# KINETICS OF IODINATION OF RESORCINOL AND ITS O-METHYL DERIVATIVES

V. Macháček, V. Štěrba and K. Valter

*Department of Organic Chemistry,*
*Institute of Chemical Technology, Pardubice*

Iodination of resorcinol monoanion proceeds by two mechanisms. At lower iodide and proton concentrations the reaction is second order in iodine in spite of monoiodoresorcinol being the reaction product. At higher iodide and proton concentrations the reaction is first order in iodine as it is the case with other phenolate ions inclusive of 3-methoxyphenolate anion. The rate constants have been determined for iodination of undissociated resorcinol, 3-methoxyphenol and 1,3-dimethoxybenzene, and the influence of $O^-$, OH and $OCH_3$ groups on the reaction rate has been discussed.

Iodination of phenol and 4-nitrophenol was studied by Grovenstein[1,2] who was the first to propose the Eq. (*1*) where $[B_i]$ is the basic buffer component concentration, [SH] and $[I_2]$ are the total phenol and iodine concentrations respectively, $K_A$ is the dissociation constant of phenol, and $K$ is the equilibrium constant of the reaction $I_3^- = I_2 + I^-$.

$$v = -\,d[I_2]/dt = \frac{k_1}{k_{-1}} \sum k_i^B [B_i] \frac{[SH]\,K_A}{[H^+]} [I_2] \frac{K}{K + [I^-]} [I^-]^{-1}\,. \qquad (1)$$

On the basis of this equation the author suggested the following reaction mechanism:

$$I_3^- \underset{}{\overset{K}{\rightleftharpoons}} I_2 + I^-$$

$$SH \underset{}{\overset{K_A}{\rightleftharpoons}} S^- + H^+$$
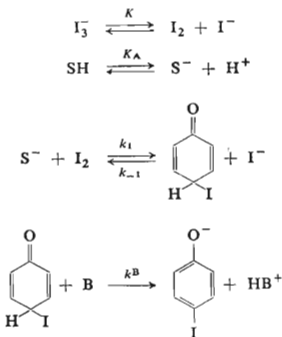




**Scheme 1**

Later on the iodination kinetics of o-substituted p-cresols[3] and p-substituted phenols[4] were studied, and it was found that the reaction mechanism is identical with that proposed by Grovenstein. In the case of p-substituted phenols a far better correlation was found between log $k$ and ($\sigma_m$ + + a $\Delta\sigma_p^-$) than between log $k$ and mere $\sigma_m$ constants. This was explained as a consequence of a decreased conjugation of the substituent having $-M$ effect with the oxygen atom in the activated complex.

The aim of this work was to determine the activating influence of the groups having a strong $+M$ effect, viz. $O^-$, OH and OR groups. Resorcinol and its O-methyl derivatives were chosen as substrates for these studies; they served successfully for the same purpose in the study of coupling reactions[5]. When following the iodination kinetics of resorcinol monoanion in acetate buffer, we found that the reaction course was different from the abovementioned scheme and kinetic equation. Therefore a special attention was focused in this case on the study of dependences of the reaction rate on reaction conditions especially iodide and proton concentrations.

## EXPERIMENTAL

The O-methyl derivatives of resorcinol were prepared by its methylation[5]. The other chemicals were commercial samples of p.a. purity grade. The proton NMR spectra were measured with the use of a BS 487 A apparatus (Tesla) at 26 + 2°C in CDCl₃ using HMDS as internal standard. IR spectra were measured with the use of a UR-20 apparatus (Zeiss, Jena) in CCl₄ solution.

*Isolation of reaction products.* A solution of 2·54 g iodine (0·01 mol) in 10 ml ethanol was added dropwise to a solution of 5·5 g resorcinol and 1 g potassium iodide in 50 ml acetate resp. citrate buffer or 0·5M-H₂SO₄ with stirring. After 12 h the solution was concentrated *in vacuo*, and the organic components were extracted with 2 × 50 ml mixture of ether and ethyl acetate 1 : 1. After drying and distilling off the solvents the residue was chromatographed on a column packed with silica gel (Spolana, Velvary) using chloroform as eluent. From the citrate buffer it was thus possible to obtain 0·5 g 2,4-diiodoresorcinol and 1·45 g 2-iodoresorcinol. From acetate buffer 0·3 g 2,4-diiodoresorcinol, 1·4 g 2-iodoresorcinol and 0·15 g 4-iodoresorcinol were obtained. From 0·5M-H₂SO₄ 0·5 g 2-iodoresorcinol and 1·7 g 4-iodoresorcinol were obtained. The iodination products of 3-methoxyphenol were obtained analogously by iodination of 12 g of the substance with 5·2 g iodine. Due to low solubility of 3-methoxyphenol, 20% ethanol was added. After finishing the reaction and diluting the reaction mixture, the products were extracted in chloroform and worked up as in the case of resorcinol. From 0·5M-H₂SO₄ 5·3 g 6-iodo-3-methoxyphenol was obtained. From acetate buffer 8·3 g of a mixture was obtained containing equal amounts of mono and diiodo derivatives. The iodination products of 1,3-dimethoxybenzene were prepared similarly as those of 3-methoxyphenol in 0·5M-H₂SO₄ by iodination of 4 g 1,3-dimethoxy-benzene with 5 g iodine. After removing a slight excess of unreacted iodine (NaSO₃) and dilution with water an oil separated and was extracted in chloroform. The organic layer was separated, dried and after distilling off the solvent the residue was crystallized from methanol. 3·2 g 4-iodo-1,3-dime-thoxybenzene was thus obtained. Physical properties of the substances prepared are given in Table I.

*Chromatography of the reaction products.* Iodinations of resorcinol, 3-methoxyphenol and 1,3-dimethoxybenzene were carried out under the conditions corresponding to the kinetic experiments, the concentrations of iodine and the substrate being about ten times higher than in the kinetic experiments. The reaction mixtures were treated in the same way as in the above cases of isola-

tion of the reaction products, the chromatography being carried out on a thin layer (Silufol, chloroform) instead of column. The composition of the products was compared with authentic iodo derivatives. The spots were detected with iodine vapours.

*Kinetic measurements.* The reaction was followed by measuring the extinction decrease of $I_3^-$ complex at $\lambda_{max}$ 350 nm. 5 ml $5 \cdot 10^{-4}$M-$I_2$ solution in 0·1 or 0·01M-KI was added at 20°C to 45 ml solution of the substrate in buffer or 0·5M-$H_2SO_4$ containing a known quantity of potassium iodide and the amount of potassium chloride necessary to adjust the ionic strength 0·1. A part of the sample was placed in 1 cm cell located in a thermostated cell holder of a VSU-2 P spectrophotometer (Zeiss, Jena), and the time dependence of the extinction was measured. The reaction was followed up to at least 80—90%. The final extinction of the solution was practically zero. The rate constants of the first and second order reactions were calculated in the usual way.

## RESULTS AND DISCUSSION

### Iodination of Resorcinol and 3-Methoxyphenol Monoanions

In the first experiments the iodination of resorcinol was kinetically followed in acetate buffers in the pH range 4·6—5·0 using the iodide ion concentrations 0·5 to $1 \cdot 10^{-1}$M
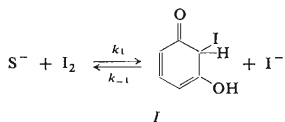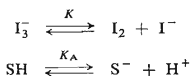
TABLE I

Physical Properties of Iodination Products of Resorcinol and its O-Methyl Derivatives

| Compound | M.p.[a] °C | Chemical shifts ($\tau$) of the protons in positions | | | | Interaction constants Hz |
|---|---|---|---|---|---|---|
| | | 6 | 5 | 4 | 2 | |
| 2-Iodoresorcinol | 95— 96[b] | 3·52[c] | 2·52[d] | 3·52[c] | — | $I_{6,5} = I_{6,4} = 8$ |
| 4-Iodoresorcinol | 62— 63[e] | 3·76[d] | 2·52[c] | — | 3·48[c] | $I_{6,5} = 8·3, I_{6,2} = 2·9$ $I_{5,2} = 0·1$ |
| 2,4-Diiodoresorcinol | — | 2·57[c] | 3·65[c] | — | — | $I_{6,5} = 9·0$ |
| 3-Methoxy 6-iodophenol | 72— 73[f] | 3·69[d] | 2·53[c] | — | 3·42[c] | $I_{6,5} = 8·8, I_{6,2} = 2·8$ $I_{5,2} = 0·1$ |
| 3-Methoxy-4,6-diiodophenol | 98—100 | — | 2·07 | — | 3·46 | $I_{5,2} = 0·1$ |
| 1,3-Dimethoxy-4-iodobenzene | 42[g] | | | | | |

[a]Crystallized from benzene–cyclohexane or benzene–chloroform. [b]Sublimated. For $C_6H_5IO_2$ (236·0) calculated: 30·51% C, 2·13% H; found: 30·64% C, 2·08% H. [c]Doublet. [d]Pair of doublets. [e]For $C_6H_5IO_2$ (236·0) calculated: 30·51% C, 2·13% H; found: 30·50% C, 2·00% H. [f] For $C_7H_7IO_2$ (259·0) calculated: 32·46% C, 2·72% H; found: 32·23% C, 2·46% H. A very strong band at 3 502 cm$^{-1}$ and a weak at 3 593 cm$^{-1}$ for the bonded and free OH group respectively were present in IR spectra. [g]Ref.[10] 42°C.

and an about twentyfold excess of resorcinol, *i.e.* the conditions under which the reaction should take the pseudomonomolecular course. The reaction velocity, however, dropped more rapidly than it should decrease according to a reaction first order in iodine. In the first phase the reaction was 2nd order in iodine. Approximately after one half-life the reaction order with respect to iodine concentration began to decrease. This indicates that the iodination takes two courses from which one is 1st order and the other is 2nd order in iodine, the latter being predominant at the beginning of the reaction under the conditions given, whereas the former begins to make itself felt with decreasing iodine concentration. The decrease of the proton and iodide concentrations supports the 2nd order reaction. At a pH > 4·6 and $[I^-] < 5 \cdot 10^{-2}$M the reaction was 2nd order in iodine in the whole course studied (up to 90–95% of reaction). The reaction rate was inversely proportional to $[I^-]^4$ and $[H^+]^2$ under these conditions. At constant proton and iodide concentrations the reaction rate increases with increasing buffer concentration. The dependence of the rate constant on the acetate ion concentration is linear, the intercept on *y*-axis being not zero (Fig. 1) which indicates that the reaction is catalyzed by water besides the acetate. In all the cases the reaction was 1st order in resorcinol, and 2-iodoresorcinol was the main product which was proved by isolation of the products formed under the conditions near to those of kinetic experiments. Besides that a small amount of 4-iodoresorcinol is formed. The relations found stand in accord with Eq. (2) where $K = 1 \cdot 15 \cdot 10^{-3}$ mol/l (ref.[6]) and $K_A$ is the dissociation constant of resorcinol[7] ($6 \cdot 02 \cdot 10^{-10}$ mol/l). The reaction of the intermediate *II* with base is the rate-determining step.

$$v = \frac{k_1 k_2}{k_{-1} k_{-2}} \sum k_i^B [B_i] \frac{K_A[SH]}{[H^+]} [H^+]^{-1} [I_2]^2 \left( \frac{K}{K + [I^-]} \right)^2 [I^-]^{-2} \qquad (2)$$

$$I_3^- \underset{}{\overset{K}{\rightleftharpoons}} I_2 + I^-$$

$$SH \underset{}{\overset{K_A}{\rightleftharpoons}} S^- + H^+$$



$$S^- + I_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{(structure)} + I^-$$

*I*

At pH < 3 and $[I^-] > 10^{-1}$M the reaction is 1st order in iodine in the whole range studied. The reaction rate is inversely proportional to $[I^-]^2$. The dependence of log *k* *vs* pH found, however, has the slope smaller than unity (due to a simultaneous iodination of undissociated resorcinol). The reaction is again first order in resorcinol, and it is catalyzed by both chloroacetate buffer and water (Fig. 1). The dependences

found correspond to Eq. (1). As it is shown in Scheme 2 in this case, too, the intermediate $I$ formed is in equilibrium with the starting substances, but in contrast to the previous mechanism, this intermediate reacts in a subsequent rate-determining step
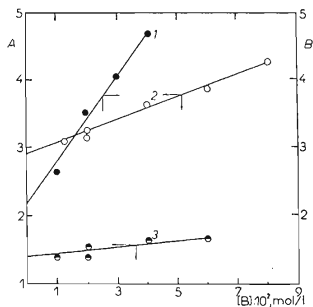


FIG. 1

Dependence of Iodination Rate Constants of Resorcinol Monoanion (1 and 3) and 3-Methoxyphenolate Ion 2 on Base Buffer Component Concentration

$A = ((k_1/k_{-1}) \Sigma k_i^{\mathbf{B}}[B_i]) \cdot 10^{-6}$, $1 \, \text{mol}^{-1}$ . . $\text{min}^{-1}$; $B = ((k_1 k_2/k_{-1} k_{-2}) \Sigma k_i^{\mathbf{B}}[B_i])$ . . $10^{-8}$, $1^{-1} \, \text{mol min}^{-1}$. Buffer: 1, 2 acetate, 3 chloroacetate.
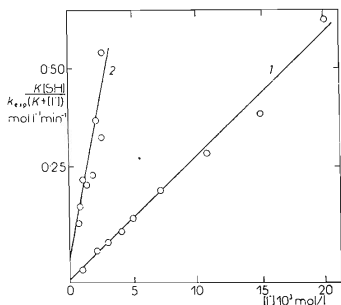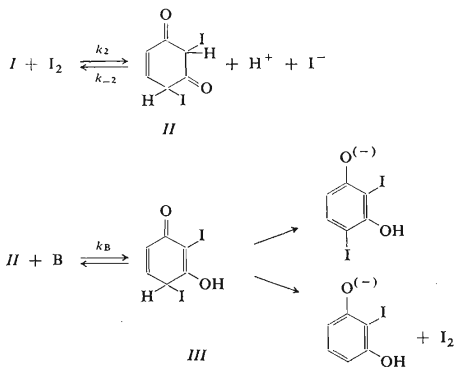
FIG. 2

Dependence according to Eq. (5) for 3-Methoxyphenol(1) and 1,3-Dimethoxybenzene (2) at pH 1·1, 20°C and Ionic Strength 0·2



$$I + I_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \quad II \quad + \; H^+ \; + \; I^-$$

$$II + B \overset{k_{\mathbf{B}}}{\rightleftharpoons} \quad III \quad \longrightarrow$$

$$+ \; I_2$$

SCHEME 2

directly to give 2-iodoresorcinol. The change of the reaction following Eq. (2) into that following Eq. (1) is caused by that the proton and iodide concentrations increases retard strongly the rate of formation of the intermediate III. Under these conditions the reaction of the intermediate I with base (giving directly monoiodoresorcinol) becomes predominant. The splitting of the O---H proton from the intermediate I is the condition for the formation of the intermediate III. This was confirmed by a study of iodination kinetics of 3-methoxyphenol, which follows Eq. (1) in the whole range of the proton and iodide concentrations studied. The reaction is catalyzed by both acetate ion and water. For calculation of the rate constants the dissociation constant of 3-methoxyphenol was used[8-10] ($K_A$ $2\cdot5 \cdot 10^{-10}$ mol/l, recalculated for the ionic strength $0\cdot2$). 3-Methoxy-6-iodophenol is practically the only reaction product.

### Iodination of Undissociated Resorcinol and its O-Methyl Derivatives

On lowering the pH value in resorcinol iodination below 3 the slope of the dependence log $k$ vs pH begins to decrease, and, at pH $1\cdot1$ the iodination velocity is practically independent of pH. In this intermediate region the reaction rate follows Eq. (3) where $k_S$ has the same meaning as the expression $(k_1/k_{-1}) \sum k_i^B[B_i]$ in Eq. (1) and $k_{SH}$ is a combined rate constant for the analogous reaction of iodine with the undissociated resorcinol.

$$v = k_{exp}[I_2] = \frac{K[I_2]}{[I^-] + K} [I^-]^{-1} \left(k_S[S^-] + k_{SH}[SH]\right) . \qquad (3)$$

By introducing $[S^-] = K_A[SH]/[H^+]$ and modification of Eq. (3) we obtain Eq. (4). The found dependence $(k_{exp}[I^-]^2)/(K[SH])$ vs $K_A/[H^+]$ is linear. The constant

$$k_{exp}([I^-] + K)[I^-]/(K[SH]) = k_S K_A/[H^+] + k_{SH} \qquad (4)$$

of the base catalysis was determined at a pH about 3 (chloroacetate) where the contribution of the undissociated resorcinol to the total reaction rate is negligible. A similar dependence on $[H^+]$ (at pH < 3) was also found in the case of iodination kinetics of 3-methoxyphenol. The application of Eq. (4) was made impossible in this case by that (due to low solubility of 3-methoxyphenol) the experiments had to be carried out at substantially lower concentrations of iodide ions in order that acceptable reaction rates might be obtained. Under these reaction conditions the dependence of the expression $k_{exp}(K + [I^-])/K[SH]$ on $1/[I^-]$ is no longer linear due to the rate of conversion of intermediate into the final product being no longer negligibly small as compared with the rate of the reverse reaction of this intermediate with iodide ion. The dependence of the reaction rate on the

$$\frac{[SH]}{k_{exp}} \cdot \frac{K}{K + [I^-]} = \frac{k_{-1}[I^-]}{k_1 k_.^B[B]} + \frac{1}{k_1} \qquad (5)$$

iodide ion concentration was studied in more detail at pH 1·1 where the iodination rate constant of 3-methoxyphenol is pH-independent. The rate constant $k_1 k^B/k_{-1}$ was determined graphically (Fig. 2) according to Eq. (5). Under the same conditions (pH 1·1; $[I^-]$ 1 . $10^{-3} - 5$ . $10^{-3}$M) the iodination kinetics of 1,3-dimethoxybenzene was measured, and the constant $k_1 k^B/k_{-1}$ was obtained in the same graphical way. 4-Iodo-1,3-dimethoxybenzene is the only reaction product. The values of the resulting rate constants are given in Table II.

Survey of Rate Constants of Iodination of O-Methyl Derivatives of Resorcinol
Measured in water at ionic strength 0·2. Average error of the constants given is $\pm 10\%$.

| Substrate | $k_1 k^B/k_{-1}$, l² mol⁻² min⁻¹ | |
|---|---|---|
| | B = ClCH$_2$CO$_2^-$ | B = H$_2$O |
| Resorcinol | 3·83 . 10⁶ | 2·27 . 10⁴ |
| | — | 2·93 . 10⁻³ [a] |
| | 9·52 . 10⁹ [b,c] | 4·11 . 10⁶ [b] |
| 3-Methoxyphenol | 1·80 . 10⁷ [b] | 5·28 . 10⁴ |
| | — | 5·93 . 10⁻⁴ [a] |
| 1,3-Dimethoxybenzene | — | 1·10 . 10⁻⁴ [a] |

[a] The rate constants of iodination of the substrate itself. All the other constants refer to iodination of the substrates dissociated to the I. degree. [b] The rate constants $k_1 k_2 k^B/k_{-1} k_{-2}$, min⁻¹ for the iodination which was second order in iodine. [c] The value found for B = CH$_3$CO$_2^-$.

## Comparison of Activating Effects of O⁻, OH and OR Groups

The ratio 25 : 5 : 1 was found for the iodination rate constants of the undissociated resorcinol, 3-methoxyphenol and 1,3-dimethoxybenzene. This reactivity order and ratio are practically the same as those found for coupling of these substrates[5]. The reason is obviously the same in this case. The activating influence of OH group is greater than that of OCH$_3$ group, because in the activated complex a partial splitting of the O—H bond occurs and the mesomeric effect of the group is increased. The iodination rate constant of resorcinol monoanion is about half of 3-methoxyphenolate ion, 2-iodoresorcinol being unexpectedly formed as the main reaction product in the former case. The amount of 4-iodoresorcinol in the reaction product is maximum 10%, wherefrom it follows that the rate of formation of 4-iodoresorcinol is lower than that of 6-iodo-3-methoxyphenol by more than one order of magnitude. This

can possibly be explained by that the ratio of the velocities of decomposition of the intermediate into starting substance and that into products is substantially higher than in the case of 3-methoxyphenol, and consequently, the overall reaction rate is lower. During iodination 3-methoxyphenolate ion is more reactive than the undissociated 3-methoxyphenol by 8 orders of magnitude which is practically the same difference as that found during coupling of this substrate with 4-nitrobenzenediazonium ion[5]. This agreement was expected as the reactivities of the both electrophilic reagents are comparable. The difference of the iodination rate constants in the position 4 of resorcinol and its anion is about 6 orders of magnitude which is less than in the case of 3-methoxyphenol and its anion by two orders of magnitude. The reason consists obviously in a relatively small reactivity of resorcinol anion at 4 position, as the rate constant found for the undissociated resorcinol is quite in accord with the iodination velocities of 3-methoxyphenol and 1,3-dimethoxybenzene.

**REFERENCES**

1. Grovenstein E., Kilby D. C.: J. Am. Chem. Soc. *79*, 2972 (1957).
2. Grovenstein E., Aprabamian S.: J. Am. Chem. Soc. *84*, 212 (1962).
3. Mayberry W. E.: Biochemistry *6*, 1320 (1967).
4. Dobáš I., Štěrba V., Večeřa M.: J. Chem. Soc., in press.
5. Macháčková O., Štěrba V., Valter K.: This Journal, *37*, 1851 (1972).
6. Davies M., Gwyne E.: J. Am. Chem. Soc. *74*, 2748 (1952).
7. Sunkel J., Staude H.: Ber. *72*, 567 (1968).
8. Bolton P. D., Hall F. M., Reece I. H.: J. Chem. Soc. (B) *1967*, 709.
9. Baker A. W.: J. Am. Chem. Soc. *80*, 3598 (1958).
10. Meerwein H., Hoffmann P., Schill F.: J. Prakt. Chem. *154*, 266 (1940).