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

Acknowledgment. Support for this work was provided by the Research Council of Croatia (Grant No. 2.03.01.00.12) and the National Science Foundation, U.S. (Grants No. JFP 545 and 841).

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

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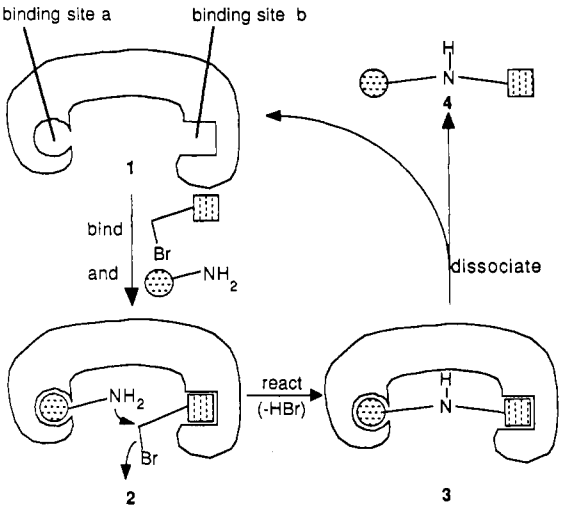
Received December 12, 1988

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.

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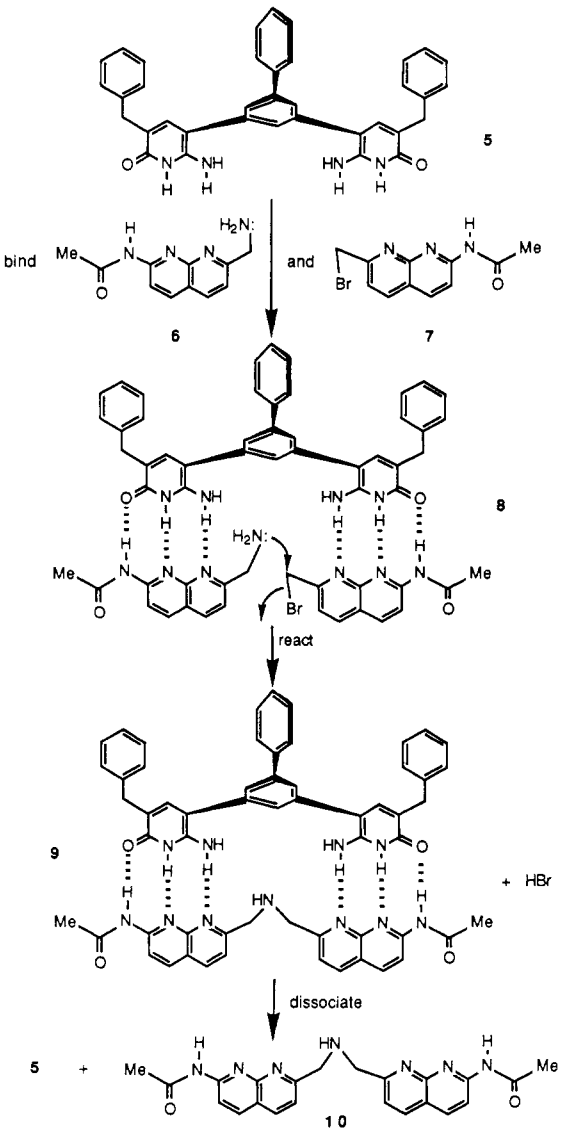
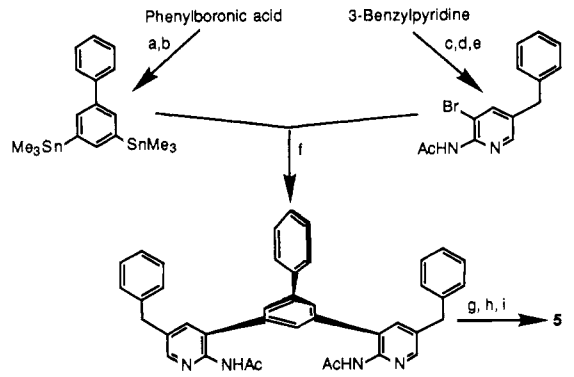
Scheme II

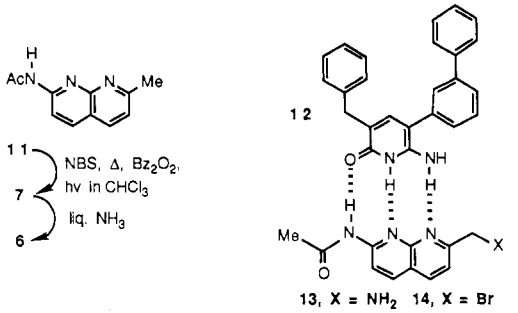


Kinetic measurements demonstrate that **5** promotes reaction between **6** and **7**, and both kinetic and binding studies are consistent with involvement of ternary complex **8**. In particular, the rate for the reaction between **6** and **7** (each 0.0040 M in $CDCl_3$) is accelerated by a factor 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.

Acknowledgments. Support of this project by a grant (GM39072) from the National Institutes of Health is gratefully acknowledged. We thank Professors E. R. Kantrowitz and D. J. Sardella for assistance in kinetic analysis and NMR studies, Dr. A. Echavarren and Professor W. W. Cleland for helpful discussions, and Dr. S. H. Bell for some preliminary experiments.

(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.