Kinetics and Mechanism of the Formation of Azoxy Compounds

BY YOSHIRO OGATA, MASARU TSUCHIDA AND YASUO TAKAGI

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The condensation of phenylhydroxylamine and nitrosobenzene to yield azoxybenzene has been studied kinetically at 50, 40, 30 and 20° in pure and aqueous methanolic solutions using the ultraviolet spectrophotometer. The rate is proportional to the concentration of both reactants. The rate constant varies with addition of acid (0.0001–0.1 N). The plots of acid concentration *versus* rate constant show downward and upward curves in pure and 30 vol. % methanol, respectively. The rate data and the acidity–rate relationship show that two mechanisms are simultaneously operating, *i.e.*, in neutral media the reaction of the free amine and the free nitrosobenzene is predominant, while in acidic media the condensation of phenylhydroxylamine and protonated nitrosobenzene becomes important. Moreover, the formation of p,p'-dichloro-, p-chloro- and unsubstituted azoxybenzenes from p-chloronitrosobenzene and phenylhydroxylamine and the related reactions are confirmed; the fact implies a preliminary rapid and reversible reaction between the reactants.

It has been supposed that the formation of azoxy compound by the reduction of nitrobenzene results from condensation between phenylhydroxylamine and nitrosobenzene. However, strange to say, the condensation of p-substituted phenylhydroxylamine with nitrosobenzene has been reported to give a mixture containing unsubstituted and p,p'-disubstituted azoxybenzene.[1] Since then, little theoretical attention has been paid to this phenomenon, and therefore it appeared valuable to examine the reaction mechanism in detail.

Our experiments indicate the truth of these observations not only with p-methyl or p-chlorophenylhydroxylamine and nitrosobenzene but also with p-chloronitrosobenzene and phenylhydroxylamine. These facts seem to indicate that azoxybenzene formation is truly a reaction between phenylhydroxylamine and nitrosobenzene, but that the reaction between substituted phenylhydroxylamines and nitrosobenzene or substituted nitrosobenzenes and phenylhydroxylamine is complicated by a preliminary rapid equilibrium between phenylhydroxylamine and nitrosobenzene.

$$p\text{-X}\text{—}C_6H_4NO + C_6H_5NHOH \rightleftharpoons$$
$$p\text{-X}\text{—}C_6H_4NHOH + C_6H_5NO$$
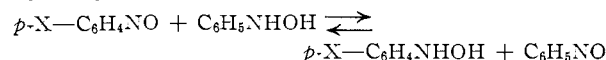
Thence we investigated spectrophotometrically the kinetics of the condensation of phenylhydroxylamine with nitrosobenzene in methanol. The reaction was found to be first-order with each reactant, and its second-order rate constant was influenced by the addition of acid or water. The present report summarizes these data which suggest a plausible mechanism.

Experimental

Materials.—Phenylhydroxylamine was prepared from nitrobenzene by reduction with zinc dust in aqueous ammonium chloride solution.[2] The crude material was purified by dissolving it in benzene and then precipitating it by the addition of petroleum ether. Repeated purification gave fine needles of m.p. 82° (lit.[3] m.p. 82°). For each kinetic run freshly purified material was used. p-Methyl and p-chlorophenylhydroxylamine were prepared and purified in the same way, m.p. 94° (lit.[4] m.p. 94°) and 88° (lit.[5] m.p. 87.5°), respectively.

Nitrosobenzene was obtained from phenylhydroxylamine by chromic acid oxidation. Recrystallization from a small amount of methanol gave colorless crystals, m.p. 67.5° (lit.[6] m.p. 68°). The product was stored in a dark place. p-Chloronitrosobenzene was prepared and purified similarly, m.p. 93° (lit.[7] m.p. 92–93°). The methanol used was of best grade and purified by rectification, b.p. 65°.

Products from p-Substituted Phenylhydroxylamine or Nitrosobenzene.—As an example, the condensation of phenylhydroxylamine and p-chloronitrosobenzene is described below. A methanolic solution (15 ml.) of phenylhydroxylamine (2 g.) was mixed with a methanolic solution (15 ml.) of p-chloronitrosobenzene (2 g.) at room temperature. The greenish color of p-chloronitrosobenzene gradually darkened on standing, and after five minutes the color became yellow by warming to 50°. A small amount of water was added, and the solution was warmed until the precipitate dissolved and then chilled. The crystalline material deposited was collected. The mother liquor was worked up similarly until no more precipitation was observed, and the last filtrate was evaporated to dryness in vacuum. Each crop was then carefully submitted to fractional recrystallization. There were obtained pure crystals of p,p'-dichloroazoxybenzene, 1.4 g., m.p. 158° (lit.[8] m.p. 158°); azoxybenzene, 0.9 g., m.p. 35° (lit.[9] m.p. 35.5°); and p-chloroazoxybenzene, 0.5 g., m.p. 62° (lit.[1b] m.p. 62°).

p-Chloroazoxybenzene was converted to p-chloroazobenzene by heating in concentrated sulfuric acid. Recrystallization from aqueous methanol gave orange-red crystals, 0.26 g., m.p. 92°, which showed no depression of m.p. on admixture with authentic specimen, m.p. 92°.[10]

In an analogous manner, the condensation of p-chlorophenylhydroxylamine (2 g.) and nitrosobenzene (2 g.) gave p,p'-dichloroazoxybenzene, 0.9 g.; azoxybenzene, 0.9 g.; and p-chloroazoxybenzene, 0.2 g. From p-methylphenylhydroxylamine (2 g.) and nitrosobenzene (2 g.) there was obtained p,p'-dimethylazoxybenzene, 1.7 g., m.p. 71° (lit.[11] m.p. 71°); and azoxybenzene, 1.0 g., m.p. 35°.

Determination of Basicity Constants.—The basicity constant[12] of phenylhydroxylamine, $K_1 = [PhNH_2OH^+]/[PhNHOH][H^+]$, and that of nitrosobenzene, $K_4 = [PhNOH^+]/[PhNO][H^+]$, were determined by measuring at appropriate wave lengths the optical densities of these materials at 0.0002 M concentration in acidic methanolic solutions as a function of acid concentrations.[13] From the estimated values of optical densities in neutral, weakly acidic and strongly acidic solutions of these materials con-

(1) (a) E. Bamberger and E. Renauld, *Ber.*, **30**, 2278 (1897); E. Bamberger and A. Rising, *Ann.*, **316**, 257 (1901); (b) V. O. Lukashevich, *Compt. rend. acad. sci. U.R.S.S.*, **21**, 376 (1938); *C. A.*, **33**, 3769 (1939).

(2) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 445.

(3) R. Willstätter and H. Kubli, *Ber.*, **41**, 1936 (1908).

(4) E. Bamberger, *ibid.*, **28**, 245 (1895).

(5) M. D. Farrow and C. K. Ingold, *J. Chem. Soc.*, **125**, 2550 (1924).

(6) E. Bamberger and L. Storch, *Ber.*, **26**, 472 (1893).

(7) C. K. Ingold, *J. Chem. Soc.*, **127**, 517 (1925).

(8) L. Zechmeister and P. Rom, *Ann.*, **468**, 130 (1929).

(9) S. Sugden, J. B. Reed and H. Willkins, *J. Chem. Soc.*, **127**, 1537 (1925).

(10) J. Burns, H. McCombie and H. A. Scarborough, *ibid.*, 2933 (1928).

(11) E. Bamberger, *Ber.*, **59**, 429 (1926).

(12) In general, the basicity constant is expressed as $[BH^+][OH^-]/[B]$, where B is a base; hence these K_1 and K_4 values should be multiplied by the solubility product of water according to this definition for coincidence with the idiomatic expression.

(13) For convenience, the acid (hydrogen chloride) concentration, measured by the acidimetry, was assumed equal to $[H]^+$, since no appreciable pH change was observed on addition of these substrates.

taining no, partly and wholly protonated substrates, respectively, the basicity constants were calculated by means of the above equations. With phenylhydroxylamine, the difference between optical density at 236 mμ and that at 280 mμ was used, while with nitrosobenzene the optical density at 260 mμ was utilized. With phenylhydroxylamine, an increase of the protonated amine concentration with increasing acid concentration became negligible at ca. 0.04, 0.2 and N acid concentrations in pure, 96 and 70% methanol, respectively; e.g., a plot of $E_{236} - E_{280}$, the difference between optical density of 0.0002 M methanolic solution of this material at 236 mμ and that at 280 mμ, against acid concentration c approaches the extreme value (zero) corresponding to complete ionization when c is 0.04 N. Using this value, zero and that for neutral solution $(E_{236} - E_{280})_0 = 0.720$, the basicity constant of phenylhydroxylamine, K_1, can be calculated by means of the relation

$$K_1 = [PnNH_2OH^+]/[PhNHOH]c = \frac{0.720 - (E_{236} - E_{280})_c}{\{(E_{236} - E_{280})_c - 0\}c}$$

Similarly, K_1 values in 96 and 70% methanolic solutions were obtained, the complete protonation here being reached when c is about 0.2 and N, respectively; the fact seems to indicate that water is a weaker acid than methanol.

The basicity of nitrosobenzene is so small that it is decomposed by acid before complete protonation of the substrate is attained, even in pure methanol. Therefore, the basicity constant K_4 was calculated by means of two simultaneous equations by inserting two different $(E_{260})_c$ values.

$$K_4 = \frac{(E_{260})_0 - (E_{260})_c}{\{(E_{260})_c - (E_{260})_\infty\}c} = \frac{0.320 - (E_{260})_c}{\{(E_{260})_c - (E_{260})_\infty\}c}$$

Here (E_{260})'s are optical densities at 260 mμ and the indicated acid concentrations, and c means any acid concentration. These data are summarized in Table I.

TABLE I

BASICITY CONSTANTS OF PHENYLHYDROXYLAMINE AND NITROSOBENZENE

Temp., °C.	Phenylhydroxylamine K_1, l. mole^{-1} 100% MeOH	96% MeOH	70% MeOH	Nitrosobenzene K_4, l. mole^{-1} 100% MeOH
5	4.75×10^3	4.77×10^2	15.0×10	1.8
25	2.90×10^3	3.02×10^2	7.95×10	1.3
40[a]	2.14×10^3	2.24×10^2	5.37×10	1.0

[a] The data were obtained by the extrapolation from the values at 5 and 25° by means of the Arrhenius equation.

Analysis of the Components of the Reaction Mixture.—Phenylhydroxylamine, nitrosobenzene and azoxybenzene absorb strongly in the range between 240–300 mμ (Fig. 1).
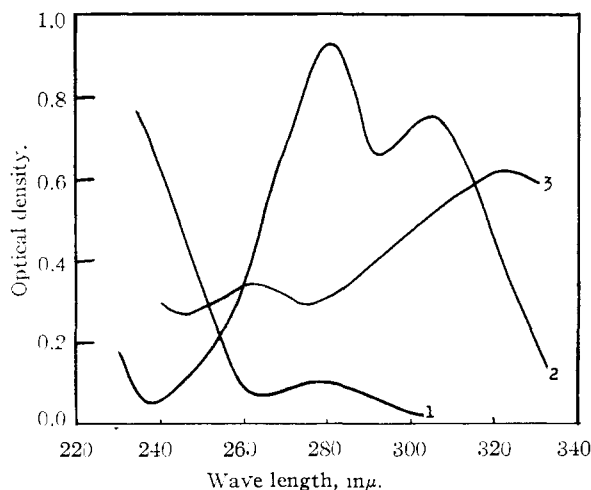

Fig. 1.—Ultraviolet absorption curves: 1, phenylhydroxylamine; 2, nitrosobenzene; 3, azoxybenzene.

An inspection of Fig. 1 will show that Vaughn's method[14] can be used to follow this condensation.

The following relationship will be deduced from Beer's law and the stoichiometry of the reaction.

$$E_1 - E_2 = (\epsilon_a^1 - \epsilon_a^2)(a - x) + (\epsilon_b^1 - \epsilon_b^2)(b - x) + (\epsilon_x^1 - \epsilon_x^2)x$$

$$E_3 - E_4 = (\epsilon_a^3 - \epsilon_a^4)(a - x) + (\epsilon_b^3 - \epsilon_b^4)(b - x) + (\epsilon_x^3 - \epsilon_x^4)x$$

Here, E_i is the optical density of a solution at wave length i; a and b are initial concentrations of phenylhydroxylamine and nitrosobenzene, respectively; x is the concentration of azoxybenzene produced; ϵ_a^i, ϵ_b^i and ϵ_x^i are the extinction coefficients of the subscripted materials at wave length i. This is a linear or first-order function of x; hence a plot of $E_1 - E_2$ (or $E_3 - E_4$) against x will show a set of parallel straight lines corresponding to each set of a and b. Accordingly, plots of $E_1 - E_2$ vs. $E_3 - E_4$ with varying x will again be represented by a set of parallel straight lines (not curves) each of which corresponds to a run with a set of a and b.

If the sum of a and b is constant, e.g., 0.0002 M, the variation of the composition of the reaction mixture during the reaction may be represented, just as Vaughn's chart, by a triangular composition diagram of Fig. 2, where P, N and A
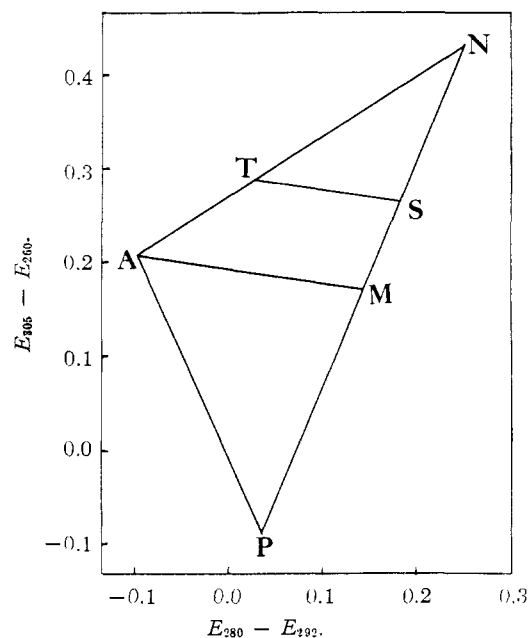

Fig. 2.—Vaughn's chart for the estimation of three components.

represent pure solutions of phenylhydroxylamine (0.0002 M), P', nitrosobenzene (0.0002 M), N', and azoxybenzene (0.0002 M × ½), respectively. For example, a reaction course of the equivolume mixture of P' and N', represented by the mid-point M of line PN, may be expressed as line MA, since the sum of [PhNO], [PhNHOH] and 2[Ph₂-N₂O] is constant during the reaction.[14] Analogously, it is apparent that with reactants containing N' and P' in a ratio of SP:NS, the reaction course is represented by line ST, where line ST is parallel to line AM and T is an intersection of NA and ST, as is apparent from the above reasoning. This is a modification of Vaughn's chart and seems very useful for the detection of side reactions, since the method determines the concentrations of all reactants and product.

Therefore, methanolic solutions of phenylhydroxylamine (0.0002 M), nitrosobenzene (0.0002 M) and azoxybenzene (0.0001 M) were prepared, their optical densities being determined at 260, 280, 292 and 305 mμ and compared with that of pure methanol by means of a Beckman DU spectrophotometer. Differences of the optical densities, $E_{280} -$

(14) R. T. Vaughn and A. E. Stearn, Anal. Chem., 21, 1361 (1949).

E_{292} and E_{305} — E_{260}, were calculated with each compound, the data being plotted in Fig. 2.

Typical Procedure for Rate Measurements.—An appropriate amount of a methanolic solution (0.002M) of nitrosobenzene was introduced into a 200-ml. three-necked flask equipped with an ice-cooled reflux condenser, nitrogen-introducing tube and a tube suitable for withdrawing samples and immersed in a thermostat. Since phenylhydroxylamine is very sensitive to air oxidation, all kinetic experiments were carried out in nitrogen atmosphere. The nitrogen was purified by passing through three washing bottles each containing an aqueous alkaline solution of pyrogallol, then dried over potassium hydroxide and bubbled during the measurement. After bubbling for ca. 10 minutes to remove a trace of oxygen, the reaction was initiated by the addition of a methanolic solution (0.0002 M) of phenylhydroxylamine. At appropriate time intervals, aliquots (5 ml.) were taken out, poured into a 50-ml. volumetric flask containing an appropriate amount of methanol, diluted accurately to 50 ml. and then cooled to 0°. It was confirmed in preliminary tests that such a procedure would stop the reaction. At the end of the reaction, usually 30–100 minutes, the optical density of the resulting solution was measured at 260, 280, 292 and 305 mμ, and the second-order rate constant was calculated using the method mentioned previously.

The hydrogen-ion concentration was determined by acidimetry, since it was confirmed that the reactants and the product have no appreciable effect on the hydrogen-ion concentration.

Results

Second-order Rate Constants and Temperature Coefficients.

—The rates were measured in three media, i.e., 100, 96 and 70% methanol (vol. %), the apparent second-order rate constants being given in Table II with varying molar ratio of both reactants (the molar ratio of phenylhydroxylamine to nitrosobenzene varies from 5 to $^1/_4$). As is shown in the table, the constancy is satisfactory, implying that the condensation involves a rate-determining combination of both reactants. The variation of the rate with temperature is shown in Fig. 3, from which the energy and entropy of activation is calculated to be 10.8 kcal. mole^{-1} and — 32.5 cal. deg.$^{-1}$mole^{-1}, respectively.

TABLE II

SECOND-ORDER CONSTANTS FOR THE FORMATION OF
AZOXYBENZENE IN PURE METHANOL AT 40°

| Initial concentration, M | | k, |
[C$_6$H$_5$NHOH]	[C$_6$H$_5$NO]	l. mole^{-1} min.$^{-1}$
0.00034	0.00166	18.3
.00051	.00149	19.9
.00079	.00121	21.4
.00118	.00082	20.4
.00146	.00054	17.9
.00158	.00042	20.5
	Av.	19.7

Acidity Dependence.—In alkaline solutions oxidation of phenylhydroxylamine to nitrosobenzene was so rapid that accurate determination of the rate was impossible, since the oxidation proceeds during the optical density estimation. On the other hand, in strong acidity nitrosobenzene was converted to an unknown substance. Hence the kinetic experiments were confined to the acidity range from 0.0001 to 0.1 N. As the acid source, hydrogen chloride and in a few cases sulfuric acid were used. The variation of the apparent second-order rate constants with acid concentration and
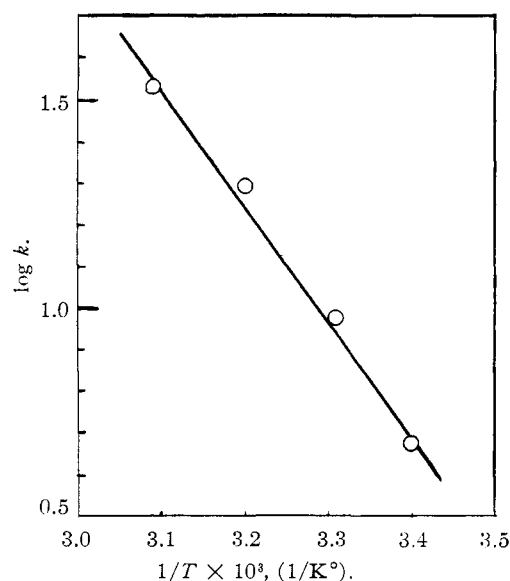
with solvent composition is given in Table III. The data with hydrogen chloride as an acid source agree with those of sulfuric acid of the same normality. No salt effect was observed with added lithium chloride.

Fig. 3.—The temperature dependence of the second-order constant.

TABLE III

VARIATION OF SECOND-ORDER CONSTANTS WITH ACID CONCENTRATION AND WITH SOLVENT COMPOSITION AT 40°

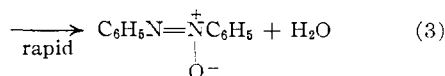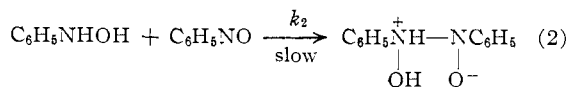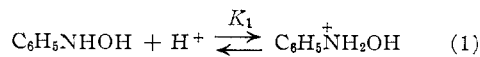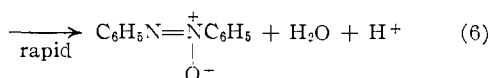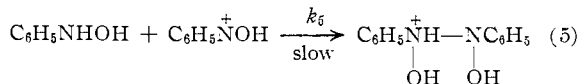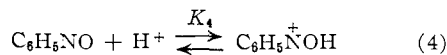| [H$^+$], N	k, l. mole^{-1} min.$^{-1}$		
	100% MeOH	96% MeOH	70% MeOH
0	19.7	22.1	39.5
.0001	18.9		
.0004	14.0		
.001	16.0^a		
.002	11.5		
.004	11.8		42.0
.004	13.0^a		
.005		22.3	
.005		21.0^a	
.0086	10.8		
.01	13.6^a	22.0	49.5
.015			56.5
.018	11.2		
.0184	12.5		
.0184	10.5^b		
.02		23.1	57.3
.028		22.3	
.03	11.7	22.9	
.0324	12.4^b		
.04		21.8	
.046	11.7		
.062	10.0		

^{a} Sulfuric acid-catalyzed. ^{b} LiCl was added.

Discussion

The results obtained, i.e., the second-order constant and its acidity dependence, may best be explained by assuming two simultaneous mechanisms, A and B.

Mechanism A

$$C_6H_5NHOH + H^+ \underset{}{\overset{K_1}{\rightleftarrows}} C_6H_5\overset{+}{N}H_2OH \qquad (1)$$

$$C_6H_5NHOH + C_6H_5NO \xrightarrow[\text{slow}]{k_2} C_6H_5\overset{+}{N}H-NC_6H_5 \qquad (2)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad | \quad\; | $$
$$\qquad\qquad\qquad\qquad\qquad\qquad OH \;\; O^-$$

$$\xrightarrow[\text{rapid}]{} C_6H_5N=\overset{+}{N}C_6H_5 + H_2O \qquad (3)$$
$$\qquad\qquad\quad |$$
$$\qquad\qquad\quad O^-$$

Mechanism B

$$C_6H_5NO + H^+ \underset{}{\overset{K_4}{\rightleftarrows}} C_6H_5\overset{+}{N}OH \qquad (4)$$

$$C_6H_5NHOH + C_6H_5\overset{+}{N}OH \xrightarrow[\text{slow}]{k_5} C_6H_5\overset{+}{N}H-NC_6H_5 \qquad (5)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad | \quad\; |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad OH \;\; OH$$

$$\xrightarrow[\text{rapid}]{} C_6H_5N=\overset{+}{N}C_6H_5 + H_2O + H^+ \qquad (6)$$
$$\qquad\qquad\quad |$$
$$\qquad\qquad\quad O^-$$

If the initial concentrations of phenylhydroxylamine and nitrosobenzene are a and b, respectively, and that of the azoxybenzene produced at time t is
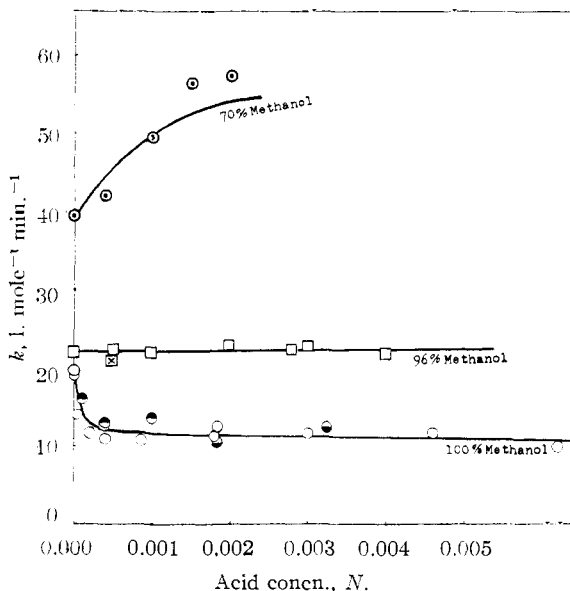

Fig. 4.—k vs. acid concentration: ●⊠, sulfuric acid-catalyzed; ◓, LiCl was added; ○⊙□, hydrogen chloride-catalyzed with various solvents.

x, the following relation is required by these mechanisms, where v, k and K are rate, rate constant and equilibrium constant of the subscripted step, respectively.

$$a - x = [C_6H_5NHOH] + [C_6H_5\overset{+}{N}H_2OH]$$

$$b - x = [C_6H_5NO] + [C_6H_5\overset{+}{N}OH]$$

$$[C_6H_5NHOH] = (a - x)\left(\frac{1}{1 + K_1[H^+]}\right)$$

$$[C_6H_5\overset{+}{N}H_2OH] = (a - x)\left(\frac{K_1[H^+]}{1 + K_1[H^+]}\right)$$

$$[C_6H_5NO] = (b - x)\left(\frac{1}{1 + K_4[H^+]}\right)$$

$$[C_6H_5\overset{+}{N}OH] = (b - x)\left(\frac{K_4[H^+]}{1 + K_4[H^+]}\right)$$

$$v_2 = k_2[C_6H_5NHOH][C_6H_5NO] =$$
$$\frac{k_2(a - x)(b - x)}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

$$v_5 = k_5[C_6H_5NHOH][C_6H_5\overset{+}{N}OH] =$$
$$\frac{k_5K_4[H^+](a - x)(b - x)}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

Since the over-all rate v is the sum of v_2 and v_5, the apparent second-order rate constant k with varying hydrogen ion concentration should be expressed as

$$k = \frac{k_2 + k_5K_4[H^+]}{(1 + K_1[H^+])(1 + K_4[H^+])} \qquad (7)$$

Equation 7 reveals that k approaches k_2 in very weak acidity. The value of k_2 is equal to that of k in a neutral medium, hence k_5 may be calculated from the values of k_2 and k at known acidities using values of K_1 and K_4 in Table I. The values of k_5 thus calculated are shown in Table IV and hold constant over a thousand fold variation in the acid concentration, in agreement with these mechanisms. Using average values of k_5K_4 (Table IV) with the three solvents, the k values were calculated again and are shown in Fig. 4 in comparison with the observed values.

TABLE IV

CALCULATED VALUES OF k_5K_4 AND k_5 AT 40°

[H⁺], N	$k_5K_4 \times 10^{-3}$, 1.² mole⁻² min.⁻¹		
	100% MeOH	96% MeOH	70% MeOH
0.0001	33[a]		
.0004	17.3		
.002	20.6		
.004	26.5		2.88
.005		5.04	
.0086	23.3		
.01	28.8	4.92	3.65
.015			4.13
.018	23.9		
.02		5.31	3.97
.03	25.2	5.15	
.046	26.0		
.062	22.6		
Av.	24.7	5.10	3.66

k_5 (av.) 2.61×10^4 1. mole⁻¹ min.⁻¹

[a] At lower acid concentration, the values show a remarkable departure from constancy. This seems unavoidable, since at 0.0001 N, for instance, a 5% decrease of k (from 18.9 to 18.0) results in a 33% decrease of k_5K_4. The k_5K_4 values calculated from the other mechanisms show over a hundred fold variation.
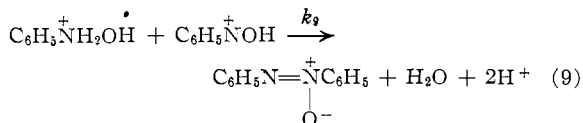
These mechanisms indicate that in neutral solutions a reaction between free phenylhydroxylamine and free nitrosobenzene (eq. 2) predominates, while in acidic solutions a reaction of free phenylhydroxylamine with protonated nitrosobenzene (eq. 5) becomes important, just like the amine-carbonyl condensation.[15] Neither equation 2 nor 5 alone explains the rate–acidity relationship, i.e., the rate constant would decrease with an increase of acidity if equation 2 alone were operating, while the rate would become equal to zero in a neutral solution if equation 5 alone were operating.

(15) J. B. Conant and P. D. Bartlett, THIS JOURNAL, 54, 2881 (1932); M. Okano and Y. Ogata, ibid., 74, 5727 (1952).

Furthermore, the possibilities of the other mechanisms will be discussed below. A rate-determining reaction of protonated phenylhydroxylamine with nitrosobenzene

$$C_6H_5\overset{+}{N}H_2OH + C_6H_5NO \xrightarrow{k_8}$$

$$C_6H_5N\!=\!\overset{+}{N}C_6H_5 + H_2O + H^+ \quad (8)$$
$$\underset{O^-}{|}$$
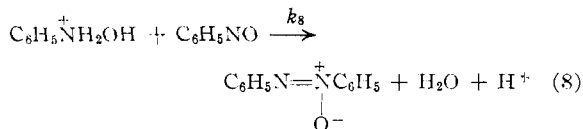
or a rate-determining condensation of both protonated reactants should lead to the rate constant expression

$$C_6H_5\overset{+}{N}H_2OH + C_6H_5\overset{+}{N}OH \xrightarrow{k_9}$$

$$C_6H_5N\!=\!\overset{+}{N}C_6H_5 + H_2O + 2H^+ \quad (9)$$
$$\underset{O^-}{|}$$

tonated reactants should lead to the rate constant expression

$$k = \frac{k_8 K_1[H^+]}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

or

$$k = \frac{k_9 K_1 K_4[H^+]^2}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

respectively; hence neither mechanism alone or combined with equation 5, where

$$k = \frac{k_5 K_4[H^+]}{(1 + K_1[H^+])(1 + K_4[H^+])}$$

agrees with the fact, since each k value should diminish to zero as the hydrogen ion concentration approaches zero. Also, equations 8 and 9 do not seem rational in the light of the electronic theory, since they involve the attack of a cation on the positive nitrogen of nitrosobenzene.

This electronic point of view can also be used to eliminate a mechanism involving the simultaneous reaction of equations 8 and 2, although the mechanism leads to a rate equation consistent with the experiment.

The Kinetics of Solvolysis of Acyl Esters of Salicyclic Acid

BY EDWARD R. GARRETT

The acid, neutral and alkaline hydrolysis of acetyl-, trimethylacetyl-, β-cyclopentylpropionyl- and diethylacetylsalicyclic acids were studied and the rate constants determined as functions of dissociation and of hydrogen and hydroxyl ion concentration. The Arrhenius parameters of entropy and heat of activation also were determined and mechanisms were considered in light of these values and the structures of the esters. Disagreement with values given in the literature was noted. An unusual increase in "spontaneous" rate was observed with increasing alcohol concentration whereas no such increase was noted with increasing dioxane content.

In order to determine the inhibition of hydrolysis of acyl salicylates by varying alkyl substitution on the acyl group, the acid and base hydrolysis of esters selectively chosen to scan substituent effects, acetyl-, trimethylacetyl-, β-cyclopentylpropionyl- and diethylacetyl salicylic acids were studied. A very complete study of the hydrolysis of acetyl salicylic acid (aspirin) had been made by Edwards.[1,2] However, since these papers had reported an unusually high alkaline hydrolysis heat of activation of 25 kcal./mole, whereas similar acyl phenates had activation energies of an order of magnitude of 12 kcal./mole,[3] the hydrolysis studies of aspirin were repeated and the Arrhenius parameters determined.

It was desired to carry out the hydrolysis studies in solutions as nearly aqueous as possible, but the inadequate water solubility of β-cyclopentylpropionyl- and diethylacetylsalicylic acids necessitated use of water–alcohol mixtures as solvents to maintain sufficient material in solution for spectrophotometric analysis. In order to place the hydrolysis studies of all these esters on comparative grounds, the hydrolysis of aspirin was studied in various water–alcohol mixtures. An unexpected increase

in the hydrolysis rates of the anion in the pH-independent region was observed. This pH-independent hydrolysis of the completely ionized compound (as represented by the plateau of rate $vs.$ pH at pH 5.5–9 in Fig. 1) had been ascribed by Edwards[1,2] to the water attack on the aspirin ion and would imply general acid–base catalysis.[4] In this light ethanol would have to be considered a more active base than water. However, Edwards[1] had also shown by studies in various concentrations of acetate buffers that the "spontaneous" hydrolysis was not subject to general acid–base catalysis.

The extraordinary magnitude of this "spontaneous" or water hydrolysis of aspirin has led to the formulation of cyclic mechanisms involving interaction of both carbonyls and their carbons in a rate-determining step.[5,6]

In order to clarify the anomalous enhancement of "spontaneous" hydrolysis with increasing alcohol content of the solvent and to determine if the rates were dependent on water content or were functions of dielectric constant, the "spontaneous" hydrolysis was studied in various dioxane–water mixtures. Surprisingly, there was small variation in hydrolysis rates.

(1) L. J. Edwards, *Trans. Faraday Soc.*, **46**, 723 (1950).

(2) L. J. Edwards, *ibid.*, **48**, 696 (1952).

(3) "Tables of Chemical Kinetics: Homogeneous Reactions," National Bureau of Standards Circular 510, U. S. Department of Commerce, Washington, D. C., 1951.

(4) J. L. Hockersmith and E. S. Amis, *Anal. Chim. Acta*, **9**, 101 (1953).

(5) J. D. Chanley, E. M. Gindler and H. Sobotka, THIS JOURNAL, **74**, 4347 (1952).

(6) D. Davidson and L. Auerbach, *ibid.*, **75**, 5984 (1953).