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The Kinetics of the Acid-catalyzed Etherification of the Tautomers of *p*-Nitrosophenol and *p*-Benzoquinoneoxime with Ethanol

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The rates of the acid-catalyzed reversible etherification reaction of the allelotrope of *p*-nitrosophenol and *p*-benzoquinoneoxime with ethanol to form *p*-nitrosophenetole have been measured by ultraviolet spectrophotometry. The rates of the forward reaction have been found to be the sum of the rate of the second-order with ethanol and the allelotrope and a small portion of the first-order with the allelotrope. The plot of the logarithm of the forward rate constant *vs.* the acidity function gave a straight line with a slope of -0.93. We have postulated a probable mechanism involving the rate-determining attack of protonated ethanol on the carbonyl O-atom of *p*-benzoquinoneoxime and a small portion of the rate-determining protonation to the allelotrope, thus forming protonated *p*-nitrosophenol, followed by a rapid attack on the hydroxyl O-atom of ethanol. The energy of the activation of the forward reaction was 16.3 kcal/mol.

The allelotrope of *p*-nitrosophenol and *p*-benzoquinoneoxime is easily etherified with methanol in the presence of acid at room temperature to form *p*-nitrosoanisole,[1] irrespective of the difficulty of the alkylation of phenols. The reaction conditions for forming *p*-nitrosophenetole have been investigated in a previous report.[2]

In this paper, the authors will describe the mechanism of the formation of *p*-nitrosophenetole on the basis of the results of measurements of the reaction rates and the ultraviolet spectra.

Experimental

Materials. The allelotrope of *p*-nitrosophenol and *p*-benzoquinoneoxime was prepared by the nitrosation of phenol with sodium nitrite at 0—5°C, according to Bridge's method[3]; it was then recrystallized from toluene, yield 65%, mp 134°C (decomp.). Ethanol was refluxed over calcium oxide for several hours to dehydrate and then rectified, bp 78.3°C. The ethanol solution of sulfuric acid was prepared from guaranteed sulfuric acid and absolute ethanol.

Reaction Product Criterion. The blue crystal obtained by the acid-catalyzed reaction of the allelotrope with ethanol did not indicate any melting-point deppression when the product was mixed with an authentic sample prepared by Rising's method[4]; mp and mmp 33°C. Furthermore, this product was reduced with a mixture of acetic acid and zinc, and then acetylated with acetic anhydride to give phenacetine; mp and mmp 135°C.[2]

Ultraviolet Spectrophotometry and Chemical Analysis. The ultraviolet spectra of methanolic solutions of the allelotrope and *p*-nitrosophenetole (each 5×10^{-5} M) are shown in Fig. 1. The absorption maxima of the allelotrope and *p*-nitrosophenetole were 240, 300 and 340 mμ respectively; besides, the absorption minimum of *p*-nitrosophenetole was 260 mμ. Mixtures of the allelotrope, *p*-nitrosophenetole, ethanol, and sulfuric acid of known concentrations

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[1] A. Schoro, A. Kraaijeveld and E. Havinga, *Rec. trav. chim.*, **74**, 1256 (1955).

[2] Y. Furuya and R. Oda, *Kogyo Kagaku Zasshi (J. Chem. Soc. Japan, Ind. Chem. Sect.)*, **65**, 214 (1962).

[3] J. L. Bridge, *Ann.*, **277**, 85 (1893); L. Vanino, "Handbuch der Preparativen Chemie," Verlag von Ferdinand Enke, Stuttgart (1937), p. 674.

[4] A. Rising, *Ber.*, **37**, 46 (1904).

(corresponding to 0, 20, 40, 60, 80 and 100% conversions) were prepared; a plot of the difference in extinctions, $(E_{240}-E_{260})$ *vs.* $(E_{340}-E_{300})$, gave a straight line, and the conversion calculated from the values of $(E_{340}-E_{300})$ at 0 and 100% conversion agreed with the conversions calculated from the composition of the mixture within a 1% error. Hence, it is possible to follow the reaction by means of ultraviolet spectrophotometry.

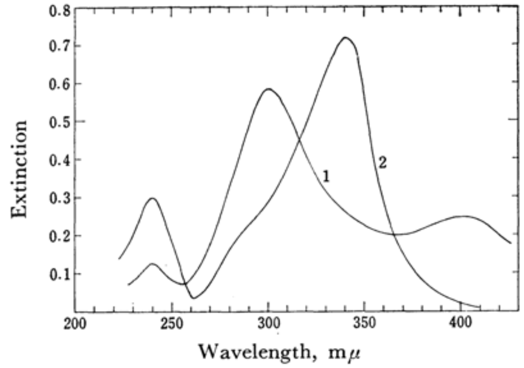

Fig. 1. Ultraviolet spectra of reactant and product in 5×10^{-5} M methanolic solution: 1, the allelotrope of *p*-nitrosophenol and *p*-benzoquinoneoxime; 2, *p*-nitrosophenetole.

A Typical Run for the Rate Measurements. A 5.56×10^{-3} M solution of the allelotrope in ethanol (9 m*l*) was allowed to reach temperature equilibrium (20°C), and then 1 N ethanol solution of sulfuric acid (1 m*l*) was added to start the reaction. Aliquots (each 0.1 m*l*) were pipetted out at appropriate time intervals, and each one was diluted with methanol to a 5.0×10^{-5} M initial concentration of the reactant for spectrophotometry. Then, the extinctions at 240, 260, 300, and 340 mμ were measured. The conversion was calculated graphically from the observed value of $(E_{340}-E_{300})$ and the values of the first-order rate constant, k; then, the forward rate constant, k_1, was calculated.

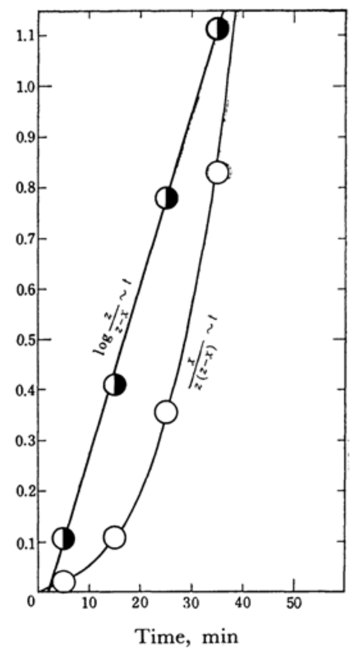

Fig. 2. Determination of reaction order in dioxane at 50°C.
Concn. of the allelotrope and ethanol: 0.2 M, concn. of sulfuric acid: 0.4 N.

Results and Discussion

Typical rate data at 20°C are shown in Table 1. The kinetics follows the first-order equation for reversible reactions, $\ln[z/(z-x)]=kt$, where z and x are the concentrations of the consumed reactant at the equilibrium stage and at time t respectively. So far as the reaction in dioxane is concerned (*cf*, Fig. 2), only the plot of $\log[z/(z-x)]$ *vs.* t gave a straight line; the plot of $x/z(z-x)$ *vs.* t did not. Moreover, in order to make sure of this, the concentration of ethanol was varied. It was found that the first-order rate constant in dioxane, k_d, is expressed as the sum of the rate constant of the first-order k_d' and the second-order k_d'', as given by $k_d=k_d'+k_d''\,[C_2H_5OH]$. Similarly, the observed first-order rate constant in ethanol, k' may be expressed as a sum of the rate constant of the first-order k' and the second-order k'', as given by $k=k'+k''[C_2H_5OH]$. The forward rate constant in ethanol, k_1, was calculated using the equation, $k_1=kz/a$,⁵⁾ where a is the initial concentration of the allelotrope. The k_1 rate constant should be given as a sum of the forward rate constant of the first-order k_1' and the second-order k_2'', as expressed by following equation:

$$k_1 = k_1' + k_2''[C_2H_5OH]$$

Of course, the k_1 rate constant gives a constant value despite any variation in the concentration of the allelotrope. The values of the rate constant, $k_1\times10^4$ sec^{-1}, at the initial concentration of the allelotrope, 1×10^{-3} M, 3×10^{-3} M, 5×10^{-3} M and 7×10^{-3} M in a solution with an acidity function of 1.727 at 20°C, were 1.91, 1.97, 1.93, and 1.97 respectively; 1.95 was obtained as the average value. The energy and entropy of activation were calculated to be 16.3 kcal/mol and −21.2 e.u. respectively from the following average values of $k_1\times10^4$ sec^{-1}: 20°C, 1.95; 25°C, 3.15; 30°C, 4.86.

The plot of $\log k_1$ *vs.* H_0 gave a straight line, with a slope of −0.93, as is illustrated in Fig. 3. Therefore, both the forward first-order rate constant, k_1', and the second-order k_2'' may be expected to contain proton activity. Thus, the mechanism involving protonation before the rate-determining step in both first-order and second-order reactions can be considered.

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5) Y. Ogata, Y. Furuya and K. Aoki, This Bulletin, **38**, 838 (1965).

TABLE 1. THE FIRST-ORDER RATE CONSTANTS OF THE ACID-CATALYZED ETHERIFICATION OF THE ALLELOTROPE WITH ETHANOL AT 20°C

H_0, 1.943; z, 76.6%

Time min	Conversion %	$z-x$	$\log[z/(z-x)]$	10^4k sec^{-1}	10^4k_1 sec^{-1}
0	0	76.60			
10	7.10	69.50	0.0492	1.89	1.44
20	16.07	60.53	0.1018	1.95	1.49
30	22.23	54.37	0.1488	1.90	1.46
40	27.78	48.82	0.1956	1.87	1.43
60	38.98	37.62	0.3086	1.97	1.51
80	46.91	29.69	0.4109	1.97	1.51
100	53.09	23.51	0.5130	1.97	1.51
140	61.83	14.77	0.7135	1.95	1.50
350	76.60			Av. 1.93	1.48

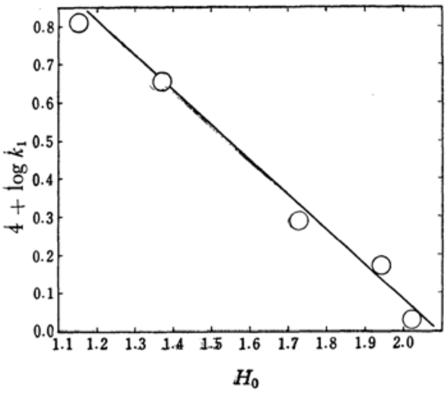

Fig. 3. The plots of $\log k_1$ *vs.* H_0 for the etherification of the allelotrope of *p*-nitrosophenol and *p*-benzoquinoneoxime in ethanol solution at 20°C.

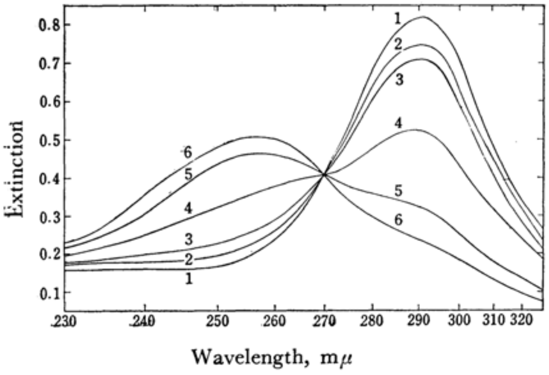

Fig. 4. Effect of sulfuric acid concentration on the allelotrope in dioxane at room temperature.
Concn. of the allelotrope: 5×10^{-5} M
Concn. of sulfuric acid: 1, 0.00 N; 2, 0.05 N; 3, 0.10 N; 4, 0.20 N; 5, 0.30 N; 6, 0.50 N

The ultraviolet absorption spectra were examined in order to confirm the protonated position on the reactants. The ultraviolet spectra of the allelotrope in dioxane are shown in Fig. 4. The absorption maximum of *p*-nitrosophenol (294 mμ) decreases and the new broad absorption maximum (254—259 mμ) increases with an increase in the acidity, as is illustrated in Fig. 4. Also, these curves have an isosbestic point at 270 mμ. Moreover, each absorption is decreased and increased with time at a certain acidity; it takes 2 or 3 hr to give final curves.

Both the absorption maxima of nitrosobenzene (283 and 306 mμ) and *p*-nitrosophenetole (324 mμ) decreased, while the broad maximum at 254—259 mμ increased, with an increase in the acidity in dioxane, and also with the time at a certain acidity. On the other hand, the curves of methyl ether of *p*-benzoquinonemonoxime (315 mμ) and phenol (273.5 and 279.5 mμ) were invariable in the same acidity range (0—1.0 N) Therefore, the new broad maximum at 254—259 mμ may belong to the *p*-nitrosophenol protonated on the O-atom of the nitrosogroup. It can also be considered that the protonation on the O-atom of quinoneoxime is not carried out so easily in this acidity range in the case of ether of quinoneoxime. These results suggest that the protonation to the carbonyl oxygen atom is somewhat difficult in comparison with that to the oxygen atom of the nitroso group; this also agrees with the fact that the products exist largely in a quinoidal form in acidic solutions.6) As the carbonyl O-atom of *p*-benzoquinoneoxime may be more easily attacked by a cationic reagent than *p*-benzoquinoneoxime ether, it can be considered that the carbonyl oxygen atom of *p*-benzoquinoneoxime is perhaps alkylated by protonated ethanol. The ease of the etherification of the allelotrope with alcohol containing catalytic acid is the result of nothing else but the existence of the keto-form derived from keto-enol tautomerism.

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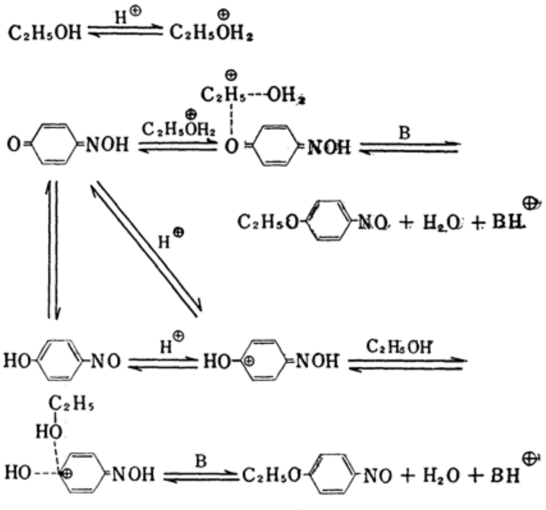
6) L. C. Anderson and R. L. Yanke, *J. Am. Chem. Soc.*, **56**, 732 (1934).

Therefore, it is considered that the protonation of the allelotrope is in part the rate-determining step in the first-order reaction, but in larger measure the attacking step of protonated ethanol on *p*-benzoquinoneoxime determines the rate in the second-order. This is reasonable in view of the fact that the equilibrium mixture of *p*-nitrosophenol and *p*-benzoquinonemonoxime exists largely in the quinoid modification in absolute alcohol and aqueous acid solutions.[6] In other words, the former is the replacement of hydroxyl by the ethoxy group and the latter is the alkylation of the O-atom of *p*-benzoquinonemonoxime. While the value of $k_1'/k_2''[C_2H_5OH]$ is nearly 3 at both 0.2 M allelotrope and ethanol in dioxane, 1/30 is obtained at 0.2 M allelotrope in pure ethanol. Hence, there may be a small replacement of phenolic hydroxyl by the ethoxy group.

It is considered that the ratio of replacement in dioxane is larger than that in ethanol, as has been mentioned above. In fact, a product containing sulfur, in spite of removing the remaining mercaptan completely, is obtained by the reaction of *p*-nitrosophenol (0.2 M) with ethylmercaptan (0.2 M) in dioxane with 0.4 N sulfuric acid at 50°C.[7] It has been pointed out that the phenolic hydroxyl group undergoes a nucleophilic replacement with ^{18}O-enriched water and also mercaptan, forming ^{18}O-enriched phenol[8] and thioether[9] respectively.

These results suggest the over-all mechanism for the reaction as follows:



(B: HSO_4^-, C_2H_5OH, H_2O, *etc.*)

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[7] According to unpublished data obtained in our laboratory.

[8] S. Oae, T. Fukumoto and R. Kiritani, This Bulletin, **36**, 346 (1963); S. Oae and R. Kiritani, *ibid.*, **37**, 770 (1964).

[9] S. Oae and R. Kiritani, *ibid.*, **38**, 1381 (1965).