Systematic studies along these lines are under way in our laboratory.

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Supplementary Material Available: Drawings of the cryostat, description of the matrix deposition procedure, and IR spectra of 1-adamantyl cation, the two precursor chlorides **3** and **4**, and cyclohexanone-pentafluoroantimony (4 pages). Ordering information is given on any current masthead page.

A Bisubstrate Reaction Template

T. Ross Kelly,* Chen Zhao, and Gary J. Bridger

Department of Chemistry, Boston College
Chestnut Hill, Massachusetts 02167

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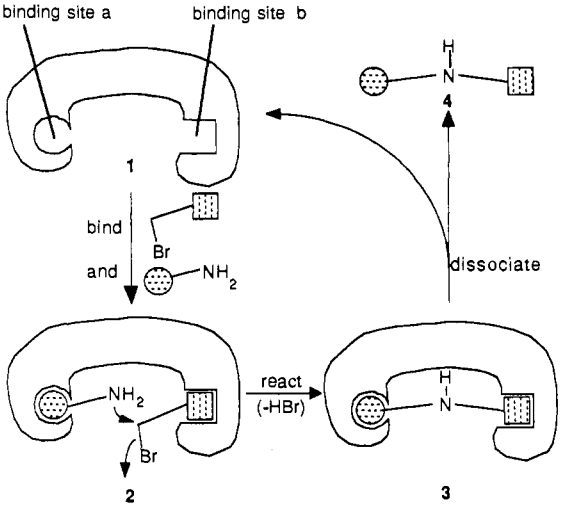
The ability to construct artificial "enzymes" for which there are no natural counterparts would render possible innumerable chemical transformations that are beyond the reach of current methodology.[1] Natural enzymes in part[2] exploit the kinetic advantage[5] of converting normally intermolecular reactions into intramolecular ones by binding substrate(s) prior to the commencement of bond reorganization. To date,[6] studies in the area of artificial enzymes have focussed almost exclusively on processes involving a single substrate, with bond cleavage being the dominant theme; the serine protease mimics of Cram[6c,7b] and Breslow[6d,7a] are prominent examples.

Scheme I



We now report the first[8] example of a fully synthetic system wherein *two* organic substrates are bound simultaneously—but temporarily—by a designed[8b] receptor possessing two binding sites, and reaction *between* the two substrates is accelerated because of this transient intramolecularity.[5] The system is rudimentary at present, but it demonstrates the validity of the basic concept.

The mechanistically straightforward S_N2 alkylation of an amine by an alkyl halide was selected for initial study. The overall process is represented in general terms in Scheme I: the ditopic receptor **1** binds the two substrates, giving the ternary complex **2** and placing the two potentially interacting functional groups in relative proximity to each other. Bond formation (→ **3**) followed by dissociation of the template-product complex (**3**) completes the process. Scheme II supplies molecular detail. The specifics of **5**–**8** were designed using CPK models, taking into account synthetic accessibility and solubility in nonpolar organic solvents (which would not interfere with the requisite hydrogen bonding[10] between template and substrates). For initial simplicity the binding sites a and b of **1** are identical in **5**, but such identity is not required (nor, ultimately, desirable). It was hoped that **5** (and **8**) possessed a satisfactory balance between conformational flexibility and preorganization[11] such that any imprecisions in design, although perhaps debilitating, would not be fatal. The synthesis of **5** relies heavily on recent developments in organopalladium chemistry[12,13,15] and is outlined in Scheme III; the two substrates were prepared from **11**[16] as indicated.

(1) For some possible long term applications, see: Drexler, K. E. *Engines of Creation*; Anchor Press/Doubleday: Garden City, NY, 1986.

(2) Pauling's proposal[3] that, in addition to rendering reactions effectively intramolecular, enzymes also selectively stabilize transition states is widely—but not universally[4]—accepted. (a) For a recent discussion, see: Kraut, J. *Science (Washington, D.C.)* **1988**, *242*, 553-540. See, also: (b) Jencks, W. P. *Cold Spring Harbor Symposia on Quantitative Biology* **1987**, *52*, 65-73. (c) Fersht, A. *Enzyme Structure and Mechanism*, 2nd ed.; W. H. Freeman: New York, 1985.

(3) Pauling, L. *Chem. Eng. News* **1946**, *24*, 1375. See, also: Haldane, J. B. S. *Enzymes*; Longmans, Green and Co.: London, 1930; p 182.

(4) For a recent summary, see: (a) Page, M. I. In *Enzyme Mechanisms*; Page, M. I., Williams, A., Eds.; Royal Society of Chemistry: London, 1987; pp 1-13. (b) See, also: Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128-134.

(5) (a) Page, M. I. *Chem. Soc. Rev.* **1973**, *2*, 295-323. (b) Jencks, W. P. *Adv. Enzymol.* **1975**, *43*, 219-410.

(6) (a) For a review, see: Tabushi, I. *Tetrahedron* **1984**, *40*, 269-292. Among more recent *leading* references to this burgeoning field, see: (b) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89-112. (c) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009-1020. (d) Breslow, R. *Adv. Enzymol.* **1986**, *58*, 1-60. (e) Rebek, J., Jr. *Science (Washington, D.C.)* **1987**, *235*, 1478-1484. (f) Wolfe, J.; Nemeth, D.; Costero, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 983-984. (g) Lutter, H. D.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1125-1127. (h) Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362-386. (i) Menger, F. M.; Whitesell, L. G. *J. Am. Chem. Soc.* **1985**, *107*, 707-708. (j) Sasaki, S.; Shionoya, M.; Koga, K. *J. Am. Chem. Soc.* **1985**, *107*, 3371-3372. (k) Klotz, I. M. in ref 4a, pp 14-34. (l) Stoddart, J. F. in ref 4a, pp 35-55. (m) Bender, M. L. in ref 4a, pp 56-66. (n) Kirby, A. J. in ref 4a, pp 67-77. (o) Corey, E. J. *Chem. Soc. Rev.* **1988**, *17*, 111-133. (p) Note, also: Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1987**, *109*, 3145-3146. (q) A number of other highly relevant papers (presented at the *International Symposium of Bioorganic Chemistry*; New York, May 1985) are assembled in the following: *Ann. N.Y. Acad. Sci.* **1986**, *471*, 1-325.

(7) (a) Trainor, G. L.; Breslow, R. *J. Am. Chem. Soc.* **1981**, *103*, 154-158. Breslow, R.; Trainor, G. L.; Veno, A. *J. Am. Chem. Soc.* **1983**, *105*, 2739-44. (b) Cram, D. J.; Katz, H. E. *J. Am. Chem. Soc.* **1983**, *105*, 135-137. Cram, D. J.; Lam, P. Y.-S. *Tetrahedron* **1986**, *42*, 1607-1615.

(8) (a) An aza crown ether which sequentially (rather than simultaneously) operates on two substrates (by a "ping pong"[9] mechanism) has been reported by Lehn and colleagues (Lehn, J.-M. *Ann. N.Y. Acad. Sci.* **1986**, *471*, 41-50, and references therein). (b) For "undesigned" hosts which promote bimolecular reactions, see: Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816-7817. Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Manimaran, T. L. *J. Org. Chem.* **1983**, *48*, 3619-3620.

(9) Walsh, C. *Enzymatic Reaction Mechanisms*; W. H. Freeman: New York, 1979; pp 220-222. See, also: ref 2c, pp 114-119, and references therein.

(10) For earlier studies of receptor-substrate binding from this laboratory, see: Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549-6551. Kelly, T. R.; Bilodeau, M. T.; Bridger, G. J.; Zhao, C. *Tetrahedron Lett.*, in press.

(11) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039-1057.

(12) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513-519. (b) Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 5997-6000.

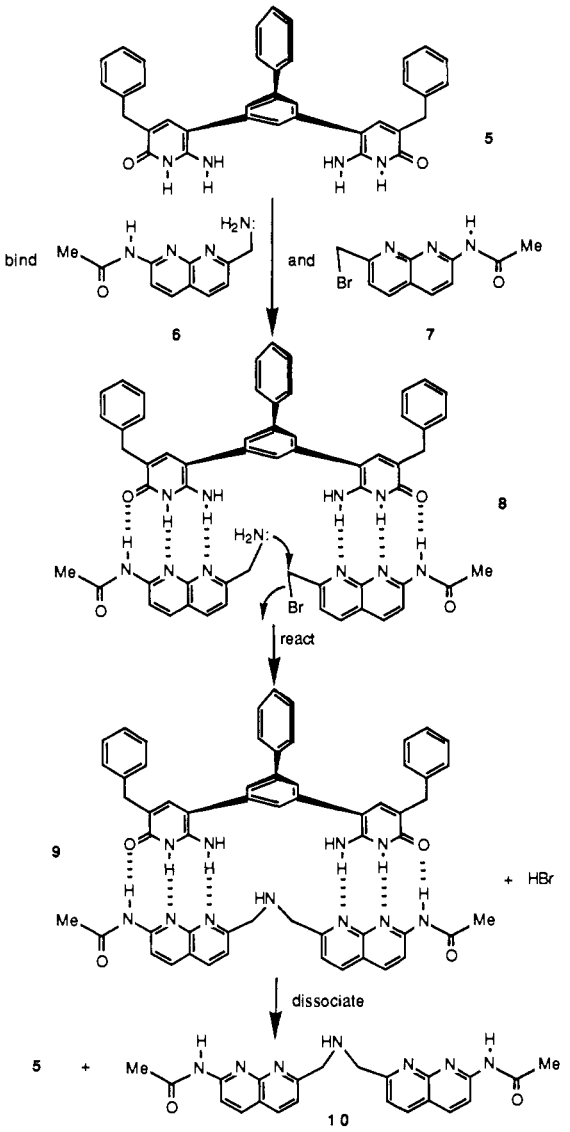
(13) Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49-58.

(14) Robison, M. M.; Robison, B. L. *J. Am. Chem. Soc.* **1955**, *77*, 457-460.

(15) (a) Bailey, T. R. *Tetrahedron Lett.* **1986**, *27*, 4407-4410. (b) Kosugi, M.; Koshiba, M.; Atoh, A.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 677-679. (c) Malstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992-4998.

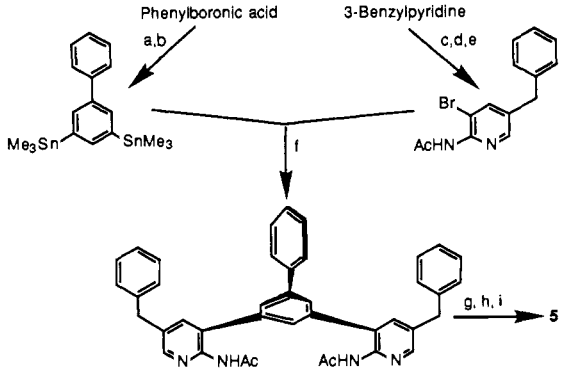
0002-7863/89/1511-3744$01.50/0

Scheme II

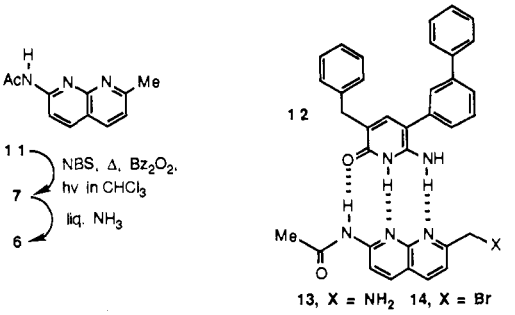


Kinetic measurements demonstrate that **5** promotes reaction between **6** and **7**, and both kinetic and binding studies are consistent with involvement of ternary complex **8**. In particular, the rate for the reaction between **6** and **7** (each 0.0040 M in $CDCl_3$) is accelerated by a factor of six if **5** (0.0040 M) is also included;[17] in both cases **10** precipitates as its HBr salt during the course of reaction. That the rate enhancement is not due to catalysis by some subunit of **5** was established by showing that addition of either 1 or 2 equiv of **12** to a $CDCl_3$ solution 0.020 M in both **6** and **7** does not itself affect the rate of reaction between **6** and **7**. Titration of **5** with **11**[18] confirms that **5** is capable of simultaneously binding two substrate molecules.[19] Binding constants ($CDCl_3$) of 1.2×10^4 (±10%) M^{-1} for **13** (**6**·**12**) and 1.7×10^4 (±10%) M^{-1} for **14** (**7**·**12**) indicate that ternary complex **8** is a major constituent in a mixture of **5**, **6**, and **7** under the reaction conditions.

Scheme III[a]



[a] (a) 1.2 equiv of 1,3,5-tribromobenzene, 2 mol % $Pd(PPh_3)_4$, toluene/H_2O/EtOH, 90 °C, 8 h;[12] 67%. (b) 2.5 equiv of $(Me_3Sn)_2$, 5 mol % $Pd(PPh_3)_4$, toluene, 110 °C, 4.5 h;[13] 85%. (c) $NaNH_2$, *p*-cymene, 170 °C, 9 h;[14] 17% (plus 36% of 2-amino isomer). (d) $Br_2/CHCl_3$, 20 °C; 100%. (e) Ac_2O, 20 °C, 72 h; 65%. (f) 2.5 equiv of bromide, 3 mol % $PdCl_2(PPh_3)_2$, toluene, 110 °C, 16 h;[15] 60%. (g) 4 equiv of *m*-CPBA, CH_2Cl_2, 20 °C, 12 h (→*N*-oxides, 68%). (h) Ac_2O, 140 °C, 2.5 h; 20%. (i) Na_2CO_3/MeOH, 20 °C, 15 h; 68%.



With a functioning bisubstrate system now in hand a number of questions can be asked. Those questions include the following: (i) How does one optimize the catalytic efficiency of **5**; for instance, what will be the result of increasing or decreasing the flexibility/rigidity of **5**? (ii) What other reactions are amenable to catalysis by **5** and related bisubstrate receptors? (iii) Is it possible to incorporate into systems akin to **5**/**8** features which not only bind reactants but also stabilize transition states[2] of ensuing reactions? Answers to those and other questions are presently being pursued.

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(16) Brown, E. V. *J. Org. Chem.* **1965**, *30*, 1607–1610.

(17) This value was calculated from the initial rates of reaction of **6** with **7** in the presence and absence of **5**. Kinetic experiments were carried out at 25 °C in $CDCl_3$ using ^1H NMR to monitor the consumption of **6** and **7** by integration against *sym*-tetrachloroethane as an internal standard. The initial rates (±7%) in the presence and absence of **5** are 0.12×10^{-6} and 0.018×10^{-6} mol·L^{-1}·s^{-1}. Also (a) a 5-fold increase in the concentrations (→ 0.020 M) of both **6** and **7** led to a 24.9-fold rate increase (theory for S_N2 = 25×) in the absence of **5**; (b) in the presence of 0.020 M **5** (**6** and **7** also 0.020 M), a rate enhancement of only 16× was observed, which is consistent with intervention of **8**. [One might predict only a 5-fold increase, but at higher concentrations a somewhat (note the K_{assoc}'s for **13** and **14**) larger fraction of **6** and **7** are in the form of ternary complex **8**. Probably more importantly, due to the identity of the two binding sites in **5** two "nonproductive," ternary complexes (**5**·**6**·**6** and **5**·**7**·**7**) whose concentrations are similar to that of **8** (= **5**·**6**·**7**) are also present; reaction *between* (as opposed to *within*) ternary complexes to give **10** will exhibit a second-order response to an increase in concentration.]

(18) A 0.020 M suspension of **5** in $CDCl_3$ required 2 equiv of **11** to give a homogeneous solution. The chemical shift of the AcN*H* proton of **11** (in the absence of **5**) is somewhat concentration dependent: δ's are 8.63, 8.82, 8.96, and 9.20 ppm when [**11**] = 0.020, 0.040, 0.060, and 0.080 M. For 2:1, 3:1, and 4:1 ratios of **11**:**5** (always 0.020 M in **5**) δ is 12.41, 11.58, and 10.74 ppm, respectively (exchange is rapid).

(19) Since (i) the rate acceleration is relatively modest and because of (ii) the estimated (based on **13** and **14**) K_{assoc} of **8** and (iii) experimental limitations due to both binding sites in **5** being identical, we have not been able to unequivocally demonstrate (or disprove) that **5** exhibits turnover. The possibility of severe product inhibition (which was, a priori, a concern since, in **9**, **10** is bound to **5** via six hydrogen bonds) is avoided in the present instance by the fortuitous precipitation of **10**·HBr. In principle, serious product inhibition can be prevented by placing the binding site of one reactant within a unit that functions as a leaving group.