An off-white solid was obtained (84 mg, 25% overall yield): m.p. 253 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 3379, 3217, 2958, 1698, 1467, 1383, 1308, 1200 cm^{-1}; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.42 (s, 4H), 9.18 (s, 4H), 8.25 (s, 4H), 7.48 (s, 8H), 6.87–6.84 (m, 2H), 6.02 (brs, 2H), 5.92 (s, 4H), 2.67 (d, J = 13.9 Hz, 8H), 2.02 (J = 13.5 Hz, 4H), 1.83–1.75 (m, 8H), 1.60–1.00 (m, 52H), 0.95–0.85 (m, 36H); HRMS (FAB): *m/e* calcd for $C_{104}H_{137}N_{10}O_{12}$ (M + H): 1718.0418; found: 1718.0380.

***m*-Xylene bis-receptor 5c**: This compound was prepared by the same procedure as for **5b** starting with α,α′-dibromo-*m*-xylene. The corresponding tetranitrodicarbazole: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.32 (d, J = 2.0 Hz, 4H), 8.12 (dd, J = 9.1, 2.3 Hz, 4H), 7.54 (d, J = 9.1 Hz, 4H), 7.38 (t, J = 6.3 Hz, 1H), 7.29 (d,

J = 6.7 Hz, 2H), 5.89 (s, 1H), 5.69 (s, 4H). Bis-receptor **5c** was obtained in 40% overall yield as an off-white solid: m.p. 231 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 3379, 3219, 2958, 1698, 1467, 1198, 801 cm^{-1}; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.40 (s, 4H), 9.15 (s, 4H), 8.15 (s, 4H), 7.44 (s, 8H), 7.35 (s, 1H), 7.01 (t, J = 7.7 Hz, 1H), 6.71 (d, J = 7.7 Hz, 2H), 5.55 (s, 4H), 2.67 (d, J = 13.7 Hz, 8H), 2.02 (d, J = 12.2 Hz, 4H), 1.87–1.70 (m, 8H), 1.55–1.00 (m, 52H), 0.95–0.75 (m, 36H); HRMS (FAB): m/e calcd for $C_{104}H_{137}N_{10}O_{12}$ (M + H): 1718.0418; found: 1718.0380.

p-Xylene bis-receptor 5d: This compound was prepared by the same procedure as for **5b** starting with α,α'-dibromo-p-xylene. Owing to the low solubility of the tetranitrodicarbazole, the hydrogenation was run at 120 °C for the first 2 h. Bis-receptor **5d** was obtained in 10% overall yield as an off-white solid: m.p. 235 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 3379, 2958, 1698, 1467, 1308, 1197, 802 cm^{-1}; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.35 (s, 4H), 9.11 (s, 4H), 8.10 (s, 4H), 7.41 (s, 8H), 6.99 (s, 4H), 5.50 (s, 4H), 2.64 (d, J = 13.7 Hz, 8H), 2.01 (d, J = 13 Hz, 4H), 1.85–1.70 (m, 8H), 1.55–1.00 (m, 52H), 0.95–0.75 (m, 36H); HRMS (FAB): m/e calcd for $C_{104}H_{137}N_{10}O_{12}$ (M + H): 1718.0418; found: 1718.0363.

1,10-Phenanthroline bis-receptor 5e: 3,6-Dinitrocarbazole (1.061 g, 5.150 mmol) and K_2CO_3 (5.70 g, 41.2 mmol) were mixed in DMF (80 mL), and the mixture was stirred at 120 °C for 20 min. A DMF (5 mL) solution of 2,9-bis(chloromethyl)-1,10-phenanthroline (381 mg, 1.376 mmol) was added all at once, and the resulting mixture was maintained at 120 °C for 14 h. After cooling the precipitate was filtered off and washed with H_2O, EtOH, and hexanes. The yellowish tetranitro compound was obtained (930 mg, 94%); m.p. > 300 °C; IR (KBr): $\tilde{\nu}$ = 3420, 1628, 1602, 1588, 1509, 1474, 1336, 1199, 1101, 860, 822, 751, 720, 666 cm^{-1}; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.56 (d, J = 1.9 Hz, 4H), 8.40–8.30 (m, 2H), 8.37 (dd, J = 9.1 and 2.2 Hz, 4H), 8.05 (d, J = 9.1 Hz, 4H), 7.88 (s, 2H), 7.40 (d, J = 8.3 Hz, 2H), 6.23 (s, 4H); HRMS (EI): m/e calcd for $C_{38}H_{22}N_8O_8$: 718.1561; found: 718.1565. The tetranitrodicarbazole was hydrogenated and coupled as before and gave **5e** as a cream-colored solid (25% overall yield); m.p. 270 °C (dec.); IR (KBr): $\tilde{\nu}$ = 3379, 2958, 1698, 1466, 1197, 806 cm^{-1}; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.38 (s, 4H), 9.18 (s, 4H), 8.26 (d, J = 8.6 Hz, 2H), 8.23 (d, J = 1.7 Hz, 4H), 7.84 (s, 2H), 7.58 (d, J = 9.0 Hz, 4H), 7.47 (dd, J = 8.8, 1.6 Hz, 4H), 6.75 (d, J = 8.3 Hz, 2H), 6.14 (s, 4H), 2.67 (d, J = 13.7 Hz, 8H), 2.02 (d, J = 12.7 Hz, 4H), 1.92–1.70 (m, 8H), 1.55–1.00 (m, 52H), 0.95–0.85 (m, 36H); HRMS (FAB): m/e calcd for $C_{110}H_{139}N_{12}O_{12}$ (M + H): 1820.0635; found: 1820.0619.

***N,N'*-(2,6-pyridinylene)dicarbazole (8)**: A mixture of 2,6-dibromopyridine (1.0 g, 4.2 mmol), carbazole (2.8 g, 16.7 mmol), Cu_2O (2.7 g, 18.9 mmol), and xylenes (3 mL) were heated at reflux for 72 h. The mixture was cooled and toluene (40 mL) was added. The suspension was filtered, and the filtrate concentrated. The residue was then dissolved in boiling CCl_4 (minimum amount). Upon cooling a precipitate of carbazole formed, which was filtered off. The filtrate was concentrated and chromatographed on silica gel. It eluted with CCl_4 and yielded 0.60 g (35%) of **8**: m.p. 220 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.15 (d, J = 7.4 Hz, 4H), 8.14 (t, J = 7.8 Hz, 1H), 8.03 (d, J = 8.1 Hz, 4H), 7.65 (d, J = 7.9 Hz, 2H), 7.43 (t, J = 7.8 Hz, 4H), 7.34 (t, J = 7.3 Hz, 4H); IR (KBr): $\tilde{\nu}$ = 1599, 1570, 1452, 1331, 1223, 1188, 1151, 800, 742, 720 cm^{-1}; HRMS (EI): m/e calcd for $C_{29}H_{19}N_3$: 409.1579; found: 409.1569.

Pyridinyl bis-receptor 5f: A suspension of **8** (100 mg, 0.244 mmol) in AcOH/Ac_2O (1/2, 9 mL) was heated to 35 °C and $Cu(NO_3)_2 \cdot 2.5H_2O$ (0.70 g, 3.0 mmol) was added portionwise. After stirring at 35 °C for 24 h the mixture was poured onto ice water. The resulting solid was filtered off, washed with concentrated aqueous ammonia, followed by water, and dried over P_2O_5. The tetranitrodicarbazole was hydrogenated and coupled as before and gave **5f** as an off-white solid (6% overall yield): m.p. 257–259 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 10.40 (s, 4H), 9.28 (s, 4H), 8.36 (t, J = 8.0 Hz, 1H), 8.32 (s, 4H), 7.87 (d, J = 8.8 Hz, 4H), 7.78 (d, J = 7.9 Hz, 2H), 7.47 (d, J = 9.1 Hz, 4H), 2.69 (d, J = 13.4 Hz, 8H), 2.03 (d, J = 13.5 Hz, 4H), 1.79 (m, 8H), 1.60–1.00 (m, 52H), 0.88 (t, J = 6.7 Hz, 24H), 0.81 (t, J = 7.2 Hz, 12H); IR (KBr): $\tilde{\nu}$ = 3379, 2958, 1701, 1447, 1310, 1189, 803 cm^{-1}; HRMS (FAB): m/e calcd for $C_{101}H_{131}N_{11}O_{12}$ (M + H): 1691.0057; found: 1691.0149.

***N,N'*-(4,4'-biphenylene)dicarbazole (7)**: A mixture of 4,4'-dibromobiphenyl (3.0 g, 9.6 mmol), carbazole (4.1 g, 24.5 mmol), ground K_2CO_3 (3.3 g, 23.9 mmol), copper bronze (0.2 g, 3.1 mmol), and 1-methyl-2-pyrrolidinone (3 mL) was heated at 240 °C for 72 h. After cooling, toluene (40 mL) was added, and the suspension refluxed for 1 h, then cooled, and filtered through Celite. The filtrate was washed with water (3 × 100 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in boiling CCl_4 (minimum amount). Upon cooling, a precipitate of carbazole formed, which was filtered off. The filtrate was concentrated and chromatographed on silica gel. The product eluted with CCl_4. A white solid was obtained (2.5 g, 55%): m.p. 281 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.27 (d, J = 7.8 Hz, 4H), 8.10 (d, J = 8.4 Hz, 4H), 7.79 (d, J = 8.3 Hz, 4H), 7.48 (m, 8H), 7.29 (m, 4H); IR (KBr): $\tilde{\nu}$ = 1601, 1508, 1448, 1334, 1226, 828, 750, 718 cm^{-1}; HRMS (EI): m/e calcd for $C_{36}H_{24}N_2$: 484.1940; found: 484.1937.

Biphenyl bis-receptor 5h: A suspension of **5** (137 mg, 0.283 mmol) in AcOH/Ac_2O (1/2, 15 mL) was heated to 35 °C, and $Cu(NO_3)_2 \cdot 2.5H_2O$ (1.5 g, 6.4 mmol) was added portionwise. Stirring at 35 °C was continued for 96 h, and the suspension was poured onto ice. The solid was filtered off, washed with concentrated aqueous ammonia followed by water, and dried over P_2O_5. The tetranitrodicarbazole was hydrogenated and coupled as before to give **5h** as an off-white solid (7% overall yield): m.p. 310–315 °C (decomp.); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.39 (s, 4H), 9.25 (s, 4H), 8.33 (s, 4H), 8.10 (d, J = 8.1 Hz, 4H), 7.76 (d, J = 8.1 Hz, 4H), 7.51 (d, J = 9.3 Hz, 4H), 7.41 (d, J = 8.8 Hz, 4H), 2.69 (d, J = 13.4 Hz, 8H), 2.03 (d, J = 13.5 Hz, 4H), 1.79 (m, 8H), 1.60–1.00 (m, 52H), 0.88 (t, J = 6.7 Hz, 24H), 0.81 (t, J = 7.2 Hz, 12H); IR (KBr): $\tilde{\nu}$ = 3380, 3220, 2958, 1699, 1499, 1466, 1201, 805 cm^{-1}; HRMS (FAB): m/e calcd for $C_{108}H_{137}N_{10}O_{12}$ (M + H): 1766.0417; found: 1766.0402.

***N*-(3-(methoxycarbonyl)phenyl)-3,6-diaminocarbazole (20)**: Methyl 3-bromo-benzoate (2.67 g, 12.4 mmol), carbazole (2.08 g, 12.4 mmol), and Cu_2O (4.44 g, 31.03 mmol) were suspended in xylenes (4 mL). The mixture was heated at reflux under Ar for 26 h. After cooling to room temperature, CH_2Cl_2 (20 mL) was added. The suspension was filtered and the filtrate concentrated and chromatographed on silica gel with toluene/hexanes (4/6) yielding 3.02 g (81%) of *N*-(3-(methoxycarbonyl)phenyl)carbazole: m.p. 109 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (m, 1H), 8.15 (m, 3H), 7.79 (m, 1H), 7.70 (dd, J = 7.7, 7.7 Hz, 1H), 7.40 (m, 4H), 7.31 (m, 2H), 3.95 (s, 3H); IR (KBr): $\tilde{\nu}$ = 3052, 1722, 1587, 1495, 1448, 1290, 1264, 1223, 1081, 756 cm^{-1}; HRMS (EI): m/e calcd for $C_{20}H_{15}NO_2$: 301.1103; found: 301.1095. Some of this material (400 mg, 1.33 mmol) was suspended in AcOH (7 mL). The mixture was heated to 70 °C, and nitric acid (70%, 3.5 mL) was added dropwise. After stirring for 3 h at 70 °C, the suspension was cooled with an ice bath, and water was added. The yellow precipitate was filtered and dried. After dissolving it in DMF (10 mL), Pd/C (10%, 40 mg) was added. The suspension was shaken at room temperature under a H_2 atmosphere for 24 h. The catalyst filtered off using celite, and the filtrate was concentrated and chromatographed on silica gel with 2% MeOH in CH_2Cl_2 yielding 260 mg (59%) of **20**: m.p. 210–212 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.01 (t, J = 1.7 Hz, 1H), 7.94 (dt, J = 7.6, 1.4 Hz, 1H), 7.83 (m, 1H), 7.73 (dd, J = 7.8, 7.8 Hz, 1H), 7.11 (m, 4H), 6.70 (dd, J = 8.5, 2.1 Hz, 2H), 4.82 (brs, 4H), 3.88 (s, 3H); IR (KBr): $\tilde{\nu}$ = 3397, 3333, 3212, 1716, 1630, 1578, 1493, 1465, 1291, 1215, 1081, 808, 755 cm^{-1}.

Diimide ester 17c: A solution of diamine **20** (120 mg, 0.36 mmol) and imide acid chloride **6** (248 mg, 0.73 mmol) in pyridine (2 mL) was heated at reflux for 4 h. The pyridine was removed, and the residue was chromatographed on silica gel with 1.5% MeOH in CH_2Cl_2 to yield 305 mg (90%) of **17c**: IR (KBr): $\tilde{\nu}$ = 3223, 2957, 2871, 1693, 1491, 1466, 1292, 1200, 798 cm^{-1}; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 10.37 (s, 2H), 9.24 (s, 2H), 8.29 (d, J = 1.3 Hz, 2H), 8.07 (m, 2H), 7.93 (m, 1H), 7.83 (dd, J = 8.0, 8.0 Hz, 1H), 7.48 (dd, J = 8.9, 1.4 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 2.67 (d, J = 13.5 Hz, 4H), 2.03 (d, J = 11.9 Hz, 2H), 1.79 (m, 4H), 1.60–1.00 (m, 26H), 1.36 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 6.7 Hz, 12H), 0.81 (t, J = 7.3 Hz, 6H); HRMS (FAB): m/e calcd for $C_{56}H_{71}N_5O_8$ (M + H): 942.5318 found: 942.5381.

Diimide acid 17d: The methyl ester **17c** (300 mg, 0.32 mmol) was dissolved in EtOH/THF (1/1, 40 mL). A 1 N solution of NaOH (1.9 mL, 1.9 mmol) was added, and the mixture was stirred at room temperature for 24 h. The reaction was quenched with aqueous HCl (10%), and most of the EtOH and THF was removed in vacuo. Water (10 mL) was added, and the product was extracted with CH_2Cl_2 (30 mL). The organic phase was concentrated, and the residue was chromatographed on silica gel (15% MeOH/CH_2Cl_2) to give 271 mg (92%) of **17d**: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.34 (s, 2H), 9.23 (s, 2H), 8.27 (d, J = 1.5 Hz, 2H), 8.04 (m, 2H), 7.63 (m, 2H), 7.46 (dd, J = 8.7, 1.5 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 2.67 (d, J = 13.5 Hz, 4H), 2.03 (d, J = 11.9 Hz, 2H), 1.79 (m, 4H), 1.60–1.00 (m, 26H), 0.88 (t, J = 6.7 Hz, 12H), 0.81 (t, J = 7.3 Hz, 6H); IR (KBr): $\tilde{\nu}$ = 3378, 2959, 2872, 1700, 1466, 1400, 1295, 1198, 807 cm^{-1}; HRMS (FAB): m/e calcd for $C_{55}H_{70}N_5O_8$ (M + H): 928.5224; found: 928.5228.

Diimide tetrabutylammonium carboxylate 17g: Acid **17d** (50 mg, 0.054 mmol) was dissolved in CH_2Cl_2 (2 mL), and a 1 M solution of Bu_4NOH in THF (54 µL, 0.054 mmol) was added. The mixture was concentrated and the solid residue was dried under high vacuum over P_2O_5 to give **17d** in quantitative yield: IR (KBr): $\tilde{\nu}$ = 3383, 2959, 2872, 1700, 1570, 1466, 1364, 1293, 1182, 880, 806, 769 cm^{-1}; ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 10.40 (s, 2H), 9.23 (s, 2H), 8.29 (s, 2H), 7.92 (m, 2H), 7.50 (m, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 3.14 (m, 8H), 2.67 (d, J = 13.5 Hz, 4H), 2.03 (d, J = 11.9 Hz, 2H), 1.79 (m, 4H), 1.60–1.00 (m, 42H), 1.00–0.70 (m, 30H).

Diimide carboxamide 17e: The acid **17d** (100 mg, 0.11 mmol), pentafluorophenol (60 mg, 0.33 mmol), and DMAP (21 mg, 0.17 mmol) were dissolved in anhydrous THF (3 mL), and EDC (62 mg, 0.32 mmol) was added. The mixture was stirred at room temperature for 20 h. After cooling in an ice bath, anhydrous NH_3 was gently bubbled through for 10 min. It was then stirred at room temprature for 1 h, and concentrated. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with 1.2 N HCl (30 mL) followed by saturated $NaHCO_3$ solution (30 mL). The organic phase was concentrated and the residue was chromatographed on silica gel (15% MeOH/CH_2Cl_2) to give 58 mg (58%) of **17e**: IR (KBr): $\tilde{\nu}$ = 3377, 2958, 2871, 1699, 1522, 1466, 1387, 1293, 1198, 807 cm^{-1}; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.36 (s,

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2H), 9.23 (s, 2H), 8.30 (s, 2H), 8.14 (brs, 1H), 8.07 (m, 1H), 7.99 (m, 1H), 7.76 (m, 2H), 7.53 (brs, 1H), 7.48 (dd, J = 8.7, 1.2 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 2.67 (d, J = 13.5 Hz, 4H), 2.03 (d, J = 11.9 Hz, 2H), 1.79 (m, 4H), 1.60–1.00 (m, 26H), 0.88 (t, J = 6.7 Hz, 12H), 0.81 (t, J = 7.3 Hz, 6H); HRMS (FAB): *m/e* calcd for $C_{55}H_{70}N_6O_7$ (M + H): 927.5438; found: 927.5438.

Diimide methylamide 17f: Acid **17d** (100 mg, 0.11 mmol) was treated similarly as in the preparation of primary amide **17e**. Anhydrous methylamine was used instead of NH_3. Yield 86 mg (85%); IR (KBr): $\tilde{\nu}$ = 3378, 2959, 2872, 1700, 1654, 1534, 1488, 1293, 1198, 807 cm^{-1}; ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 10.35 (s, 2H), 9.23 (s, 2H), 8.60 (m, 1H), 8.30 (s, J = 1.8 Hz, 2H), 8.02 (s, 1H), 7.94 (m, 1H), 7.75 (m, 2H), 7.48 (dd, J = 8.7, 1.2 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 2.80 (d, J = 3.3 Hz, 3H), 2.67 (d, J = 13.5 Hz, 4H), 2.03 (d, J = 11.9 Hz, 2H), 1.79 (m, 4H), 1.60–1.00 (m, 26H), 0.88 (t, J = 6.7 Hz, 12H), 0.81 (t, J = 7.3 Hz, 6H); HRMS (FAB): *m/e* calcd for $C_{56}H_{72}N_6O_7$ (M + H): 941.5541; found: 941.5518.

***N*-(3-(Methoxycarbonyl)phenyl)-3,6-bis(*tert*-butylcarbonylamino)carbazole (21)**: To a solution of **20** (120 mg, 0.363 mmol) in THF (5 mL) at 0 °C were added NEt_3 (0.14 mL, 1.0 mmol) and trimethylacetyl chloride (0.13 mL, 1.1 mmol). The mixture was stirred at room temperature for 4 h and concentrated. The residue was chromatographed on silica gel (15% MeOH/CH_2Cl_2) to yield 175 mg (97%) of **21**: m.p. 255–257 °C; IR (KBr): $\tilde{\nu}$ = 3315, 2957, 1731, 1651, 1587, 1514, 1368, 1292, 1268, 1214, 870, 803, 754, 691 cm^{-1}; ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 9.31 (s, 2H), 8.48 (d, J = 1.5 Hz, 2H), 8.06 (m, 2H), 7.94 (m, 1H), 7.83 (dd, J = 8.1, 8.1 Hz, 1H), 7.57 (dd, J = 8.8, 1.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 1.27 (s, 18H); HRMS (EI): *m/e* calcd for $C_{30}H_{33}N_3O_4$: 499.2471; found: 499.2467.

***N*-(3-Carboxyphenyl)-3,6-bis(*tert*-buylcarbonylamino)carbazole (18a)**: Ester **21** was saponified following the same procedure as for ester **17c**. Yield 55%: m.p. 252 °C; IR (KBr): $\tilde{\nu}$ = 2964, 1654, 1534, 1489, 1384, 1303, 1211, 807 cm^{-1}; ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 9.31 (s, 2H), 8.48 (s, 2H), 8.04 (m, 2H), 7.75 (m, 2H), 7.57 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 1.27 (s, 18H); HRMS (EI): *m/e* calcd for $C_{29}H_{31}N_3O_4$: 485.2315; found: 485.2311.

***N*-(3-(Aminocarbonyl)phenyl)-3,6-bis(*tert*-butylcarbonylamino)carbazole (18b)**: The same procedure was used as for the preparation of primary amide **17e**. Acid **18a** (50 mg, 0.10 mmol) was used and the product was chromatographed on silica gel (2.5% MeOH/CH_2Cl_2) to give 38 mg (78%) of **18b**: m.p. 184–186 °C; IR (KBr): $\tilde{\nu}$ = 3332, 2960, 1654, 1528, 1489, 1397, 1209, 921, 808, 696 cm^{-1}; ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 9.29 (s, 2H), 8.49 (s , 2H), 8.14 (brs, 1H), 8.07 (s, 1H), 7.99 (m, 1H), 7.75 (m, 2H), 7.57 (d, J = 8.7 Hz, 2H), 7.54 (brs, 1H), 7.33 (d, J = 8.7 Hz, 2H), 1.28 (s, 18H); HRMS (EI): *m/e* calcd for $C_{29}H_{32}N_4O_3$: 484.2474; found: 484.2469.

Tetrabutylammonium salt (18c): The same procedure was used as for the preparation of **17g** starting from **18a** to give **18c** in quantitative yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.29 (s, 2H), 8.24–8.15 (m, 2H), 7.78 (s, 2H), 7.49 (t, J = 7.5 Hz, 1H), 7.43–7.37 (m, 3H), 7.32–7.25 (m, 2H), 3.24–3.15 (m, 8H), 1.60–1.20 (m, 34H) including 1.36 (s, 18H), 0.83 (t, J = 7.4 Hz, 12H).

Diimide pyridine (19): A mixture of 3-bromopyridine (2.46 g, 15.6 mmol), carbazole (2.62 g, 15.6 mmol), ground K_2CO_3 (2.38 g, 17.2 mmol), Cu powder (147 mg, 2.31 mmol), and 1-methyl-2-pyrrolidinone (5 mL) was heated at reflux for 24 h. After cooling, CH_2Cl_2 (200 mL) was added, and the suspension was filtered. The filtrate was washed with water (3 × 100 mL), dried ($MgSO_4$), and concentrated to give 2.2 g (58%) of *N*-(3-pyridinyl)carbazole: m.p. 111–113 °C; IR (KBr): $\tilde{\nu}$ = 1578, 1452, 1425, 1334, 1228, 1179, 1024, 804, 752, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.91 (s, 1H), 8.73 (d, J = 4.2 Hz, 1H), 8.16 (d, J = 7.8 Hz, 2H), 7.94 (d, J = 8.1 Hz, 1H), 7.58 (dd, J = 8.1, 5.1 Hz, 1H), 7.44 (dd, J = 7.7, 7.7 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 7.33 (dd, J = 7.2, 7.2 Hz, 2H); HRMS (EI): *m/e* calcd for $C_{17}H_{12}N_2$: 244.1001; found: 244.0999. A suspension of *N*-(3-pyridinyl)carbazole (400 mg, 1.64 mmol) in AcOH/Ac_2O (1/2, 12 mL) was heated at 35–40 °C, and $Cu(NO_3)_2 \cdot 2.5(H_2O)$ (0.8 g, 3.4 mmol) was added over 30 min. The mixture was stirred at 35–40 °C for 24 h. Water (50 mL) was added and stirring was continued for 30 min. The precipitated dinitrocarbazole was filtered, washed with concentrated aqueous ammonia followed by water, and dried. It was hydrogenated as in the preparation of **20** and the resulting diamine was coupled with imide acid chloride **6** as in the preparation of **17c**. Pyridine **19** was obtained as a beige solid: IR (KBr): $\tilde{\nu}$ = 3377, 3221, 2958, 2871, 1695, 1488, 1466, 1202, 805 cm^{-1}; ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 10.37 (s, 2H), 9.24 (s, 2H), 8.85 (d, J = 2.4 Hz, 1H), 8.71 (dd, J = 4.9, 1.3 Hz, 1H), 8.32 (d, J = 1.8 Hz, 2H), 8.08 (ddd, J = 8.3, 1.9, 1.9 Hz, 1H), 7.71 (dd, J = 8.1, 5.1 Hz, 1H), 7.48 (dd, J = 8.8, 1.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 2.67 (d, J = 13.5 Hz, 4H), 2.03 (d, J = 11.9 Hz, 2H), 1.79 (m, 4H), 1.60–1.00 (m, 26H), 0.88 (t, J = 6.7 Hz, 12H), 0.81 (t, J = 7.3 Hz, 6H); HRMS (FAB): *m/e* calcd for $C_{53}H_{68}N_6O_6$ (M + H): 885.5279; found: 885.5233.

Diimide pyridine *N*-oxide (17h): A solution of the pyridine **19** (75 mg, 0.085 mmol) and *m*-CPBA (70%, 21 mg, 0.085 mmol.) in $CHCl_3$ (2 mL) was stirred at room temperature for 48 h. After addition of $CHCl_3$ (20 mL), the organic layer was washed with saturated $NaHCO_3$ solution (20 mL), dried ($MgSO_4$) and concentrated. The residue was chromatographed on basic alumina with CH_2Cl_2/MeOH to yield, in addition to recovered **19** (12 mg), the *N*-oxide **17h** (32 mg, 42%): IR (KBr): $\tilde{\nu}$ = 3378, 2958, 2871, 1697, 1527, 1490, 1465, 1377, 1202, 1002, 805, 683 cm^{-1}; ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 10.38 (s, 2H), 9.25 (s, 2H), 8.59 (s, 1H), 8.35 (d, J = 6.0 Hz, 1H), 8.32 (d, J = 1.6 Hz, 2H), 7.65 (m, 2H), 7.50 (dd, J = 8.9, 1.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 2.67 (d, J = 13.5 Hz, 4H), 2.03 (d, J = 11.9 Hz, 2H), 1.79 (m, 4H), 1.60–1.00 (m, 26H), 0.87 (t, J = 6.7 Hz, 12H), 0.80 (t, J = 7.3 Hz, 6H); HRMS (FAB): *m/e* calcd for $C_{53}H_{68}N_6O_7$ (M + H): 901.5228 found: 901.5215.

Adenosine amide 15 was obtained by treating the active ester **2** [2o], prepared in situ, with anhydrous NH_3, followed by addition of EtOAC and washing with a saturated $NaHCO_3$ solution and brine. After drying ($MgSO_4$) and concentration the residue was triturated with $CHCl_3$ to give pure **15** (6% yield). No further fractions were pursued; m.p. 221–223 °C; IR (KBr): $\tilde{\nu}$ = 3411, 3304, 3180, 1687, 1654, 1424, 1381, 1208, 1094, 1061, 866 cm^{-1}; ^1H NMR (250 MHz, [D$_6$]acetone): δ = 8.17 (s, 1H), 8.13 (s, 1H), 7.05 (brs, 2H), 6.67 (br. s, 1H), 6.38 (brs, 1H), 6.29 (d, J = 2.0 Hz, 1H), 5.48–5.40 (m, 2H), 4.55 (d, J = 1.8 Hz, 1H), 1.57 (s, 3H), 1.37 (s, 3H). HRMS (EI): *m/e* calcd for $C_{13}H_{16}N_6O_4$: 320.1233; found: 320.1224.

Aminolysis kinetics: Typically, $CHCl_3$ solutions of the amine (125 μL, 0.4 mM adenosineamine or 40 mM $BuNH_2$), NEt_3 (125 μL, 32 mM), and other additives (template, catalyst, inhibitors) were mixed together in a quartz cuvette (1 cm pathlength). The volume was adjusted to 875 μL with $CHCl_3$, and a solution of active ester was added (125 μL, 0.4 mM). The cuvette was closed with a Teflon cap, shaken, and quickly transferred to the temperature-controlled (25 ± 0.1 °C) compartment of the spectrometer. The reaction was periodically monitored at 330 nm. The data were collected using the PECSS software package v. 4.2 (Perkin-Elmer). The reactions were generally followed to at least 80% completion. Initial rates were determined from the first 10% of reaction. Reactions were run in duplicate or triplicate and numbers were averaged. Reactions were run with and without amine nucleophile to ensure the *p*-nitrophenolate release was due to aminolysis rather than hydrolysis from residual water or undetected impurity.

Hydrolysis kinetics: The hydrolysis kinetics with **5e** were measured in the same way as the aminolysis kinetics except that no amine was added. The solvent consisted for 50% of "wet" $CHCl_3$ and 50% of "dry" $CHCl_3$ as defined by Wilcox et al [13].

Analysis of the product in the butylamine reaction: The UV data were confirmed by quenching a reaction with a large amount of MeOH and, after allowing it to stand for 20 min, analyzing the ratio of **22** to quenching product **14** by ^1H NMR in [D$_6$]DMSO. After 40 s, the aminolysis of **1** (0.05 mM) by $BuNH_2$ (5 mM) was over 95% completed in the presence of 1 equiv of **9** and only 5% in its absence. Ester **14**: m.p. 240–241 °C. IR (KBr): $\tilde{\nu}$ = 3306, 3319, 1726, 1672, 1600, 1582, 1088, 836, 664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.25, (s, 1H), 7.93, (s, 1H), 6.19 (s, 1H), 5.70 (dd, J = 6.0, 1.4 Hz, 1H), 5.52 (s, 2H), 5.50 (d, J = 6.0 Hz, 1H), 4.83 (s, 1H), 3.40 (s, 3H), 1.61 (s, 3H), 1.43 (s, 3H); HRMS (EI): *m/e* calcd for $C_{14}H_{17}N_3O_3$: 335.1230; found: 335.1220. Amide **22**: m.p. 154–155 °C; IR (KBr): $\tilde{\nu}$ = 3298, 3158, 2960, 1727, 1677, 1604, 1531, 1478, 1380, 1331, 1248, 1208, 1158, 1093, 1060, 870, 790 cm^{-1}; ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 8.25 (s, 1H), 8.08 (s, 1H), 7.52 (t, J = 5.4 Hz, 1H), 7.31 (s, 2H), 6.31 (s, 1H), 5.37 (m, 2H), 4.52 (s, 1H), 2.77 (m, 2H), 1.52 (s, 3H), 1.32, (s, 3H), 0.97 (m, 4H), 0.74 (t, J = 6.1 Hz, 3H); HRMS (EI): calcd for $C_{17}H_{24}N_6O_4$: 376.1859; found: 376.1857.

UV titrations: A 0.01 mM host solution in $CHCl_3$ was prepared. Guest solutions of equal concentration were prepared in both $CHCl_3$ and the host solution. Two cuvettes were placed in the double-beam spectrophotometer: one with the host solution and a reference cuvette containing an equal amount of $CHCl_3$. A spectrum was taken, and incremental guest additions were made to both the host solution cuvette (with the host containing guest solution) and the reference cuvette (with the $CHCl_3$ guest solution) until no further changes in the spectra occurred. From the collected data the absorbance changes at 312 nm were fitted to a 1:1 binding isotherm using a nonlinear least-squares regression.

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[29] Note added in proof (received April 21, 1995): Recent dilution experiments by Dr. Frank Würthner on carbazole-based receptors with small substituents at the carbazole nitrogen, such as compound **9**, indicate dimer formation in chloroform (K_a = 3000 M^{-1}). Therefore some peculiarities of these receptors at higher concentrations (downfield-shifted imide ^{1}H NMR signals, somewhat inconsistent binding data) are likely to be caused by dimerization rather than by intramolecular hydrogen bonding between the two imide groups. However, the experiments in this paper were performed at much lower concentrations, where dimer formation is not of importance.

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