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The Kinetic Studies of the Acid-catalyzed Etherification of the Tautomers of *p*-Nitrosophenol and *p*-Benzoquinoneoxime with Ethanol in Dioxane

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The rates of the acid-catalyzed reversible etherification of the allelotrope of *p*-nitrosophenol and *p*-benzoquinoneoxime with ethanol in dioxane-forming *p*-nitrosophenetole have been measured by ultraviolet spectrophotometry. The rate of the forward reaction was expressed as the sum of the second- and the third-orders over a fairly large concentration region of the allelotrope and of ethanol. The plots of the logarithm of the apparent forward second-order rate constant against $-\log(C_{BH^+}/C_B)$ gave a straight line with a slope of -0.95. A probable mechanism involving the rate-determining formation of a σ-complex by the nucleophilic attack of the hydroxyl O-atom of ethanol on the α-carbon of the hydroxyl group of protonated *p*-nitrosophenol, and also the rate-determining deprotonation from the oxime group of the σ-complex by the allelotrope of *p*-nitrosophenol, was postulated.

The introduction of a nitroso group at the para position of phenol facilitates the etherification of the phenolic hydroxyl group.[1] The investigation of the optimum reaction conditions for the formation of *p*-nitrosophenetole has previously been reported by one of the present authors.[2] It has been considered, on the basis of synthetic results, that the facile equilibrium between the allelotrope of *p*-nitrosophenol and its ether presumably depends on the powerful activating effect of the protonated nitroso group.[3] However, the kinetics of this reaction was expressed as the sum of the second and third-orders under the conditions of these studies. It is interesting to investigate the reaction mechanism expressed by two terms.

Experimental

Materials. The allelotrope of *p*-nitrosophenol was prepared according to Bridge's method[4] and then recrystallized from benzene; yield 67%, mp 134°C (decomp). The ethanol was refluxed over calcium oxide for several hours and then rectified; bp 78.3°C. The dioxane was boiled under reflux for 7 hr with 10% of its volume of 1N aqueous hydrochloric acid, a slow stream of air being passed in through the condenser in order to remove the acetaldehyde formed. The organic layer was separated after treatment with potassium hydroxide and then distilled from the sodium; bp 101°C. The dioxane solution of sulfuric acid was prepared from guaranteed sulfuric acid and the anhydrous dioxane obtained as above.

Ultraviolet Spectrophotometry and Chemical Analysis. The reactions were followed by means of a Hitachi Perkin-Elmer UV-VIS spectrophotometer, model 139. The absorption maxima of the allelotrope and *p*-nitrosophenetole were 300 and 343 mμ respectively. Dioxane solutions of the allelotrope, *p*-nitrosophenetole, sulfuric acid, and ethanol of known concentrations (corresponding to 0, 20, 40, 60, 80 and 100% conversion) were prepared; a plot of the difference of extinction, $(E_{370}-E_{315})$ *vs.* $(E_{343}-E_{315})$, gave a straight line, and the conversion calculated from the values of $(E_{343}-E_{315})$ at 0 and 100% conversion agreed well (within a 1% error) with the conversions obtained from the composition of the solution.

Criterion of the Reaction. As the $(E_{370}-E_{315})$ *vs.* $(E_{343}-E_{315})$ plots of the actual reaction did not deviate at all from the calibration curve obtained above, it can be considered that the reaction forming *p*-nitrosophenetole occurs without any side reaction.

The reaction mixtures obtained using ethyl mercaptan and/or ethanol were extracted with ether; they were washed with water in order to eliminate the acid and then dried. The solutions were examined by means of gas chromatography employing a Yanagimoto gas chromatograph, model GCG-550FTP, operated with an F.I.D. and a 1.5-m column packed with 1.5% SE-30 coating Celite 545, using nitrogen with a flow rate of 45 m*l*/min from 50 to 150°C and with a programing rate of 12°C/min and a chart speed of 1 cm/min. The retention times of the authentic samples in ether and the two ethereal solutions prepared as described above are as follows:

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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. T. Hays, E. H. de Butts and H. L. Young, *J. Org. Chem.*, **32**, 153 (1967).

[4] J. L. Bridge, *Ann.*, **277**, 85 (1893).

Table 1. The retention times of authentic samples and the products obtained from the etherification of the allelotrope with ethyl mercaptan and/or ethanol

	Authentic samples and unknown products							
	EtSH	PhSH	PhOEt	PhOH		PhSEt	*p*-EtO–C_6H_4–NO	The Allelo.
Retention time (min)	1.20	1.35	1.50	1.85		2.95	4.55	6.75
	Reaction mixture treated with EtSH							
	1.10	—	—	—	2.30	—	—	6.50
	Reaction mixture treated with EtOH							
	—	—	—	—	—	—	4.55	6.55

A Typical Run for the Rate Measurements. A solution of 0.25 m*l* of 2N sulfuric acid in dioxane was poured into a solution of 4.75-m*l* portions of both 0.211M allelotrope and ethanol in dioxane in order to start the reaction after both solutions had attained temperature equilibrium. Aliquots (each 0.1 m*l*) were taken out at appropriate time intervals; each one was diluted with methanol to a 5×10^{-5}M total concentration of the allelotrope and *p*-nitrosophenetole. The conversion percentage was calculated from the observed value of $(E_{343}-E_{315})$, while the values of the apparent forward second-order rate constant, k_2', were calculated graphically.

Determination of the Water in the Reaction System. The remaining water in the reaction system was determined to be 0.2M by the Karl Fischer method.

Measurement of the Isotope Effect. The preparation of the dioxane containing heavy water was carried out as follows: the water present in dioxane as a reaction solvent was removed by distillation after the solvent had been heated under reflux with metal sodium. Heavy water, D_2O, was added, and then removed as above. These procedures were repeated three times. The dioxane containing the usual water was treated in the same manner.

The mobile hydrogen in the allelotrope of *p*-nitrosophenol was exchanged with deuterium as follows: the allelotrope (1.01 g, 0.0082 mol) was dissolved in a mixture of absolute methanol (11.2 g, 0.35 mol) and deuterium oxide (0.94 g, 0.047 mol), after which the mixture was allowed to stand for 4 hr at room temperature. Then the medium was removed under reduced pressure. These procedures were repeated three times. It was determined by infrared analysis[*1] that some of the mobile hydrogen in the allelotrope was exchanged with deuterium by the above treatment.

As alcohol, the usual alcohol and tetradeuteriomethanol were used for the usual reactions and for the reactions of the deuterio-compounds respectively. *p*-Nitrosoanisole, as an authentic sample, was prepared by the acid-catalyzed reaction of *p*-nitrosophenol with methanol and was recrystallized 3 times from petroleum ether; mp 24°C.

The rate constants, k_2 and k_3, were expressed as $k_{2\mathrm{H}}$ and $k_{3\mathrm{H}}$ for the usual reactions of the allelotrope with methanol and as $k_{2\mathrm{D}}$ and $k_{3\mathrm{D}}$ for the reactions of the deuterio-allelotrope with tetradeuteriomethanol in the presence of dideuteriosulfuric acid in dioxane containing deuterium oxide only.

Results and Discussion

A typical rate plot of the reaction at 60°C is shown in Fig. 1. The reaction follows the second-order reversible kinetics:

$$\mathrm{d}x/\mathrm{d}t = k_2'(a-x)(b-x) - k'_{-2}(c+x)x, \qquad (1)$$

where *a*, *b*, and *c* are the initial concentrations of the allelotrope, ethanol, and water respectively, and where *x* is the concentration of the consumed reactant at time *t*. The following equation is obtained by integrating Eq. (1):

$$\log\frac{x+m}{z-x} = \frac{ab(c+2z)-(a+b+c)z^2}{2.303z(c+z)}k_2't + \log\frac{m}{z} \qquad (2)$$

where:

$$m = \frac{ab(c+z)}{ab-(a+b+c)z}$$

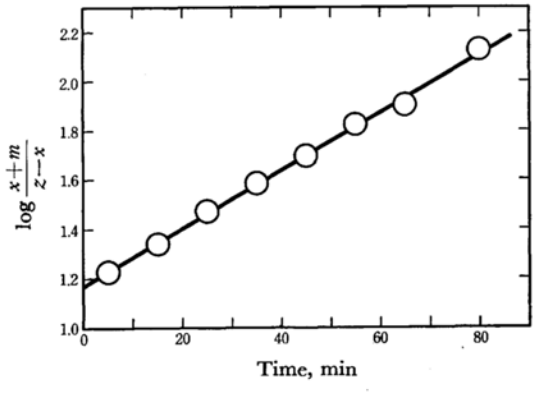

Fig. 1. The reversible second-order rate plot for the acid-catalyzed etherification of the allelotrope in dioxane at 60°C.
Concn. of H_2SO_4: 0.1N
Initial concn. of the allelotrope: 0.2M
Initial concn. of H_2O: 0.2M
Initial concn. of C_2H_5OH: 0.3M

[*1] For this analysis, the potassium bromide tablet method was used. The intermolecular hydrogen bonding band in 3450 cm^{-1} was decreased and the hydroxyl stretching band in 2780 cm^{-1} was increased in the case of this sample.

and where z is the concentration of the consumed reactant at equilibrium. The plots of $\log(x+m)/(z-x)$ *vs.* t gave a straight line, and the value of the forward rate constant, k_2', was calculated from the slope. Here, the plots for the reversible second-order reaction, $\log(x+m)/(z-x)$ *vs.* t, bear a close resemblance to that for the reversible first-order reaction, $\log z/(z-x)$ *vs.* t. Therefore, we have misapprehended the reaction order in a previous report.5) During repeated measurements, the first-order rate constant, k_d', has scarcely ever been found.

On the variation of the initial concentration of the ethanol, the apparent forward second-order rate constant, k_2', holds constant, as is obvious in Fig. 2. The plots of the k_2' rate constant against the initial concentration of the allelotrope gave a straight line with a definite slope, a line which did not pass through the point of origin, as is shown in Fig. 3. Thus, the forward rate equation may be given by:

$$v_{\text{forward}} = k_2'[\text{Allelo.}][\text{Ethanol}]$$
$$= \{k_2 + k_3[\text{Allelo.}]\}[\text{Allelo.}][\text{Ethanol}] \quad (3)$$

The rate was also affected by the acidity of the reaction medium. The indicator ratio, $C_{\text{BH}^+}/C_{\text{B}}$, at 373 m$\mu$ for each medium was determined spectrophotometrically using *p*-nitroaniline. The values of $\log k_2'$ were plotted against $-\log(C_{\text{BH}^+}/C_{\text{B}})$ instead of H_0. As is illustrated in Fig. 4, a straight line with a slope of -0.95 was obtained. Therefore, both the k_2 and k_3 rate constants should involve the term of h_0.

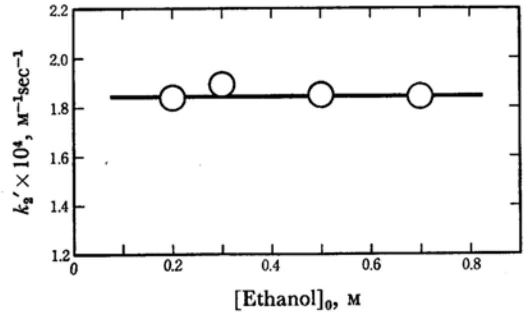

Fig. 2. The plots of $\log k_2'$ *vs.* initial concentration of ethanol for the etherification of the allelotrope in dixoane at 60°C.
Concn. of H_2SO_4: 0.1N
Initial concn. of the allelotrope: 0.2M
Initial concn. of H_2O: 0.2M

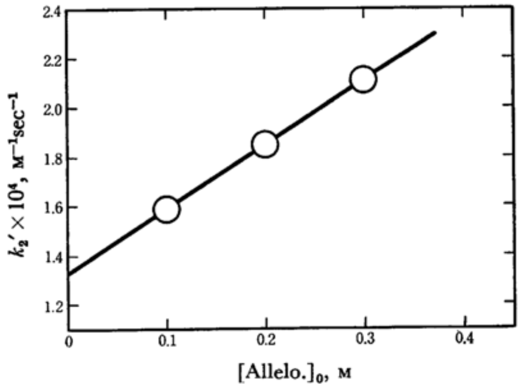

Fig. 3. The plots of $\log k_2'$ *vs.* initial concentration of the allelotrope for the etherification of the allelotrope in dioxane at 60°C.
Concn. of H_2SO_4: 0.1N
Initial concn. of C_2H_5OH: 0.5M
Initial concn. of H_2O: 0.2M

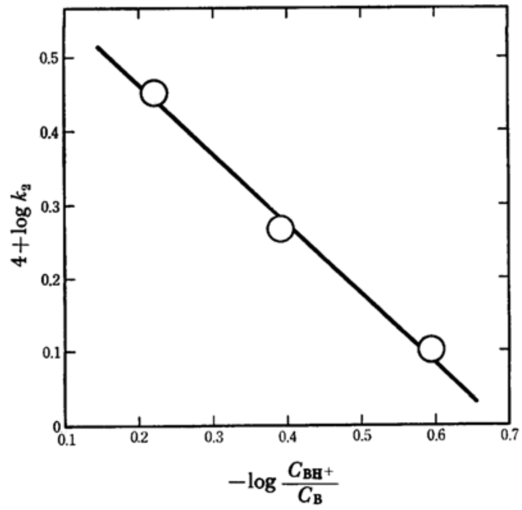

Fig. 4. The plots of $\log k_2'$ *vs.* $-\log(C_{\text{BH}^+}/C_{\text{B}})$ for the etherification of the allelotrope in dixoane at 60°C.
Initial concn. of the allelotrope: 0.2M
Initial concn. of C_2H_5OH: 0.5M
Initial concn. of H_2O: 0.2M

It has been reported that the ratio of quinoidal (keto) and benzenoid (enol) forms in an equilibrium was determined by the difference in hydrogen-bond fission in the aggregated molecules.6) The present authors have thought that the promoting forces are protonation and/or deprotonation. As the tendency of protonation to the nitroso group on the benzenoid form, I, is larger than that to the carbonyl group in the quinoidal form, II,5) the rate of the formation of II is larger than that of I. An analogous situation holds in a protic solvent such as alcohols. In the case of an aprotic solvent such as dioxane, deprotonation is probably the promoting force. As deprotonation from the O-atom of the oxime group in II may be more difficult than that from the hydroxyl group in I, and as protonation to the

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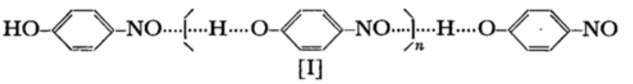
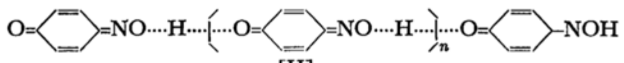
5) Y. Furuya, D. Morikawa and K. Itoho, This Bulletin, **40**, 1425 (1967).

6) E. Havinga and A. Schors, *Rec. trav. chim.*, **69**, 457 (1950).



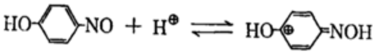
[I]



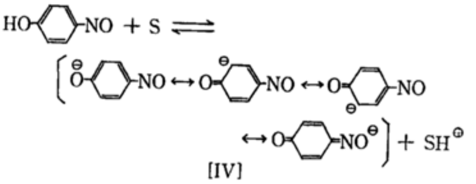
[II]

nitroso group in **I** is easier than that to the carbonyl group in II,[5] the allelotrope probably exists largely in the quinoldal form. These presumptions agree well with the experimental results.[6]

The allelotrope seems to be in the monomolecular state, mostly in dioxane ranging from 0.1 to 0.3M.[7] Therefore, the intermediate of tautomerism is the protonated *p*-nitrosophenol in an acidic and/or protic solvent and the deprotonated *p*-nitrosophenol anion, IV, in an aprotic solvent:



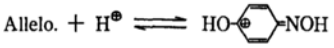
[III]



[IV]

The participation of the proton in this reaction system can be considered to be as follows:

$$C_2H_5OH + H^{\oplus} \rightleftharpoons C_2H_5\overset{\oplus}{O}H_2 \qquad (4)$$



(5)

$$C_2H_5OH + H^{\oplus} \rightleftharpoons C_2H_5^{\oplus} + H_2O \qquad (6)$$

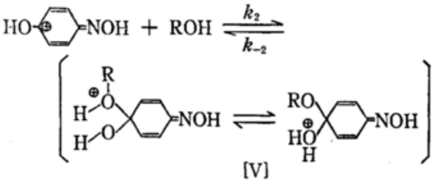
When two equilibria, (4) and (5), occur in a reaction mixture, the slope of the straight line obtained from the plots of $\log k_2'$ *vs.* H_0 should be -1. Considering the relationship of H_0 and J_0,[8] the value of the slope should be smaller than -1 when the (5) and (6) equilibria take place. As has been described above, the plots of $\log k_2'$ against H_0 gave a straight line with a slope of -0.95. Thus, the protonation to ethanol will give a protonated ethanol, not an ethyl cation.

Now, the pK_{BH^+} values of ethanol, dioxane, and the allelotrope are -2.5,[9] -4.4,[10] and -3.4[11] respectively. Thus, the order of the ease of the protonation is as follows: ethanol > the allelotrope > dioxane.

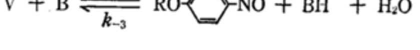
The ethyl cation, $C_2H_5^+$, is not formed under the reaction conditions described above. Hence, we may conclude the attack of protonated *p*-nitrosophenol on the hydroxyl O-atom of ethanol. This can be assumed also from the fact that a new peak, which is probably due to *p*-nitrosothiophenetole, is found by gas chromatography in the reaction mixture using ethyl mercaptan. If the ethereal O-atom of *p*-nitrosophenetole is derived from *p*-nitrosophenol, *p*-nitrosothiophenetole should not be formed by the reaction of *p*-nitrosophenol with ethyl mercaptan whose C–S bond is firm. Therefore, the promoting force of the reversible reaction forming *p*-nitrosophenetole from the allelotrope does not depend on the protonated ethanol, but on protonated *p*-nitrosophenol. Thus, the reaction will be promoted by a nucleophilic attack of the hydroxyl O-atom of ethanol on the α-C of the hydroxyl group of protonated *p*-nitrosophenol.

In constructing the second term of Eq. (3), the following three cases can be considered: (1) the formation of a π-complex between a molecule of protonated ethanol and the allelotrope, (2) the existence of the dimer of the allelotrope, and (3) the behavior of the allelotrope as a base in the deprotonation step. The formation of π-complex was scarcely observed at all under these reaction conditions. Also, the molecular association of the allelotrope was not found by the freezing-point-depression method, as has been mentioned above. Thus, the allelotrope can be expected to behave as a base in the deprotonation step from the σ-complex, V. For caution's sake, the kinetic isotope effects of hydrogen were also examined. The ratios of k_{2H}/k_{2D} and k_{3H}/k_{3D} were 0.83 and 2.58 respectively.

Therefore, we may consider that the first and second terms correspond to Steps (7) and (8) respectively. The value of k_2 is comparable to that of k_3. When the proton is abstracted by strong



[V] (7)



(8)

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[7] From the molecular weight of the allelotrope obtained by the freezing-point-depression method, scarcely no molecular association was found.

[8] M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957).

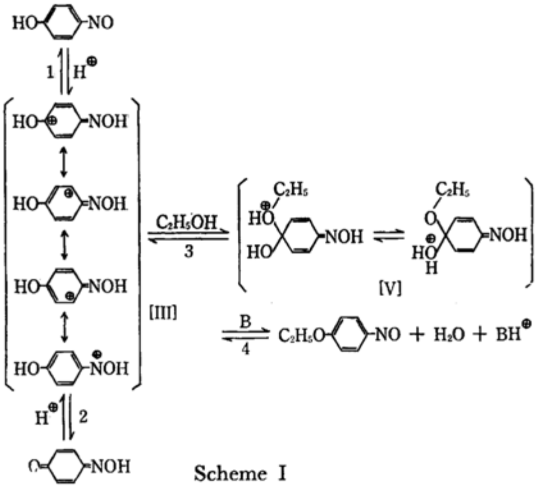
[9] It was presumed that the pK_{BH^+} value of ethanol was nearly equal to that of methanol; *cf.* N. C. Deno and J. O. Turner, *J. Org. Chem.*, **31**, 1969 (1966).

[10] H. Lemaire and H. J. Lucas, *J. Am. Chem. Soc.*, **73**, 5198 (1951).

[11] According to our measurements using the UV method.

bases, such as water and alcohol, the value of k_3 in Step (8) becomes very large. Thus, Step (7) controls the rate in a pathway participated in by a strong base; this step is expressed as the first term in Eq. (3). This is demonstrated also by the fact that the k_2' rate constant does not contain the concentration of ethanol; moreover, the isotope effect was not observed. On the other hand, in the case of the deprotonation by a weak base such as the allelotrope of *p*-nitrosophenol, it is obvious, from the kinetics and isotope effect, that Step 8 determines the rate.

From these findings the following probable mechanism may be suggested (Scheme I).



Scheme I

B: H_2O, C_2H_5OH, the allelotrope, dioxane and HSO_4^-, *etc.*

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