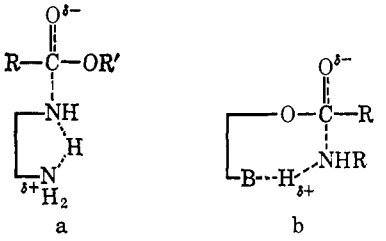
Intramolecular Amine-Catalyzed Aminolysis of an Ester

Sir:

Kinetic studies of the aminolysis of phenyl esters have received considerable attention in the past few years.[1] These investigations have established that formation of amide from primary and secondary amines proceeds to a considerable extent through transition states composed of ester and two molecules of amine (k_{gb}[amine]^2[ester]). The ability to detect this kinetically third-order reaction is due to the fact that both activation parameters $\Delta H^{\pm}$ and $T\Delta S^{\pm}$ are more negative than in the case of the bimolecular term k_n[amine][ester] (*i.e.*, the second molecule of amine performs a catalytic role, thereby lowering the potential energy barrier; this decrease in $\Delta F^{\pm}$ offsets the increase in the kinetic energy barrier due to the increase in order by one[2]). The catalytic role of the second amine has generally been considered as due to a general-base abstraction of a proton from the nucleophilic amine molecule. A mechanism of this type suggests that: (a) the deuterium solvent kinetic isotope effect ($k_{gb}^{H_2O}/k_{gb}^{D_2O}$) might be expected to be *ca.* 2.0, and (b) intramolecular general-base catalysis of a kinetic second order should be realized for aminolysis reactions involving appropriate diamines, (1a), or esters con-



(1)

a b

taining properly placed basic groups, (1b). However, the term $k_{gb}^{H_2O}/k_{gb}^{D_2O}$ does not approach 2.0.[3] Also, in studies of the aminolysis of phenyl acetate by α,ω-diamines [$H_2N(CH_2)_nNH_2$, n = 2, 3, 4, 5, 6],[4] lysine, and *trans*-1,2-diaminocyclohexane[5] no intramolecular assistance to nucleophilic attack by the second amino group was evident. The hydrolysis of aspirin is known to involve carboxyl anion assisted general-base catalysis of the attack of water at the ester bond;[6] yet intramolecular catalysis of the aminolysis of aspirin does not occur (with the possible exception of the weak base semicarbazide).[7] The inability to detect a solvent deuterium isotope effect and to observe what should be favored intramolecular catalysis (molecularly second order) over the k_{gb} reaction path (kinetically third order) appeared to throw some doubt upon the mechanism associated with the k_{gb} term.

We report here the first example of intramolecular general-base catalysis of an aminolysis reaction in water. The second-order rate constants (k_n[B][Q]) for the reaction of H_2O, HO^-, and a series of primary, secondary, and tertiary amines with 8-acetoxyquinoline and the electronically similar 6-acetoxyquinoline (relative electron densities at the 8 and 6 positions, 1.003 and 0.989, respectively)[8] were obtained. In Figure 1, log k_n for the reaction of the 8 isomer *vs.* like values for the 6 isomer is plotted. Inspection of Figure 1 reveals that

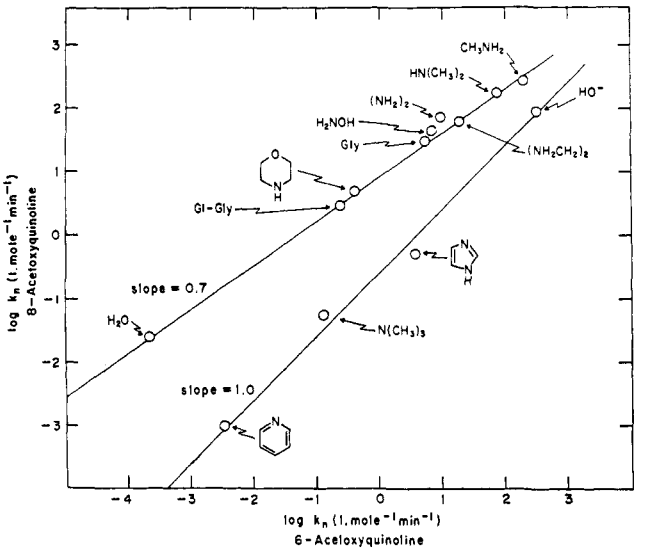


Figure 1. A plot of the log of the second-order rate constants (k_n) for reaction of bases with 8-acetoxyquinoline *vs.* the same function for 6-acetoxyquinoline.

the nucleophilic bases fall on two separate lines. Water and the primary and secondary amines fit nicely a line of slope 0.7 while HO^- and the tertiary amines fit a line of slope 1.0. The two slopes are related to the Brønsted β coefficients and indicate that the mechanisms associated with attack of H_2O, primary, and secondary amines on the two esters differ while the mechanism of reaction of HO^- and the tertiary amines with both esters is the same.[9] The difference in the mechanism for the reaction of H_2O and primary and secondary amines with the two esters is attributed to intramolecular general-base assistance by the quinoline nitrogen in the 8 isomer and simple nucleophilic attack upon the 6 isomer. Thus, those bases falling on the line of slope 0.7 are those which are subject to general-base catalysis (dissociable proton) while those falling on the line of slope 1.0 are not. In the reaction of water with the 8 isomer $T\Delta S^{\pm}$ = −8.70 kcal mol^{-1} (25°) and $k_n^{H_2O}/k_n^{D_2O}$ = 2.35, supporting an intramolecular general-base mechanism [compare to $T\Delta S^{\pm}$ = −6.7 (25°) and $k_n^{H_2O}/k_n^{D_2O}$ = 2.2 for spontaneous hydrolysis of aspirin[6]]. The reaction of HO^- and the tertiary amines with both esters must be *via* simple nucleophilic attack at the ester carbonyl group.

This first convincing demonstration of an intramolecular general-base-catalyzed aminolysis reaction supports the interpretation of the kinetically third-order

(1) For pertinent references see: T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Amer. Chem. Soc.*, **89**, 2106 (1967).
(2) T. C. Bruice and S. J. Benkovic, *ibid.*, **86**, 418 (1964).
(3) See T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin and Co., New York, N. Y., 1966, Chapter I.
(4) T. C. Bruice and R. G. Willis, *J. Amer. Chem. Soc.*, **87**, 531 (1965).
(5) R. W. Huffman, A. Donzel, and T. C. Bruice, *J. Org. Chem.*, **32**, 1973 (1967).
(6) A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, **89**, 4853, 4857 (1967).
(7) T. St. Pierre and W. P. Jencks, *ibid.*, **90**, 3817 (1968).
(8) H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, **43**, 87 (1947).
(9) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2121 (1967).

term k_{gb}[amine]^2[ester] as a general-base-assisted nucleophilic attack of amine at the ester carbonyl group.[10]

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Intramolecular Oxidative Phenol Coupling. A New Method

Sir:

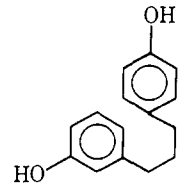
Intramolecular oxidative phenol coupling has long been recognized as the key step in the biosynthesis of phenolic alkaloids and other natural products.[1] The nonenzymic analog of this reaction can lead to elegantly simple *in vitro* syntheses of these compounds, but in practice often results in low yields of desired products, along with relatively large amounts of polymeric materials.[1a,2] We wish to report a new approach that shows considerable promise in alleviating this problem.[3]

In the belief that the above-mentioned difficulties result at least in part from the use of an "external" oxidizing agent (*e.g.*, potassium ferricyanide, ferric chloride, or manganese dioxide), we sought to devise a procedure whereby the oxidizing agent is incorporated into the diphenol molecule prior to actual oxidation. The electron-transfer step could then be carried out under conditions of high dilution, in an inert solvent, and in the absence of excess oxidizing agent (eq 1). The observation by Funk and coworkers[4] that treatment of

$$\text{HOArXArOH} \longrightarrow \text{MOArXArOM} \longrightarrow [\cdot\text{OArXArO}\cdot] \longrightarrow \text{HOAr—ArOH} \quad (1)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \diagdown X \diagup$$

vanadium oxytrichloride with phenols gave rise in certain cases to isolable phenoxyvanadium(V) compounds prompted us to investigate the use of this reagent in the above scheme.

The 1,3-bis(hydroxyphenyl)propane **1**, mp 75–77.5°, was prepared by standard methods from 3,4′-dimethoxychalcone.[5] The reaction of **1** with vanadium oxytrichloride was studied under a variety of conditions. In a typical experiment, a solution of 1.0 mol equiv of **1** in anhydrous ether was added slowly to a solution of 2.5 mol equiv of vanadium oxytrichloride in ether (dark red solution, probably due to a vanadium etherate[4]) at −78° under nitrogen. Hydrogen chloride evolution began immediately; the resulting dark blue solution (2.5×10^{-3} *M* in **1**) was stirred in the cold for 2.5 hr, then refluxed for 10 hr. After extraction of the dark green solution with water and evaporation of the ether there was obtained a crystalline crude product, from



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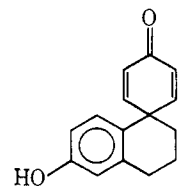

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which the phenolic dienone **2** was isolated by recrystallization in 76% yield:[6] mp 221–222°; ir (KBr) 3.22, 6.07 μ; uv (C_2H_5OH) 237 mμ (ε 29,900), 280 mμ (ε 2570); nmr (DMSO-d_6) δ 1.80 (4 H), 2.10 (s, 1 H), 2.80 (2 H), 6.20 (d, 2 H, J = 10 Hz), 6.65 (m, 3 H), 7.16 (d, 2 H, J = 10 Hz); mol wt 226 (mass spectrum).[7]

Hydrolysis of the reaction mixture prior to refluxing yielded only starting material, indicating oxidation to be quite slow at −78°. The utilization of less than 2.5 mol equiv of vanadium oxytrichloride resulted in lower yields of **2**, along with appreciable amounts of unreacted starting material. As yet none of the isomeric *ortho–para* coupling product has been detected.

In order to provide a basis for comparison of the vanadium oxytrichloride results with traditional methods for effecting intramolecular oxidative phenol coupling, the following experiments were carried out. (1) Oxidation of **1** with aqueous alkaline potassium ferricyanide in chloroform gave rise to a mixture of at least six components, from which **2** was isolated in 4% yield. (2) Treatment of **1** with ferric chloride under a variety of conditions afforded, in the best case, a 7% yield of **2** (corrected for unreacted starting material). (3) Oxidation of **1** with the recently reported[3c] manganic tris(acetylacetonate) in refluxing acetonitrile gave rise to **2** in 10% yield. Again, in none of these experiments could the isomeric *ortho–para* coupling product be detected.

Studies on the application of this method to the biogenetic-type synthesis of phenolic alkaloids are in progress. Preliminary results indicate the formation of desired coupling products where no such products could be obtained with other oxidizing agents. Full details will be reported in due course.[8]

Acknowledgment. This work was supported by Public Health Service Grant CA-10136 from the National Cancer Institute.

(1) (a) A. I. Scott, *Quart. Rev.* (London), **19**, 1 (1965); (b) D. H. R. Barton, Pedler Lecture, *Chem. Brit.*, **3**, 330 (1967).

(2) See, for example, T. Kametani and K. Fukumoto, *Chem. Commun.*, 26 (1968).

(3) There has been considerable recent interest in new methods for phenol oxidation, dealing mainly, however, with intermolecular coupling: (a) M. L. Larson and F. W. Moore, *Inorg. Chem.*, **5**, 801 (1966); (b) J. M. Bobbitt, J. T. Stock, A. Marchand, and K. H. Weisgraber, *Chem. Ind.* (London), 2127 (1966); (c) M. J. S. Dewar and T. Nakaya, *J. Am. Chem. Soc.*, **90**, 7134 (1968); (d) W. L. Carrick, G. L. Karapinka and G. T. Kwiatkowski, *J. Org. Chem.*, in press.

(4) H. Funk, W. Weiss, and M. Zeising, *Z. Anorg. Allg. Chem.*, **296**, 36, (1958).

(5) B. J. F. Hudson, *J. Chem. Soc.*, 754 (1946).

(6) Kwiatkowski and coworkers[3d] have very recently reported good yields (56–65%) in the intermolecular coupling of naphthols with vanadium oxytrichloride in carbon tetrachloride, but only polymer was obtained with *m*-cresol under the same conditions. We thank Dr. Kwiatkowski for communicating his results to us prior to their publication.

(7) The nmr spectrum of the tetrahydro derivative of **2** exhibited aromatic proton absorption consistent with a 3,4-disubstituted phenol moiety, thus establishing **2** as the *para–para* coupling product.

(8) All new compounds had satisfactory elemental analyses.

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