

Intracomplex Catalysis of Acylation Reactions

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In a recent publication, we explored the role of geometrical factors in template enhanced reactions.¹ While proper positioning of reaction partners provides catalysis²—and even autocatalysis³—through lowering activation entropies, chemical catalysis with functional groups trained on the high-energy intermediates and transition states is the goal.⁴ Here, we report preliminary results of our screening various functionalities, as catalysts, in the context of amine acylation.

As before,¹ the system involves the positioning of adenine derivatives through the weak intermolecular forces of molecular recognition. The recognition event is the chelation of the purine nucleus of adenine by synthetic receptors based on Kemp's triacid and a carbazole spacer element. High affinities of these receptors for adenine in nonpolar solvents result from the additive incremental effects of hydrogen-bonding and aromatic stacking.⁵ Chelation of the purine nucleus between the imide functions results in a well-defined geometry of the complex, allowing the positioning of catalytic groups or a reaction partner with some predictability.

We studied the formation of amide **2** from *p*-nitrophenyl (PNP) adenosine ester **1** and *n*-butylamine in CHCl₃ (Scheme 1).⁶ The aminolysis of active esters in nonpolar media is believed to be rate-limited by the breakdown of a tetrahedral intermediate.⁷ Molecules that can stabilize the ammonium group of the intermediate (hydrogen bond donors) or help its deprotonation (bases, tautomeric catalysts) accelerate this reaction.^{8,9}

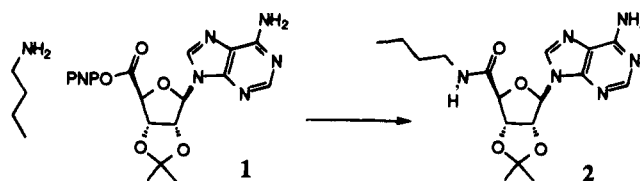
A series of receptors bearing various polar groups at different positions was prepared (see Table 1).¹⁰ In the presence of these

Table 1. Ratio between the Initial Rates (Calculated from the First 10% of Reaction) of the Butylaminolysis of **1** in the Presence and in the Absence of 0.05 mM Concentrations (1 Equiv) of Various Catalysts (Observed Acceleration)^a

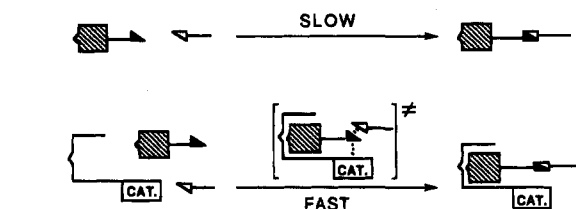
CAT.	Obs. Accel.	7	8	9	10	11
3	1.2	5	5	95	12	4
4	2					
5	3					
6	8					

^a Standard deviations are ±20%.

Scheme 1



Scheme 2



molecules (1 equiv), accelerations of up to 100-fold were observed.¹¹ These accelerations were interpreted as the result of the high effective molarities of the catalytic functions in the complex. This mechanism is depicted in Scheme 2. The receptor has a better complementarity for the reaction intermediate (or the rate-determining transition state) than for the reagent or product.

The following results support the associative nature of the mechanism. Firstly, control derivatives **12–14** (1 equiv), which lack the recognition elements, had no effect on the reaction. Secondly, the presence of 100 equiv of benzamide did not result in a rate enhancement, showing that the effective concentration of the amide group of **7** in the complex is considerably higher than 100 times its actual concentration. Thirdly, lower reaction

(11) For all compounds **3–14**, no release of *p*-nitrophenol was observed in the absence of amine nucleophile, showing that hydrolysis from residual water is small and that, in the case of **9**, no mixed anhydride forms between the carboxylate and the active ester.

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 (6) Unless specified, all reactions were performed at 25 °C, in the presence of [Et₃N] = 4 mM, and with [1] = 0.05 mM and [BuNH₂] = 5 mM. Under these conditions, the reaction proceeds at an initial rate of 6.8 × 10⁻⁷ Mmin⁻¹. For experimental details, see: Pieters, R. J.; Huc, I.; Rebek, J., Jr. *Tetrahedron*, in press.
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 (9) However, these accelerations are not observed unless relatively high concentrations of "catalyst" are used, generally several hundred times higher than those of the reagents (see ref 8).
 (10) For typical synthetic procedures, see: Kato, Y.; Conn, M. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 3279. All new compounds were characterized by ¹H NMR, HRMS, and IR. Experimental details will be published elsewhere.

rates were observed in the presence of competitive binder 9-ethyladenine. For example, in the case of **9**, the presence of [9-Et-Ad] = 0.5 mM reduced the acceleration by 1 order of magnitude.

Since all the molecular complexes are expected to have the same geometry, the different activities of the carbonyl derivatives **5–9** reflect their intrinsic ability to stabilize the transition state for the breakdown of the intermediate. Ester carbonyls have weak hydrogen-bonding ability in chlorinated solvents;¹² the more basic amides¹³ show slightly higher activities. The primary amide **7** is not measurably more active than the trans secondary amide **8**; therefore, concerted or tautomeric catalysis by **7** is unlikely. The high activity of the carboxylate **9**¹⁴ likely arises from its enhanced basicity.¹⁵ The catalytic activity observed for the corresponding acid **6** may be attributed to its partial deprotonation by the large amount of base present. The lower activity of para-substituted derivatives **3** and **4** illustrates the importance of positioning the catalytic groups in a complex of favorable geometry.

Based on these observations, we propose that a complex of **9** and the reaction intermediate, as shown in Figure 1, is responsible for the observed acceleration. For **9**, hydrogen-bonding to the ammonium group of the intermediate is compatible with the adenine–receptor interaction. This hydrogen bond is not possible with **4**; these interactions are not additive and

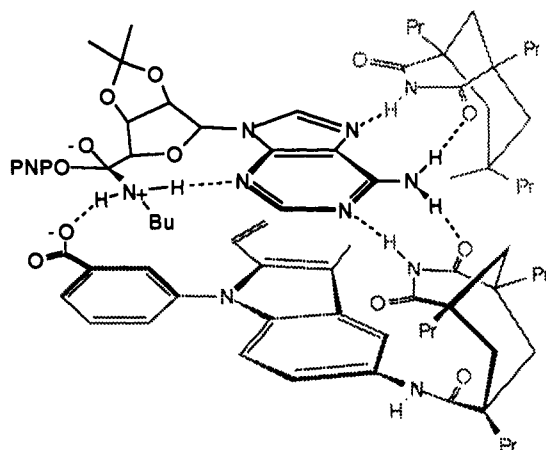


Figure 1. Proposed structure of the complex of **9** and the reaction intermediate.

do not result in a specific stabilization of the intermediate. The additional contact with N₃ of the adenine is postulated to account for the unusually high reactivity of the PNP ester.¹

In summary, significant rate enhancements result from the high effective molarities of catalytic groups in a reagent–receptor complex. The relative positioning of the guest reagent and the catalytic function determines the efficiency of the catalysis. Ultimately our goal is to merge recognition and catalysis—in space as well as time—to approach the Pauling principle of maximum binding to transition states.¹⁶

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(14) The UV data were confirmed by ¹H NMR: integrations showed that after 40 s, the aminolysis of **1** (0.05 mM) by BuNH₂ (5 mM) was over 95% completed in the presence of 1 equiv of **9** and only 5% in its absence.

(15) As the pK_a values of a carboxylic acid and an ammonium are much closer to equality in aprotic nonpolar media than in water (Kokesh, F. C.; Westheimer, F. H. *J. Am. Chem. Soc.* **1971**, *93*, 7270), the formation of a low-barrier hydrogen bond may be responsible for the observed acceleration. See: (a) Cleland, W. W.; Kreevoy, M. M. *Science* **1994**, *264*, 1887. (b) Frey, P. A.; Whitt, S. A.; Tobin, J. B. *Ibid.* **1994**, *264*, 1927. (c) We note that only the less basic syn lone pair of the oxygen can reach the ammonium group. Grandour, R. D. *Biorg. Chem.* **1981**, *10*, 169.

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