Communications

Proximate Charge Effects. 7.[1] Preassembly of Reactants by Electrostatic Attraction

Summary: Preassembly of the reactants into a reacting ion pair promoted the aminolysis of *p*-nitrophenyl (γ-(trimethylammonio)butyrate fluoborate by tetra-*n*-butylammonium taurinate in 95.3 mol % dioxane–water solvent, yielding an effective molarity of 4.5 M, compared to analogous neutral reagents.

Sir: The efficiency of a nucleophile in an intramolecular reaction has been expressed as the "effective molarity" of the neighboring nucleophile.[3] The EM is determined by dividing the first-order rate constant, k_1 (s^{-1}), of the intramolecular reaction by the second-order rate constant, k_2 (L mol^{-1} s^{-1}), of a model bimolecular reaction. The resulting ratio, k_1/k_2, has the units of concentration and can be regarded as the hypothetical concentration of the nucleophile in the bimolecular reaction which would cause it to proceed at the same rate as the intramolecular reaction. This EM, which may have a value which is unobtainable in the actual bimolecular reaction, is a measure of the rate enhancement caused by the juxtaposition of the two reagents.

One can also imagine a nucleophile which is brought into juxtaposition with a reactive site by a neighboring *electrostatic* bond, rather than by a *covalent* bond. The efficiency of such a nucleophile over that of a suitable model could then be estimated in a similar way. There are many examples of electrostatic binding of substrates to polymeric catalysts[4-7] and to micelles and similar charged aggregates.[8-10] Much of the catalytic effect of enzymes is due to the proximity of reactants, and electrostatic interactions constitute the most common force which binds substrates or inhibitors to an active site.

In a medium of low polarity it should be possible to look for the preassembly of two reagents in solution by the charges proximate to their reaction centers. Thus, if B and D are the reactive sites on two molecules and A and C are (oppositely) charged inert fragments proximate to B and D respectively, then the mechanism of the reaction ought to follow the steps shown in eq 1. Comparison of the rate of the reaction between A–B and C–D with the rate of the reaction between model compounds B and D, which lack proximate charges, would then produce an assessment of the value of such an assembly mechanism. Does such a process require a rigid or polymeric surface or can it also take place in solution?

$$^-A—B + {}^+C—D \overset{K}{\rightleftharpoons} \begin{matrix} ^-A—B \\ {}^+C—D \end{matrix} \overset{k_1}{\longrightarrow} \begin{matrix} ^-A \\ {}^+C \end{matrix}\!\!\boxed{\begin{matrix}\text{reaction}\\ \text{complex}\end{matrix}} \longrightarrow \text{products} \quad (1)$$

Here we report the results of experimental work designed to answer this question. The reaction employed is the aminolysis of two *p*-nitrophenyl esters, a neutral one and one having a proximate positive charge, by two amines, one neutral and one having a proximate negative charge. The two esters are *p*-nitrophenyl hexanoate and (*p*-nitrophenyl) γ-(trimethylammonio)butyrate fluoborate and the two amines are benzylamine and tetra-*n*-butylammonium taurinate.[11]

Tetra-*n*-butylammonium taurinate (A–B) was prepared by adding taurine (2-aminoethanesulfonic acid, Aldrich) to an aqueous solution of tetrabutylammonium hydroxide. Evaporation of this solution, followed by crystallization from methylene chloride and trituration with hexane yielded the salt as a white solid, mp 116–118 °C. *p*-Nitrophenyl γ-(trimethylammonio)butyrate fluoborate (C–D) was prepared as follows. γ-Butyrolactone (Antara) was converted via thionyl chloride in ethanol to ethyl γ-chlorobutyrate, which on treatment with aqueous trimethylamine (Aldrich) yielded ethyl γ-(trimethylammonio)butyrate chloride. This was hydrolyzed with aqueous HCl, converted to the acid chloride with thionyl chloride and then treated with *p*-nitrophenol in nitrobenzene to yield *p*-nitrophenyl γ-(trimethylammonio)-butyrate chloride, mp 205–207 °C dec, which was characterized by NMR spectroscopy, by potentiometric chloride titration, and by hydrolysis with aqueous NaOH to produce the theoretical quantity of *p*-nitrophenoxide ion. This chloride was then converted to the fluoborate by treatment with HBF_4 in aqueous ethanol. Recrystallization from acetone and acetone–ether yielded *p*-nitrophenyl γ-(trimethylammonio)butyrate fluoborate, mp 132–133 °C, which was characterized by elemental analysis and by release of the theoretical amount of *p*-nitrophenoxide upon hydrolysis.

$$^-O_3SCH_2CH_2NH_2$$
$$^-A–B$$
$$(CH_3)_3N^+CH_2CH_2CH_2CO_2C_6H_4NO_2\text{-}p$$
$$^+C–D$$

Table I. Rates[a] of Aminolysis of *p*-Nitrophenyl Esters by Amines in 95.3 mol % Dioxane–Water at 25.0 °C

amines	esters: $BF_4^-,(CH_3)_3N^+(CH_2)_3$-$CO_2C_6H_4NO_2$-*p*	esters: $CH_3(CH_2)_4CO_2$-$C_6H_4NO_2$-*p*
$(n\text{-}C_4H_9)_4N^+,^-O_3S$-$CH_2CH_2NH_2$	K = 1.4 k_1 = 0.0188 s^{-1}	k_2 = 0.682 L mol^{-1} s^{-1}
$C_6H_5CH_2NH_2$	k_2 = 0.242 L mol^{-1} s^{-1}	k_2 = 0.00421 L mol^{-1} s^{-1}

[a] k_2 values are second-order rate constants, K and k_1 values are as defined by eq 1. K was obtained from the rates of ammolysis at varying concentration of ester and taurinate. The details of the method of treating the data are available as supplementary material.

(1) Part 6: Haberfield, P.; Cincotta, J. J. *J. Org. Chem.* **1984**, *49*, 4188.
(2) Taken in part from: Cincotta, J. J. Ph.D. Thesis, The City University of New York, 1983.
(3) For a discussion and data on EM, see: Kirby, A. J. "Effective Molarities for Intramolecular Reactions" *Advances in Physical Organic Chemistry*; Academic: New York, 1980; Vol. 17, p 183.
(4) Letsinger, R. L.; Klaus, I. *J. Am. Chem. Soc.* **1964**, *86*, 3884.
(5) Overberger, C. G.; Yuen, P. S. *J. Am. Chem. Soc.* **1970**, *92*, 1667.
(6) Pecht, I.; Levitzki, A.; Anbar, M. *J. Am. Chem. Soc.* **1967**, *89*, 1587.
(7) Ise, N.; Okubo, T.; Kitano, H.; Kunugi, S. *J. Am. Chem. Soc.* **1975**, *97*, 2882.
(8) Fendler, J. H.; Fendler, E. J. *Catalysis in Micellar & Macromolecular Systems*; Academic: New York, 1975.
(9) Kunitake, T.; Shinkai, S. "Catalysis by Membranes, Micelles & Other Aggregates" *Advances in Physical Organic Chemistry*; Academic: New York, 1980; Vol. 17, p 435.
(10) Moss, R. A.; Swarup, S. *J. Am. Chem. Soc.* **1986**, *108*, 5341.
(11) The choice of these two amines was dictated by the fact that they have very similar basicities, taurine having pK_B = 4.94 and benzylamine pK_B = 4.65.

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Rates of aminolysis were measured by following the appearance of the *p*-nitrophenoxide color. For the three model systems this was done by conventional spectroscopy and for the reaction of A–B with C–D, the stopped-flow method was used.

Table I shows the second-order rate constants for the rates between the neutral–neutral, positive–neutral, and neutral–negative reagents. For the reaction between the positive–negative reagents an equilibrium constant and a first-order rate constant as defined by eq 1 are shown.[12] Dividing the k_1 of the reaction of interest by the k_2 values for the three model reactions yields effective molarities of 4.5, 0.028, and 0.078 mol/L, respectively.

The use of three model reactions demonstrates that a simple two reaction comparison (uncharged reactants vs. oppositely charged reactants) would yield an EM which is too high. Even considering the two lower values, we do, however, obtain a fairly high effective molarity. It can be compared to the molarity of the solvent which is 11 M in dioxane and 0.56 M H_2O.[13] On the other hand, it does not compare to the often enormous proximity effects observed when the reactants are held together by a *covalent* bond.[14] Following Menger's recent conclusion[15] that "proximity effects manifest themselves in intramolecular reactions but *not* in intermolecular reactions" we would thus have to place juxtaposition by *one electrostatic bond* in the category of an intermolecular reaction. This conclusion may, of course, not necessarily apply to the cases of two or three point attachment found in enzyme binding and other biological recognition processes.

The ion-pair exchange equilibrium constant, K, which governs the formation of the reacting ion pair, $^-$A–B,$^+$C–D, and was found to have a value near unity, serves as a model for the internal equilibrium constants which enable an intermediary metabolite to move along a metabolic pathway.[16]

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Registry No. $BF_4^-(CH_3)_3N^+(CH_2)_3CO_2$-*p*-$C_6H_4NO_2$, 109686-78-4; $CH_3(CH_2)_4CO_2$-*p*-$C_6H_4NO_2$, 956-75-2; $(n\text{-}C_4H_9)_4N^+{}^-O_3S(CH_2)_2NH_2$, 91900-05-9; $C_6H_5CH_2NH_2$, 100-46-9.

Supplementary Material Available: The equations and method used to calculate K and k_2 (5 pages). Ordering information is given on any current masthead page.

(12) The first-order rate expression, rate = k_1 [$^-$A–B,$^+$C–D] applies only at low amine concentrations, [A–B] < 10^{-4} M. At high amine concentrations, [A–B] > 10^{-2} the reaction follows second-order kinetics, rate = k_2[$^-$A–B,$^+$C–D][A–B], with a second molecule of amine assisting in proton removal from the tetrahedral intermediate. At intermediate amine concentration, a two-term rate expression is required, rate = k_1[$^-$A–B,$^+$C–D] + k_2[$^-$A–B,$^+$C–D][A–B].

(13) The solvent, 95.3 mol % dioxane–water, dielectric constant = 2.53, contains the least amount of water necessary to dissolve enough of the two charged reagents to prepare solutions for the kinetic runs ([AB] = 10^{-5} to 5×10^{-3} M, [C–D] = 10^{-5} to 5×10^{-5} M).

(14) An intramolecular reaction analogous to the reaction of A–B with C–D is the cyclization of *p*-nitrophenyl *N*-(2-aminophenyl)-*N*-methylcarbamate which has been estimated to have an EM ≥ 10^8 (Fife, T. H.; Hutchins, J. E. C.; Wang, M. S. *J. Am. Chem. Soc.* **1975**, *97*, 5878).

(15) Menger, F. M.; Venkataram, U. V. *J. Am. Chem. Soc.* **1985**, *107*, 4706.

(16) Srivastava, D. K.; Bernhard, S. A. *Science (Washington, D.C.)* **1986**, *234*, 1081.

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Synthesis and Crystal Structures of Thioether-Strapped Porphyrins

Summary: Porphyrins containing a thioether linked by hydrocarbon chains and strapped from opposite corners of the macrocycle have been prepared and their structures determined crystallographically.

Sir: The active electron-transporting site of cytochrome *c* contains iron protoporphyrin IX coordinated axially by an imidazole (His-18) and a thioether (Met-80).[1] Attempts to prepare models for this system have been frustrated by the poorer ligand binding of thioethers to iron porphyrins compared with imidazoles. Indeed, only by covalently attaching either the imidzole[2-5] or the thioether[6-8] or both[9] to the porphyrin periphery can the unsymmetrical metalloporphyrin, Im-M-SR_2, be approached. The most successful model to date, the "tailed-imidazole" porphyrin of Mashiko et al.,[5] employs this strategy by covalent attachment of the imidazole to a tetraphenylporphyrin and use of an excess of the free thioether, tetrahydrothiophene. While the X-ray crystal structure of the ferrous derivative has been obtained, isolation of a ferric form has been complicated by head-to-tail dimerization, giving a mixture of six- and five-coordinate species. Herein we report the synthesis and X-ray crystal structures of a pair of novel porphyrins in which a thioether is constrained into a position above the porphyrin core by covalent attachment to diagonally opposite corners of the prophyrin macrocycle. For the longer chain compound **14a**, it was anticipated that the sulfur atom would be held in a favorable geometry for binding to a metal at the prophyrin core, while the shorter chain compound **14b** would demonstrate the effect of ring distortion on such metal–sulfur interaction.

In compound **14** the strap is sufficiently short that attachment to opposite corners of a preformed porphyrin will undoubtedly be impossible. Instead **14** was synthesized by a variation of the synthetic strategy previously reported for the preparation of strapped porphyrins.[10] This synthesis, which is outlined in Scheme I, is a general route for the preparation of strapped porphyrins bearing potential ligands in the strap. Because of the reactivity of the thioether, manipulation of the pyrrole α-methyl group must be carried out before the strap is set in place. Dimerization of the α-(free-iodoalkyl)pyrrole **8** using Na_2S to give compound **9** followed by reaction with the α-(chloromethyl)pyrrole **10** afforded the chain-linked bis(dipyrromethane) **11**. Deprotection and deesterification was followed by thermal decarboxylation to give the unstable **13** which was subjected to acid-catalyzed intramolecular cyclization under high dilution conditions to

(1) Timkovich, R. *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. VII, p 262.

(2) Lautsch, V. W.; Wiemer, B.; Zschenderlein, P.; Kraege, H. G.; Bandel, W.; Gunther, D.; Schulz, G.; Gnichtel, H. *Kolloid Z.* **1958**, *161*, 36–49.

(3) Momenteau, M.; Loock, B. *Biochem. Biophys. Acta* **1974**, *343*, 535–545.

(4) Castro, C. E. *Bioinorg. Chem.* **1974**, *4*, 45–65.

(5) Mashiko, T.; Reed, C. A.; Haller, K. G.; Kastner, M. E.; Scheidt, W. R. *J. Am. Chem. Soc.* **1981**, *103*, 5758–5767.

(6) Goulon, G.; Goulon, C.; Niedercorn, F.; Selve, C.; Castro, C. *Tetrahedron* **1981**, *37*, 3707–3712.

(7) Buckingham, D. A.; Rauchfuss, T. B. *J. Chem. Soc., Chem. Commun.* **1978**, 705–707.

(8) Collman, J. P.; Brauman, J. I.; Doxsee, K. M.; Halbert, T. R.; Bunnenberg, E.; Linder, R. E.; LaMar, G. N.; Del Gaudio, J.; Lang, G.; Spartalian, K. *J. Am. Chem. Soc.* **1980**, *102*, 4182–4192.

(9) Warme, P. K.; Hager, L. P. *Biochemistry* **1970**, *9*, 1599–1605.

(10) Wijesekera, T. P.; Paine, J. B, III; Dolphin, D. *J. Am. Chem. Soc.* **1983**, *105*, 6747–6749.

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