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# Studies on the Baudisch Reaction. IV. The Reaction Mechanism[1]

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Mechanism of the Baudisch reaction was investigated using semicarbazide hydrochloride in lieu of hydroxylamine hydrochloride which is one of the reacting components. It was suggested that pyrocatechol-copper-hydroxylamine complex formed as a reaction intermediate is oxidized to *o*-benzoquinone-copper complex by hydrogen peroxide and one of the carbonyl groups of *o*-benzoquinone reacts with hydroxylamine hydrochloride to give *o*-benzoquinone monooxime, *i.e.* 2-nitrosophenol.

The Baudisch reaction is of interest with respect to the direct production of *o*-nitrosophenols from the corresponding hydrocarbons by the reaction with hydroxylamine hydrochloride, hydrogen peroxide and copper(II) salt.[2,3] We found that the copper-hydroxylamine complex combined with the phenol formed at the first stage of reaction played a key role in the reaction.[1a,b] In our recent studies,[1c] it was demonstrated that *p*-cresol gave 5-methyl-2-nitrosophenol and 3,5-dimethylphenol gave 4,6-dimethyl-2-nitrosophenol; the hydroxy group of *p*-cresol or 3,5-dimethylphenol was replaced by nitroso group and a new hydroxy group was introduced into the position *ortho* to this nitroso group. Furthermore, 2-nitroso-1-naphthol which is the product starting from 1-naphthol was also produced exclusively in the Baudisch reaction of 2-naphthol. These results suggest the essential contribution of pyrocatechol-copper(II) complex (Fig. 1) as a reaction intermediate. For the sake of confirmation we examined whether pyrocatechols, in lieu of phenol, give *o*-nitrosophenols under the same conditions of the Baudisch reaction or not. It was found that pyro-

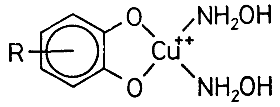

Fig. 1. Pyrocatechol-copper(II) complex.

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[1] a) Part I: K. Maruyama, I. Tanimoto, and R. Goto, *J. Org. Chem.*, **32**, 2516 (1967). b) Part II: I. Tanimoto, This Bulletin, **43**, 139 (1970). c) Part III: I. Tanimoto, *ibid.*, **43**, 1182 (1970).

[2] a) O. Baudisch, *Naturwissenschaften*, **27**, 768 (1939). b) O. Baudisch and S. H. Smith, *ibid.*, **27**, 769 (1939). c) O. Baudisch, *Science*, **92**, 336 (1940). d) O. Baudisch, *Arch. Biochem.*, **5**, 301 (1944).

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

Table 1. Formation of hydroxyphenylazoformamides and nitrosophenols from catechols

| Pyrocatechols | Nitrosophenols | Hydroxyphenylazoformamides | | |
|---|---|---|---|---|
| | | | Elemental analysis, % | Mp °C |
| Pyrocatechol | 2-Nitrosophenol[1c] | 2-Hydroxyphenyl-azoformamide | Found: C, 50.74; H, 4.14; N, 25.19%<br>Calcd for $C_7H_7N_3O_2$:<br>C, 50.91; H, 4.27; N, 25.44% | 99.5—101.5 |
| 4-Methyl-pyrocatechol | 5-Methyl-2-nitrosophenol[1c] | 4-Methyl-2-hydroxyphenyl-azoformamide | Found: C, 53.36; H, 5.11; N, 23.20%<br>Calcd for $C_8H_9O_2N_3$:<br>C, 53.63; H, 5.06; N, 23.45% | 152—153.5 |
| 4-Chloro-pyrocatechol | 5-Chloro-2-nitrosophenol | 4-Chloro-2-hydroxyphenyl-azoformamide | Found: C, 42.36; H, 3.33; N, 20.79%<br>Calcd for $C_7H_6O_2N_3Cl$:<br>C, 42.12; H, 3.03; N, 21.05% | 164—165 |
| 3-Methyl-pyrocatechol | 6-Methyl-2-nitrosophenol | 3-Methyl-2-hydroxyphenyl-azoformamide | | 122—124 |

catechols rapidly change into *o*-nitrosophenol-copper (II) complexes. All the mechanisms so far postulated[2c,d,3,4] failed to give an explanation. In this paper we would like to discuss the route by which *o*-nitrosophenol was produced from the pyrocatechol-copper(II) complex and try to elucidate the whole mechanism of the Baudisch reaction.

## Results and Discussion

Pyrocatechol did not react with semicarbazide hydrochloride as well as hydroxylamine hydrochloride at pH 2.50 even in the presence of copper(II) ion. The reaction was started, however, by the addition of hydrogen peroxide. After the reaction was completed, the red solution was acidified and the product was extracted with a solvent. The elemental analysis of the purified products coincided with the calculated value for 2-hydroxyphenylazoformamide, *i.e.* semicarbazone of *o*-benzoquinone. The semicarbazone formed a characteristic reddish violet complex with copper(II) ion in water. Electronic spectra of the semicarbazone and of its copper(II) complex are shown in Fig. 2. The absorption peak of semicarbazone at 325 nm is ascribed to the azo group conjugating with aromatic ring, and the peak observed in copper salt at 527 nm seems to indicate the formation of an *o*-hydroxyazo copper chelate. By a similar procedure semicarbazones of substituted *o*-benzoquinones were obtained from the corresponding pyrocatechols. The results are summarized in Table 1. As one of the two hydroxy groups is apparently substituted by an azoformamide group, two isomeric products may result from substituted pyrocatechols. As an example, 4-methyl-2-hydroxyphenylazoformamide and 3-methyl-6-hydroxyphenylazoformamide can be produced from 4-methyl pyrocatechol. However, since the reduction of the product by tin(II) chloride gave only 6-amino-*m*-cresol, it can be deduced that 4-methyl-2-hydroxyphenylazoformamide was produced exclusively. Table 1 shows that in every case the hydroxy group replaced by the azoformamide group was the same as the one which was replaced by the nitroso group in the Baudisch reaction. These results imply that hydroxylamine hydrochloride or semicarbazide hydrochloride reacts with pyrocatechol in a similar manner.

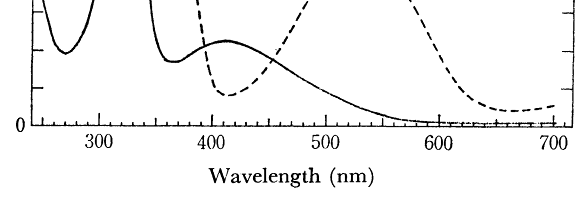

Fig. 2. Absorption spectra.
——: 2-hydroxyphenylazoformamide in chloroform
----: $Cu^{2+}$ salt of 2-hydroxyphenylazoformamide in water

According to Horner and Drückheimer,[5] *o*-benzoquinonediazides are obtained by the reaction between *o*-benzoquinones and *p*-toluenesulfonyl hydrazide. Reduction of quinonediazides by hypophosphorus acid gives a mixture of isomeric phenols. Utilizing this reaction, one can determine which carbonyl group of substituted *o*-quinone was preferentially attacked. As an example, 4-chloro-*o*-benzoquinone gives 3-chlorophenol (91%) and 4-chlorophenol (8%); the carbonyl group *para* to chlorine atom is preferentially attacked by hydrazine.[5] Thus, we recognize that the position of the carbonyl group attacked by hydrazide in Horner and Drückheimer's reaction corresponds to the position of the hydroxy group replaced by nitroso or azoformamide group in our reaction. The results seem to indicate the following possible reaction sequence. Pyrocatechol-copper complex is oxidized to *o*-benzoquinone-copper complex and then one of the carbonyl groups of *o*-benzoquinone is attacked by hydroxylamine (or semicarbazide). In line with the above consideration, *o*-benzoquinones gave *o*-nitrosophenols under Baudisch reaction conditions, and no reaction of pyrocatechols with hydroxylamine(or semicarbazide) hydrochloride started until addition of hydrogen peroxide even in the

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

5) L. Horner and W. Drückheimer, *Chem. Ber.*, **95**, 1206 (1962).

presence of copper(II) ion. Examination of the electron density using simple HMO method gave no fruitful guide for the preferential attack of Schiff bases(hydroxylamine, semicarbazide or *p*-toluenesulfonyl hydrazide) to one of two carbonyl groups of *o*-quinones.

On the other hand, the Baudisch reaction in methanol does not take place when no hydroxy group exists in a molecule,[1a] and the reaction of benzene, for example, might proceed *via* phenol formation. Thus, we examined the effect of copper(I) ion on the Baudisch reaction. A mixture of copper(I) and copper(II) in various molar ratio was used in the reaction, the total molar quantity of both ions being kept constant. The result is shown in Fig. 3. *o*-Nitrosophenol formation from the phenols decreased gradually with the increase of molar ratio of copper(I) ion. However, in the case of aromatic hydrocarbons the amounts of *o*-nitrosophenols produced was somewhat increased with the increase of the relative molar ratio of copper(I). This is conceivable by considering that copper(I) ion is essential for the decomposition of hydrogen peroxide to form hydroxy radical which attacks aromatic hydrocarbons to afford phenols.

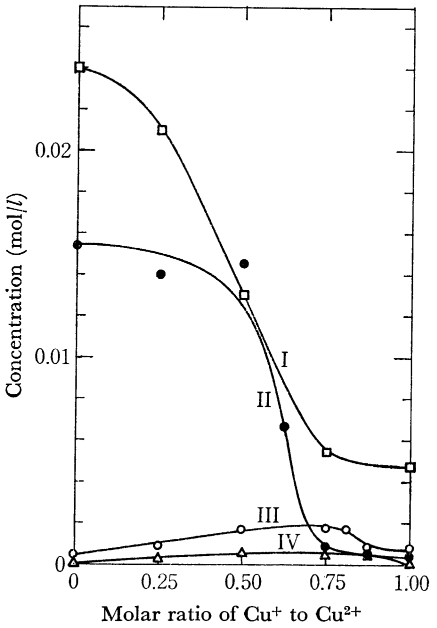
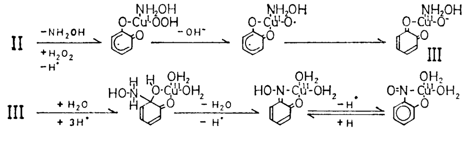


Fig. 3. Effect of copper(I) on the production of *o*-nitrosophenols from phenols or benzenes.
I: *p*-chlorophenol, II: phenol, III: benzene
IV: chlorobenzene

The whole sequence of the Baudisch reaction can be summarized as follows.



A part of copper(II) ion is reduced at first to copper(I) by hydroxylamine and copper(I) reacts with hydrogen peroxide to produce hydroxy radical. Complex I is then formed from phenol, copper(II), hydroxylamine and hydrogen peroxide, and the complex produces pyrocatechol-copper complex II. In the next stage, complex II may be oxidized to *o*-benzoquinone-copper complex III. In this stage, hydrogen peroxide will substitute the hydroxylamine ligand of complex II and then successive oxidation proceeds. As copper species can easily change their oxidation states,[6] electron of pyrocatechol can be transferred with no difficulty to peroxide through copper atom.[7] Finally, complex III might be oximated to *o*-nitrosophenol-copper(II) complex.

## Experimental

*Materials.* 4-Chlorocatechol was prepared by the chlorination of pyrocatechol.[8] Copper(I) chloride was prepared by the reduction of copper(II) sulfate.[9] After being washed with glacial acetic acid, the crystal was dried and used. Other reagents were the same as described previously.[1a,b,c]

*Formation of Hydroxyphenylazoformamide.* A typical example is the following: In a 1*l* three-necked flask, equipped with a stirrer, were placed copper(II) nitrate (8 g, 0.033 mol), 4-methyl pyrocatechol (3.7 g, 0.030 mol), semicarbazide hydrochloride (5.6 g, 0.05 mol) and 500 m*l* of hydrochloric acid-sodium acetate buffer (pH 2.5). To this mixture was added 5 m*l* of 30% hydrogen peroxide solution diluted with 200 m*l* of water in 2 hr. The solution was stirred for 2.5 hr at 20°C. The reaction mixture was acidified after the filtration of the residue, and extracted with ethyl ether. The red product in ethyl ether was extracted as a copper salt of the product with an aqueous solution of copper(II) acetate. After the reddish violet aqueous solution was extracted repeatedly with ethyl ether and chloroform, the solution was acidified and extracted with chloroform. The extract was evaporated under a reduced pressure and orange red crude crystals, 4-methyl-2-hydroxyphenylazoformamide, were obtained (*ca.* 800 mg). After being eluted with acetone-ethanol (1:1) on an alumina column, the pure product was obtained, mp 152—153.5°C. The result of elemental analysis is shown in Table 1.

The product was confirmed as follows. The hydroxyphenylazoformamide was dissolved in an acidic tin(II) chloride solution. After the color of the solution had almost faded away, the solution was refluxed for 30 min. After being cooled and extracted with ethyl ether, the solution was made alkaline with aquous 6N NaOH solution. *O*,*N*-Dibenzoyl derivative of 5-methyl-2-aminophenol, mp 144.5—145.5°C, was obtained. No melting point depression was observed in admixture with an authentic sample.[10]

*The Effect of Copper(I) on the Production of* o-*Nitrosophenols.*

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[6] R. G. R. Bacon and H. A. O. Hill, *Ouart. Rev.* (London), **19,** 95 (1965).

[7] In the Baudisch reaction, copper(II) ion forms a stable complex with *o*-nitrosophenol or monooxime of *o*-benzoquinone. The complex can protect the product against further oxidation or oximation. This might be another important role of copper(II) ion in the Baudisch reaction.

[8] R. Willstätter and H. E. Müller, *Ber.*, **44**, 2182 (1911).

[9] C. S. Marvel and S. M. McElvain, *Org. Syn.*, *Coll. Vol.*, **1**, 170 (1941).

[10] The melting point of this compound (162°C) was reported by K. V. Auwers *et al.* (*Ber.*, **54**, 1314 (1921)), but their report should be corrected.

A mixture of copper(I) chloride and copper(II) chloride was used. The total amount of copper ions was kept 0.005 mol. This mixture and hydroxylamine hydrochloride (0.695 g, 0.01 mol) were dissolved in 100 m*l* of a Walpole buffer (pH 2.55). To the solution, benzene (0.5 m*l*) or chlorobenzene (1.0 m*l*) dissolved in 20 m*l* of *n*-hexane was added. After the addition of 30% hydrogen peroxide (1 m*l*), the mixture was stirred at 30°C for 20 min under a nitrogen atmosphere. Aliquot of the mixture (20 or 50 m*l*) was removed and was acidified with 3 m*l* of 6N HCl. The determination of *o*-nitrosophenol produced was described previously.[1a)]

*Spectrophotometry.* The electronic spectra of hydroxyphenylazoformamide in chloroform and its copper(II) salt in water were measured. The aqueous solution of hydroxyphenylazoformamide-copper(II) was obtained by shaking an ethereal solution of hydroxyphenylazoformamide with an aqueous copper(II) sulfate solution.

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