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Studies on the Baudisch Reaction. II. The Copper(II)-Hydroxylamine Complex[1]

Iwao Tanimoto

Faculty of Home Economics, Kyoto Women's University, Higashiyama-ku, Kyoto

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Kinetic investigation of the Baudisch reaction indicates that the reaction follows first-order kinetics, and the isokinetic temperature lies at −11°C. Both kinetic studies and product studies require the formation of a phenol-copper-hydroxylamine-hydrogen peroxide complex during the course of the reaction. It was found that the yield of *o*-nitrosophenol which is the main product of the Baudisch reaction is counterbalanced by that of catechol according to the pH of the reaction system. Maximum yield of *o*-nitrosophenol is attained in the lower pH region (pH=2.5—3.5). Catechol which is the main product in the higher pH region (pH>4) seems to be produced through the same complex.

Several tentative mechanisms on the Baudisch reaction—the conversion of aromatic hydrocarbons or phenols to *o*-nitrosophenol by hydrogen peroxide, hydroxylamine hydrochloride, and copper(II) ion—were submitted by several investigators,[2-4] but they could hardly explain our findings.[1,5] We pointed out that the marked steric effect of a methyl group occupying a position meta to the phenolic hydroxy group and the exclusive production of the ortho isomer might be the reflection of the formation of a bulky copper complex as an intermediate. In this paper, it is shown that this consideration has been further confirmed by spectroscopic and kinetic studies.

Results and Discussion

Copper(II)-Hydroxylamine Hydrochloride Complex in the Reaction Medium. In order to investigate the nature of the complex which might be produced during the course of the reaction, several experiments were undertaken. In methanol, the mixture of anhydrous copper(II) salt and hydroxylamine hydrochloride showed a characteristic absorption spectrum. The absorption maxima were at 230 and 273 mμ (Fig. 1).

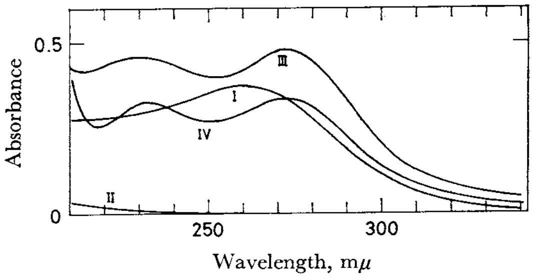

Fig. 1. Absorption spectrum of a copper-hydroxylamine hydrochloride complex in methanolic medium: I, $CuSO_4$ anhyd. (2×10^{-3}M); II, $NH_2OH\cdot HCl$ (4×10^{-3}M); III, $CuSO_4$-$NH_2OH\cdot HCl$ (1 : 2); IV, $Cu(OH)_2$-$NH_2OH\cdot HCl$ (1 : 2).

A study by the molar ratio method showed that hydroxylamine hydrochloride combined with copper(II) ion in the mole ratio of 2 : 1 to form a complex species.[6] Since a mixture of this methanolic complex solution and phenol solely produced *o*-nitrosophenol when it was treated with hydrogen peroxide, the species observed by spectroscopy seems to be a precursor of the actual complex which is produced during the course of the Baudisch reaction. The copper(II)-hydroxylamine hydrochloride complex could also be detected in aqueous medium by spectroscopy.

Kinetic Studies. Kinetic measurements for the formation of *o*-nitrosophenols from phenols were

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1) Part I: K. Maruyama, I. Tanimoto and R. Gotō, *J. Org. Chem.*, **32**, 2516 (1967).

2) a) O. Baudisch, *Naturwissenschaften*, **27**, 768 (1939). b) O. Baudisch and S. H. Smith, *ibid.*, **27**, 769 (1939). c) O. Baudisch, *J. Amer. Chem. Soc.*, **63**, 622 (1941).

3) G. Cronheim, *J. Org. Chem.*, **12**, 1 (1947).

4) J. O. Konecny, *J. Amer. Chem. Soc.*, **77**, 5748 (1955).

5) K. Maruyama, I. Tanimoto and R. Goto, *Tetrahedron Lett.*, **1966**, 5889.

6) A copper(II)-hydroxylamine complex $CuSO_4$-$2NH_2OH$ reported by M. Adams and E. Overman (*J. Amer. Chem. Soc.*, **31**, 637 (1909)) is insoluble in methanol and different from the complex described here. However, the insoluble complex also reacted with phenol and hydrogen peroxide in the acidic medium to give *o*-nitrosophenol. It seems likely that the active complex involved in the Baudisch reaction is a protonated species.

TABLE 1. KINETIC DATA FOR THE BAUDISCH REACTION[a]

	$k\times10^5$, $\mathrm{sec^{-1}}$				E kcal·mol^{-1}	$\Delta S^{\ne}$[b] e.u.
	0.0°C	10.0°C	20.0°C	30.0°C		
m-Chlorophenol	1.02	4.36	14.8	53.5	21.6±0.2	− 4.1
o-Chlorophenol	0.441[c]	1.91	6.38	16.6	20.4±0.7	− 9.2
p-Chlorophenol	1.65	4.22	12.6	42.1	18.2±0.8	−16.2
m-Cresol	1.36	5.35	12.3	36.2	17.6±0.6	−17.8
Phenol	2.39	3.56	14.0	29.8	14.9±1.5	−28.2
o-Cresol	0.301	1.11	2.92	4.10	14.7±1.5	−32.2
p-Cresol	0.856	2.19[d]	4.17	6.31	11.9±0.9	−39.7
2,5-Xylenol	0.138	0.244	0.583	0.710	9.5±0.9	−52.6
3,5-Xylenol	0.800	1.87	2.54	3.05	7.2±1.1	−56.6

a) All reactions were conducted under nitrogen atmosphere. Phenol (1×10^{-2} mol), copper (II) nitrate (1×10^{-2} mol) and hydroxylamine hydro chloride (2×10^{-2} mol) were stirred in 198 m*l* of a Walpole buffer (pH 2.50) after the addition of a hydrogen peroxide solution (30%) (2 m*l*). The temperature was controlled within ±0.1°C.

b) The entropy of activation was calculated at 10.0°C.

c) The reaction was conducted at 0.4°C.

d) The reaction was conducted at 10.3°C.

carried out. Phenol, *o*-, *m*- and *p*-cresols, *o*-, *m*- and *p*-chlorophenols, 2,5- and 3,5-xylenols were studied. The concentration of phenol at any time was assumed to be given by the difference between its initial concentration and the concentration of the product. The experimental kinetic plots gave first-order kinetics in the phenols in spite of the fact that other reactants, *i. e.* copper(II) salt, hydroxylamine hydrochloride and hydrogen peroxide, were not contained in a very large excess over the phenols in the reaction system; a logarithmic plot of the data gave a straight line from 15 min to 90 min after the reaction started. Therefore, the following reaction steps are compatible with the kinetics if we assume that steps 1 and 2 proceed fast enough to produce complex I and the conversion of complex I in step 3 is a slow rate-determining

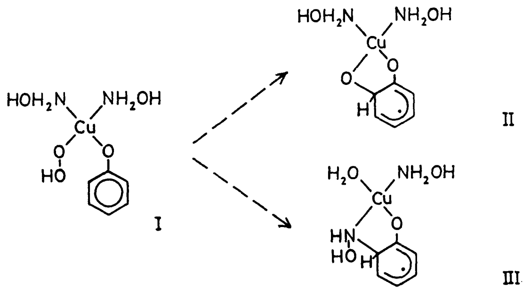
$$\mathrm{Cu^{2+}} + \text{Phenol} \xrightarrow{\text{fast}} \text{Cu-Phenolate} \qquad (1)$$

$$\text{Cu-Phenolate} + x\mathrm{NH_2OH} + \mathrm{H_2O_2} \xrightarrow{\text{fast}} \text{Complex I} \qquad (2)$$

$$\text{Complex I} \xrightarrow{\text{solw}} \cdots \longrightarrow o\text{-Nitrosophenol} \qquad (3)$$

step, because in such a case the limiting factor in determining the concentration of complex I is the amount of phenol. At present, the details of the reaction steps from complex I to *o*-nitrosophenol are not known, but the thermodynamic quantities for the reactions seem to give an important clue to this point.

In Table 1, first-order rate constants have been tabulated together with the thermodynamic quantities of the reactions. The negative values of $\Delta S^{\ne}$ for all of the reactions studied suggest that the reactions require a highly ordered arrangement of atoms in the transition state. In fact, the large negative value of $\Delta S^{\ne}$ for the reaction of phenol may be explained if one assumes the ring-closure process to form cyclic complex II or III from a copper-hydroxylamine-phenolate complex I. The reaction pathway from complex I to complex II or III is not known as yet, but radical nature of attack may be assumed[7] in spite of the fact that the activation energies suggest somewhat electrophilic attack on the aromatic ring (see Table 1). However, as can be seen from Table 1, the reactions are predominantly controlled by entropy



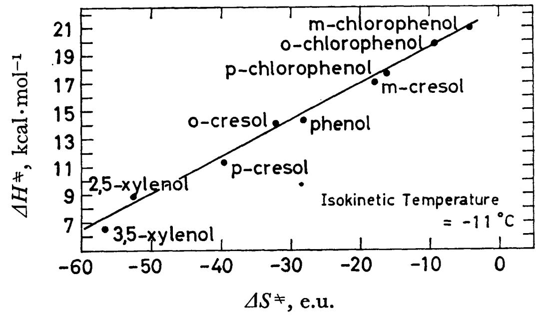


Fig.2. Isokinetic plot for the Baudisch reaction of phenols in aqueous medium. The enthalpy of activation was calculated from energy of activation by subtracting 0.6 kcal·mol^{-1}.

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[7] J. K. Kochi, *J. Amer. Chem. Soc.*, **84**, 774 (1962); *ibid.*, **85**, 1958 (1963).

factor, *viz.*, the reaction of highest energy of activation has the highest rate of reaction. A plot between enthalpy of activation and entropy of activation is sufficiently linear (Fig. 2). The existence of the linear relationship indicates a constant mechanism for the related series of reactions. The isokinetic temperature calculated by the method of least squares was -11°C. Thus, near room temperature, the Baudisch reaction is conducted in the region in which the entropy of activation is a commanding factor.

The Catechol Production. From preliminary experiments, it was found that the yield of *o*-nitrosophenol is seriously affected by pH values of the system. Therefore, the identification of other reaction products was attempted and the effect of pH on the yield of the products was investigated. In 1955, Brackman and Havinga investigated the oxidation of phenol under conditions identical with the Baudisch conditions, but they failed to find *o*-nitrosophenol and catechol.[8] However, even in the Baudisch system, phenol was converted predominantly to catechol in the pH region higher than 4.0 (Fig. 3). On the other hand, neither catechol nor hydroquinone were found under the optimum conditions for *o*-nitrosophenol formation (pH=2.5—3.5). Catechol and hydroquinone were found in the molar ratio of 1.8 at pH 5.5 where no *o*-nitrosophenol was produced. The absence of resorcinol in the reaction products was confirmed by thin layer chromatography. Since the selective formation of ortho isomer is not generally observed when a free hydroxy radical is responsible for the hydroxylation of phenol,[9,10] the predominant formation of catechol under the Baudisch conditions will be due to a copper(II)-hydroxylamine-hydrogen peroxide-phenol complex I. Furthermore, yield of catechol much higher than that formed by the reaction of phenol with simple copper(II) ion and hydrogen peroxide was observed under the Baudisch conditions (Fig. 3). This fact indicates that the production of catechol from phenol was much promoted by the formation of complex I.

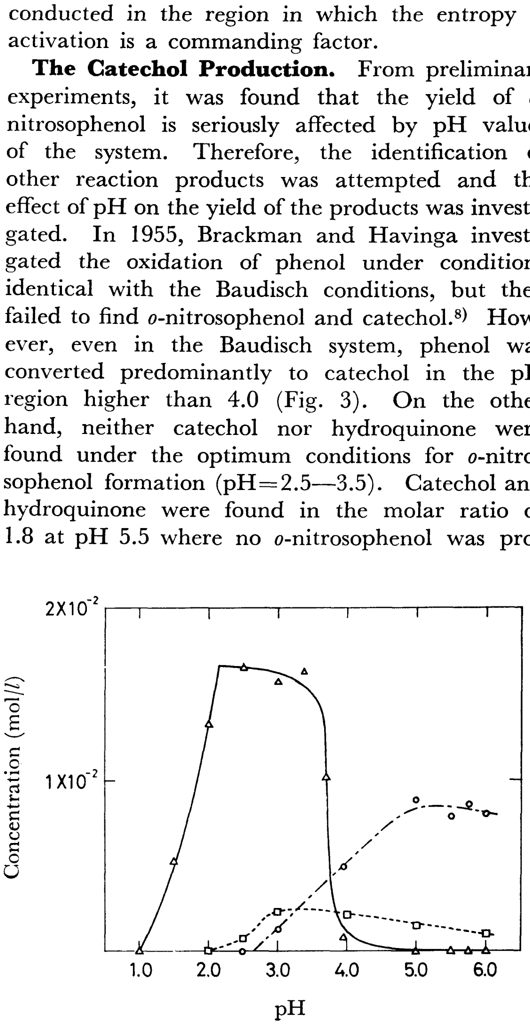

Fig. 3. pH dependence of the formation of *o*-nitrosophenol and catechol from phenol: (—△—) *o*-nitrosophenol; (---○---) catechol, under the Baudisch conditions; (—□—) catechol, by copper(II) nitrate and hydrogen peroxide. All of the reactions were conducted at 30°C for 30 min under a nitrogen atmosphere. The maximum concentration of catechol produced the Baudisch reaction may be comparable with that of *o*-nitrosophenol, because our estimation of catechol may be slightly low owing to the limited extraction of catechol.

At pH 5.5, coppper(II) nitrate was reduced to a brownish white precipitate in the aqueous mixture of phenol and hydroxylamine hydrochloride and had no ability to achieve *o*-nitrosation. However, the mixture retained the ability for catechol production. Even if the pH of the mixture was brought again to pH 2.5, the ability to achieve *o*-nitrosation was not restored. The results indicate that a reduced form of the copper complex has no ability to achieve *o*-nitrosation of phenol, but is responsible for *o*-hydroxylation.

It seems most likely that the complex which is responsible for the formation of catechol is essentially the same as that responsible for the formation of *o*-nitrosophenol. However, in the higher pH region, the copper in the complex is reduced and catalyzes *o*-hydroxylation only. In the lower pH region, the reducing power of hydroxylamine is probably suppressed by the protonation and copper(II)—indispensable for the *o*-nitrosation of phenol—is retained in the reaction system.

Experimental

Materials. *m*- and *p*-Cresols were purified according to the method of Brückner,[11] the boiling point of *m*-cresol was 202°C (lit, 202.2°C) and that of *p*-cresol was 201°C (lit, 202.5°C). *m*- and *p*-Chlorophenols were purified *via* their benzoates, as in the case of phenol.[12] The benzoate of *m*-chlorophenol (mp 69—70.5°C, lit, 71°C) and the benzoate of *p*-chlorophenol (mp 85—86°C, lit, 87—88°C) were hydrolyzed to the phenols, and the phenols were used after distillation. Copper(II) hydroxide was prepared according to literature.[13] Reagent grade 30% hydrogen peroxide solution was obtained from Mitsubishi Chemical Co. and iodometric titration showed that the concentration was 10.2 M. Other

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[8] W. Brackman and E. Havinga, *Rec. Trav. Chim., Pays-Bas*, **74**, 937, 1021, 1070, 1100, 1107 (1955).

[9] G. Stein and J. Weiss, *J. Chem. Soc.*, **1951**, 3265.

[10] G. A. Hamilton, J. W. Hanifin, Jr., and J. P. Friedman, *J. Amer. Chem. Soc.*, **88**, 5269 (1966).

[11] H. Brückner, *Z. Anal. Chem.*, **75**, 289 (1928).

[12] E. Berliner, F. Berliner and I. Nelidow, *J. Amer. Chem. Soc.*, **76**, 507 (1954).

[13] G. Brauer, "Handbuch der Präparativen Anorganische Chemie," Part 1, F. Enke Verlag, Stuttgart (1954), p. 756.

reagents were reagent grade and, if necessary, were used after further purification. Silica gel G (Merck, according to Stahl) was used as an absorbent in thin layer chromatography.

Spectrophotometry. The ultraviolet spectrum of copper(II) sulfate solution (2×10^{-3}M) or hydroxylamine hydrochloride solution (4×10^{-3}M) was determined using 1 mm quartz cell with a recording spectrophotometer.

To prepare stock copper(II)-hydroxylamine hydrochloride complex solution, anhydrous copper(II) sulfate (0.160 g, 1×10^{-3} mol) or copper(II) hydroxide (0.0976 g, 1×10^{-3} mol) was dissolved in a small amount of concentrated methanolic solution containing 0.138 g (2×10^{-3} mol) of hydroxylamine hydrochloride and the resulting mixture was diluted to 10 m*l* with methanol. After the stock solution was diluted 50-fold determination of its ultraviolet spectrum was carried out.

Determination of *o*-Nitrosophenol. General procedures for the Baudisch reaction and the determination of *o*-nitrosophenol produced were described previously.[1]

Kinetic Studies. The general procedure for the Baudisch reaction described previously[1] was used under conditions controlled by a Walpole buffer (pH 2.5). Determination of *o*-nitrosophenols was carried out at intervals of 20 min.

Determination of Catechol. Copper(II) nitrate trihydrate (1.208 g, 5×10^{-3} mol) and phenol (0.471 g, 5×10^{-3} mol) were dissolved in 100 m*l* of a suitable Walpole buffer or an acetic acid-sodium acetate buffer. After the mixture was stirred with 1 m*l* of 30% hydrogen peroxide solution for 30 min at 30°C under nitrogen atmosphere, 20 m*l* of the reaction mixture was pipetted out and acidified with 2 m*l* of concentrated hydrochloric acid. The acidified solution was extracted with 20 m*l* of ether and the twice each with 5 m*l* of the same solvent. After being washed with water, all of the extract was extracted with 10 m*l* of aqueous 5% sodium hydroxide and then with 5 m*l* of the solution. The aqueous extracts were brought together and acidified with 1N hydrochloric acid and diluted to 100 m*l*. Catechol was determined spectroscopically according to the method of Willard and Wooten.[14] In the reactions under the conditions of the Baudisch reaction, hydroxylamine hydrochloride (0.695 g, 1×10^{-2} mol) was added to the above reaction mixture just before the addition of hydrogen peroxide.

Ratio of Catechol to Hydroquinone. The ethereal extract (50 m*l*) from 50 m*l* of the reaction mixture was evaporated to about 10 m*l* and submitted to thin layer chromatography. The unidimensional ascending technique was employed in a benzene-methyl ethyl ketone-2% aqueous formic acid (90 : 10 : 10) system. When the solvent front was allowed to ascend about 15 cm, the plate was dried and run in the same solvent again. After the plate was dried, Folin-Ciocalteu reagent[15] was sprayed on it and the blue spots due to catechol and hydroquinone were scraped separately into small beakers. To each of the beakers 2.5% potassium dihydrogen phosphate solution (2 m*l*) was added[9] and then 1 m*l* of Folin-Ciocalteu reagent. The dark green solution was filtered using sintered glassfilters and each of the filtrates, together with washings, was diluted to 10 m*l* with water. The intensity was then measured at 520 mμ after the sample solution was kept at 35°C for 30 min.

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[14] H. H. Willard and A. L. Wooten, *Anal. Chem.*, **22**, 670 (1950).

[15] F. D. Snell and C. T. Snell, "Colorimetric Method of Analysis," D. Van Nostrand Company, Inc., New York, N. Y. (1953), p. 116.