Å. and $\beta = 109.5°$ and C-1, C-2, and C-6 being trigonal (77 kcal.); (k) the trisymmetric form **4** with $a = 1.54$ Å. and $\beta = 109.5°$ with C-1, C-2, and C-6 being trigonal (195 kcal.); and (l) the same form as k but with C-1, C-2, and C-6 being tetrahedral with the hydrogens pointing away from the threefold axis of symmetry of the carbon skeleton (132 kcal.). In addition to these forms, Hoffmann's calculations show that the simple undistorted norbornyl cation is less stable (51 kcal.) than form S.

A strong qualitative theoretical argument for the existence of nonclassical ions in systems such as norbornane is that the ion assumes a new geometry in order to gain energy from charge delocalization and release of strain. Since the energy decrease calculated by this E.H.T. in going from the classical carbonium ion to form S is 51 kcal., one might say this idea is confirmed. However, the difference seems much too high since norbornane has only about 18 kcal. of strain energy[8] and it seems unlikely that the ion would lose so much energy by dispersing its charge. More likely, the larger difference is a confirmation that Hoffmann's E.H.T. overemphasizes steric interactions.[2] Thus, the calculations for these two forms only are weak arguments for a nonclassical carbonium ion. However, the calculations of the slightly modified forms of form S favor the nonclassical ion since all slight changes from the truly symmetrical, nonclassical ion toward the classical ion lead to less stable ions. Hoffmann contends that the stability changes for slight geometrical variations of ions give at least the correct qualitative conclusions.[2] Thus, according to this E.H.T. the nonclassical carbonium ion is an energy minimum in going from one form to the classical norbornyl cation to the other form. This is in opposition to Brown's arguments that the nonclassical ion is an energy maximum or transition between the two classical ions.[3] Although these calculations do not prove the existence of nonclassical carbonium ions since this E.H.T. is far from being established, they do represent an additional theoretical argument in favor of nonclassical cations. Moreover, these calculations offer a potential test of this E.H.T. since they indicate it favors nonclassical ions; it is a potential test since unequivocal experimental proof or disproof of the existence of nonclassical carbonium ions is still lacking. It is highly desirable to confirm this E.H.T. since it offers the organic chemist a simple way to calculate molecular orbitals and thus preferred geometries, energies, charge distributions, substituent effects, etc., for fairly complex molecules.

Acknowledgment.—The author is indebted to Dr. R. Hoffmann for initiating him to his extended Hückel theory, for many helpful discussions during the course of these calculations, and for use of his computer time. He also acknowledges the inspiration, encouragement, and advice of Professor P. D. Bartlett and a postdoctoral fellowship from the National Science Foundation.

(8) The editor has noted that the strain energy of norbornane is calculated to be 18.5 kcal. from heats of combustion by A. F. Bedford, A. E. Beezer, C. T. Mortimer, and H. D. Springall [*J. Chem. Soc.*, 3823 (1963)].

Neighboring Hydroxyl Group Assistance. VI. In Amide Hydrolysis

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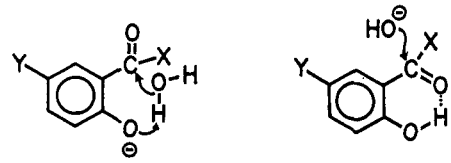
We wish to report the first instance of intramolecular general-base catalysis of the hydrolysis of an amide bond by a neighboring hydroxyl group. The model compounds employed were substituted *o*-hydroxybenzamides. It has been previously demonstrated that a hydroxyl group, suitably placed, as in γ-hydroxybutyramide, will facilitate the hydrolysis of an amide bond presumably *via* nucleophilic catalysis through intermediate lactone formation.[3,4] Suitably situated aliphatic hydroxyl groups have also been established in numerous cases to facilitate ester hydrolysis by intramolecular nucleophilic catalysis or, where direct attack of the hydroxyl group on the ester bond is sterically prevented, by specific-base, general-acid, or the kinetically equivalent general-base catalysis.[5]

Bender,[6] in an important investigation of the influence of neighboring phenolic hydroxyl groups on ester hydrolysis, found that the pH–rate profile for the hydrolysis of *p*-nitrophenyl 5-nitrosalicylate exhibits two plateaus: one in the acid and one in the alkaline region. Kinetically equivalent rate equations for intramolecular general-base (**1a**) and general-acid (**1b**) catalysis were found to fit the experimental data satisfactorily. Mechanism **1a** was favored by



1a **1b**

X = NH_2, $C_6H_4NO_2$-*p*; Y = H, NO_2

Bender on the basis that little or no facilitation was provided by the neighboring hydroxyl group for attack by nucleophiles not susceptible to general base assistance (*e.g.*, nucleophiles without acidic hydrogens as N_3^- and SO_3^{2-}).

In Figure 1 are presented pH–rate profiles for the hydrolysis of several substituted benzamides (salicylamide, I; 5-nitrosalicylamide, II; *o*-methoxybenzamide, III; and benzamide, IV). The points of Figure 1 are experimental and the curves are derived from theoretical rate equations, *viz.*

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(4) T. C. Bruice and F.-H. Marquardt, *J. Am. Chem. Soc.*, **84**, 365 (1962).

(5) For a review of work in this area, see T. C. Bruice and T. H. Fife, *ibid.*, **84**, 1973 (1962).

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salicylamide:

$$\frac{-dA_T}{dt} = \left[1.64 \times 10^{-4} + 5.77 \times 10^{-3}\left(\frac{K_w}{a_H}\right)\right] A_T\left(\frac{K_a}{K_a + a_H}\right)$$

o-methoxybenzamide:

$$\frac{-dA_T}{dt} = [6.6 \times 10^{-2}]\frac{K_w}{a_H} A_T$$

5-nitrosalicylamide:

$$\frac{-dA_T}{dt} = \left[9.38 \times 10^{-6} + 2.66 \times 10^{-2}\left(\frac{K_w}{a_H}\right)\right] A_T\left(\frac{K_a}{K_a + a_H}\right)$$

where A_T = total amide concentration; K_a = acid dissociation constant of phenolic hydroxyl group at 100°; a_H = hydrogen ion activity as measured by the glass electrode at 100°; K_w = autoprotolysis constant of water at 100°. The pH–rate profiles for the salicylamides exhibit plateaus directly related to the pK_a values of the corresponding *o*-hydroxyl groups. By comparing the values of k_{obsd} at the plateau region for compounds I and II, a choice between mechanisms **1a** and **1b** may be made.

For **1a**, electron withdrawal by the *m*-nitro group should increase the susceptibility of the amide bond to nucleophilic attack whereas the accompanying large decrease in basicity of the phenolic anion would make it a poorer general base catalyst. The predicted rate could therefore be either faster or slower depending upon the Hammett ρ and Brønsted α constants for these two effects. If **1b** is correct then II should undergo hydrolysis more rapidly than I. Thus, the determined 450-fold greater acidity of the phenolic hydroxyl group in II should greatly favor intramolecular general-acid catalysis by this group; the nitro group should also increase the susceptibility of the amide bond to attack by hydroxide ion. At pH values above the plateau the mechanism unequivocally involves OH^- attack on the ionized substrate and the approximately sixfold greater rate of hydrolysis of II in this region must be due to the greater susceptibility of the amide bond to base attack brought about by the 5-nitro group. Since values of k_{obsd} at the plateau regions for II are only *one-eighteenth* of those for I, mechanism **1b** is incorrect leaving **1a** as the preferred mechanism for salicylamide hydrolysis. Therefore, in combination with Bender's results we may conclude that **1a** is the preferred mechanism for the facilitation of alkaline hydrolysis of both esters and amides of salicylic acid.[7]

It is not possible to apply the rationale developed above to the kinetic data given by Bender for the salicylate esters. The rates of hydrolysis of the salicylate esters were determined by Bender in 32.8% ethanol while for the 5-nitrosalicylate esters the solvent was 34.4% dioxane–water. The pH measured by the glass electrode in ethanol is not a "true" pH and, since a possible kinetic solvent effect is anticipated, a choice between **1a** and **1b** for ester hydrolysis cannot be made on kinetic grounds alone.

It is not necessary, of course, that all examples of neighboring hydroxyl group facilitation proceed by the same mechanism. Bruice and Fife[5] have found that the deuterium oxide solvent isotope effects for catalysis by a vicinal aliphatic hydroxyl group of substituted cyclopentyl acetates are not consistent with mechanisms such as **1a,b**.

The hydroxyl group of peptide-bound serine is of considerable interest as a possible nucleophilic center of many hydrolytic enzymes. The role of tyrosine hydroxyl groups in enzymes such as pepsin and carboxypeptidase may be one of general base catalysis.[8,9] The present studies are being extended to the hydrolysis of the amides of hydroxyl-substituted cyclopentanoic acids, where the pK_a of the hydroxyl group approaches pK_w, in order to ascertain whether a neighboring aliphatic hydroxyl group may assist amide hydrolysis.

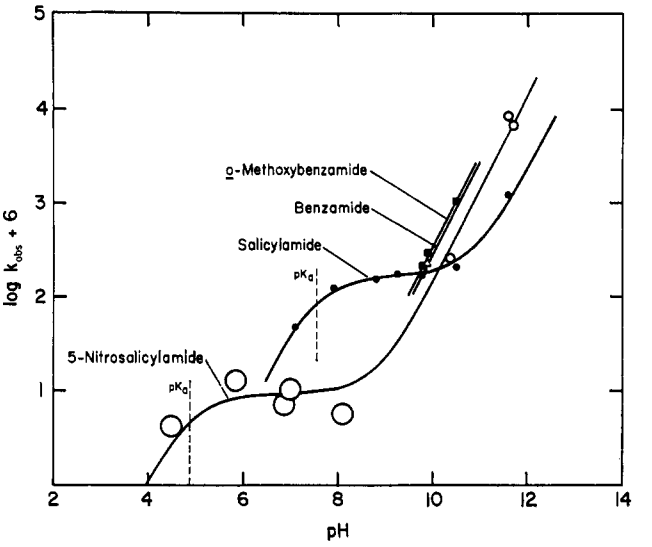

Figure 1.—The hydrolysis of several substituted benzamides in aqueous solution at 100° and ionic strength 1.0 *M* with KCl. The units of the rate constants are min.$^{-1}$ and the size of the circles is indicative of the error of their determination.

Experimental

Samples in appropriate buffers, μ = 1.0 *M*, were sealed in Corning No. 7280 glass ampoules and placed in an aluminum block thermostated at 100 ± 0.3°. Samples were withdrawn periodically and analyzed spectrophotometrically (I, 330 mμ; II, 395 mμ; III, 294 mμ; IV, 540 mμ, *via* the hydroxamate procedure outlined as in ref. 4) with a Zeiss PMQ II. Each buffer series was adjusted to the same pH before the experiment using an apparatus described previously.[4] The rate constants at each pH were extrapolated to zero buffer concentration. The pK_a values of the salicylamides were measured at 100°, μ = 1.0 *M*, in the same apparatus (salicylamide, 7.54; 5-nitrosalicylamide, 4.88).

Care was taken to ensure that each buffer employed satisfied three criteria: pH stability during the extended times necessary in the experiments, noninterference with the amide species, and the absence of any decomposition products absorbing at the wave length utilized. Borate and phosphate buffers appeared to complex with the *o*-hydroxyamides and were therefore unsuitable. The nature of this complexation is now being studied.

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(7) In **1b** electron withdrawal by Y will not only decrease the electrophilicity of the carbonyl carbon but also the basicity of the carbonyl oxygen. The latter effect is probably of minor importance and has been ignored. Thus, the value of ρ for general acid catalyzed hydrazinolysis of phenyl esters is very nearly the same as that for general base catalyzed hydrazinolysis [see T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, **86**, 418 (1964)].

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(9) R. T. Simpson, J. F. Riordan, and B. L. Vallee, *Biochemistry*, **2**, 616 (1963).