# NITROSATION KINETICS AND MECHANISM OF RESORCINOL AND ITS O-METHYL DERIVATIVES

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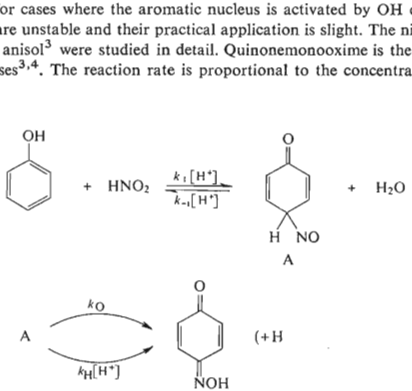
Nitrosation kinetics and mechanism of resorcinol and its O-methyl derivatives have been studied in aqueous buffers and mineral acids. The structure and proportion of individual isomers were determined after transformation of the unstable nitroso compounds into the respective nitro derivatives. Non-catalyzed or acid-catalyzed decomposition of the dienone intermediate A into oxime at pH $< 2{\cdot}5$ and the reaction of the undissociated phenol with protonated nitrous acid at pH $> 2{\cdot}5$ are the rate-determining steps of nitrosation of resorcinol and 3-methoxyphenol. In the case of 1,3-dimethoxybenzene the decomposition of the intermediate into nitrosodimethoxybenzene is rate-limiting. The difference in the overall velocities depends on the ratio of the decomposition rates of the intermediate into the products and into starting substances, because the rates of the reaction of protonated nitrous acid with the substrates are comparable and close to rates of diffusion-controlled processes.

Nitrosation of aromatic compounds has been given little attention so far. The reaction is rather difficult except for cases where the aromatic nucleus is activated by OH or $NR_2$ group. The reaction products are unstable and their practical application is slight. The nitrosation kinetics of phenol[1-3] and anisol[3] were studied in detail. Quinonemonooxime is the main reaction product in the both cases[3,4]. The reaction rate is proportional to the concentrations of undis-




SCHEME 1

sociated phenol and nitrous acid, $v = k_2[C_6H_5OH][HNO_2]$, and it is independent of chloride and bromide ion concentration[1]. The constant $k_2$ is independent of the acidity of medium at pH $>$ $> 1$ (ref.[1]), whereas it is roughly proportional to the acidity function $H_0$ in 1M and more concentrated mineral acids[2]. Therefrom it was judged[1,2] that the reaction of phenol with nitrous acid is rate-limiting under the conditions of $k_2$ being independent of pH, whereas the reaction with protonated nitrous acid is rate-limiting at higher acidities. The mechanism suggested is very unprobable in that the nitrous acid, which is not kinetically significant even with the far more reactive amino group of aniline, should be the main nitrosating agent in the reaction with undissociated phenol. Challis and coworkers found[3] that 4-deuteriophenol reacted almost four times more slowly than phenol. Therefrom a reaction mechanism was suggested involving the rate-limiting splitting of C—H bond of the dienone intermediate A, which in turn was formed in a rapid reversible step (Scheme 1). This mechanism also explains why there was not found any catalytic effect of $Cl^-$ and $Br^-$ ions. As both the rate of formation of the intermediate A and that of the reverse decomposition are proportional to $[H^+]$, the equilibrium concentration of the intermediate is pH-independent. At pH $> 1$ the non-catalyzed decomposition of the intermediate into the products predominates, and the reaction rate depends only on the concentrations of phenol and nitrous acid. As the rate of the reverse reaction decreases with increasing pH, it can be expected that the formation of the intermediate will become the rate-determining step at a sufficiently high pH. This could not, however, be observed[1] even at pH 5.

As we expected that the ratio $k_0/k_{-1}$ would be higher with 3-methoxyphenol and resorcinol than with phenol (a further OH or OR group increases the stability of the corresponding oxime), we studied the kinetics of nitrosation of the both phenol derivatives. An experimentally confirmed change of the rate-determining step would enable both a verification of the mechanism given and determination of the actual nitrosating agents. We extended this study by nitrosation kinetics of 1,3-dimethoxybenzene, as we expected a different course in this case according to analogy with anisol nitrosation[3].

## EXPERIMENTAL

The resorcinol O-methylderivatives were prepared by methylation of resorcinol[5]. Resorcinol and the other chemicals were commercial samples of p.a. purity grade.

*Isolation of reaction products.* All the nitroso derivatives were unstable. They were readily oxidized during their preparation and were not easily obtainable in pure state. Therefore, they were oxidized and identified as nitro derivatives. The nitrosation products of 3-methoxyphenol were prepared as follows: 10 ml of a solution containing 3·5 g (0·05 mol) $NaNO_2$ was added drop by drop to a suspension of 6·25 g (0·05 mol) 3-methoxyphenol in 100 ml 0·5M-$H_2SO_4$ with cooling during 30 min. Then after 10 min another 0·5 g $NaNO_2$ in 5 ml $H_2O$ and 20 ml 20% $HNO_3$ were added, and the mixture was stirred at 30°C 2 h. The crystalline precipitate was collected by suction and then steam distilled to yield 7·3 g 6-nitro-3-methoxyphenol (crystallized from methanol), m.p. 95°C (ref.[6]). The distillation residue gave 0·3 g 4-nitro-3-methoxyphenol (crystallized from ethyl acetate), m.p. 142—143°C (ref.[6] gives 144°C). The nitrosation of 3-methoxyphenol in acetate buffer was carried out in a similar way, except for that the nitroso compound was collected by suction and washed with water before oxidation.

The nitrosation products of 1,3-dimethoxybenzene were obtained as follows: 3·5 g (0·025 mol) 1,3-dimethoxybenzene was mixed with 3000 ml 5% $HNO_3$, then a solution of 1·82 g (0·026 mol)

$NaNO_2$ in 10 ml $H_2O$ was added at once at room temperature, and the reaction mixture was stirred 2 h. Then a further portion of 3·5 g 1,3-dimethoxybenzene and solution of 1·82 g $NaNO_2$ in 10 ml water were added. This was repeated three times more in 2 h intervals. Two hours after addition of the last portion the mixture was cooled at 10°C 6 h and the precipitate was collected by suction and washed with water. Yield 19·2 g 4-nitro-3-methoxyphenol chromatographically pure. The nitrosation of 1,3-dimethoxybenzene in 0·5M-$H_2SO_4$ was carried out similarly, the product, however, precipitated first after addition of excess $NaNO_2$ on standing overnight.

Nitrosation products of resorcinol in mineral acid media were obtained similarly as those of 3-methoxyphenol. The dinitroso derivative formed was, however, collected by suction before oxidation. 11·8 g raw dinitrosoresorcinol (theoretical yield 10·95 g) was obtained from 6·6 g (0·06 mol) resorcinol. No products could be obtained from nitrosation of resorcinol in acetate buffer.

### Kinetic Measurements

The reaction rate was determined by measuring the extinction increase of the respective nitrosation product at a suitable wavelength. In some cases the method of measurement of nitrous acid decrease[3] was used for comparison, 4-nitroaniline and 1,8-dihydroxynaphthalene-3,6-disulfonic acid being used for diazotization (instead of sulfanilic acid) and as coupling component, respectively. A typical experiment proceeded as follows: 0·5 ml $10^{-2}$M-$NaNO_2$ was added to 49·5 ml solution of the substrate (minimum $10^{-3}$M) in a buffer (ionic strength 0·2) at 20°C. A part of the solution was transferred into a 1 cm cell located in a thermostated cell compartment of a spectrophotometer VSU-2P (Zeiss, Jena), and the extinction was measured at the wavelength corresponding to the absorption maximum. The rate constant was obtained from the equation $kt = -2{\cdot}303 \log (E_\infty - E_t) + \text{const.}$, where $E_t$ and $E_\infty$ are the extinctions of the reaction solution at a time $t$ and $t = \infty$ (limit extinction), respectively.

## RESULTS AND DISCUSSION

6-Nitroso-3-methoxyphenol is the main nitrosation product of 3-methoxyphenol, the yield being about 90%. Besides that 10% 4-nitroso derivative is formed. The overall yield of nitrosation is practically quantitative even in the case of the ratio 3-methoxyphenol to nitrous acid being 1 : 1. The proportion of products did not depend on both pH and bromide ion concentration. During nitrosation of 1,3-dimethoxybenzene the nitroso group enters position 4, but the nitroso compound formed is readily hydrolyzed (as in the case of 4-nitrosomethoxybenzene[3]) to give 4-nitroso-3-methoxyphenol. The nitro derivative obtained on oxidation was isolated in at least 90% yield and was chromatographically pure. During nitrosation of resorcinol in mineral acid media (pH 1), 2,4-dinitrosoresorcinol was obtained as the only reaction product even under the conditions of manyfold excess of resorcinol with respect to nitrous acid. On oxidation 2,4-dinitroresorcinol was obtained, and the yield of the raw product was 40—100% depending on the way of addition of nitrite. Nitrosation of resorcinol in acetate buffer gave no nitroso derivatives even after acidification. It was found that 4-nitrosoresorcinol (prepared separately) remains in solution under these conditions. Our attempts to isolate mononitrosoresorcinol as the mononitro derivative were not successful, because the oxidation with $HNO_3$ gave the dinitro derivative and that with $H_2O_2$ gave products which remained in solution and could not be isolated. From the experiments described it follows that dinitroso derivative is formed besides mononitrosoresorcinol in acid medium, and its amount depends on the reaction conditions, whereas practically no dinitroso derivative is formed in acetate buffer.

*Nitrosation Kinetics of* 3-*Methoxyphenol*

As the resorcinol nitrosation gave different products in acid and buffer media, most kinetic experiments were carried out with 3-methoxyphenol where the composition of products was independent of medium. The kinetic experiments were carried out with an at least tenfold excess of 3-methoxyphenol as compared to nitrous acid. In some experiments this ratio was reversed, but the kinetic course was entirely different in these cases (a rapid extinction increase at the beginning followed abruptly by a slow extinction increase; we cannot explain this course). The dependence of log $k_2$ on pH is given in Fig. 1 together with the results of nitrosation of resorcinol and phenol. In the case of the experiments carried out in buffers, Fig. 1 gives the values

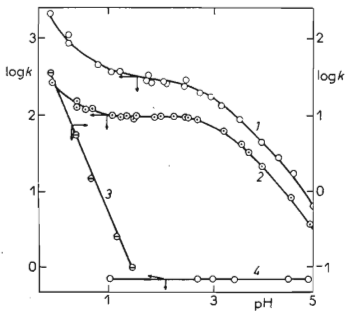



FIG. 1

Dependence log $k$ *vs* pH of Nitrosations of Resorcinol (*1*), 3-Methoxyphenol (*2*), 1,3-Dimethoxybenzene (*3*) and Phenol[1] (*4*)
Water, 20°C, ionic strength 0·2.

TABLE I

Dependence of Rate Constants (l mol$^{-1}$ s$^{-1}$) of 3-Methoxyphenol Nitrosation on Chloride ($k_{Cl^-}$), Bromide ($k_{Br^-}$) and Chloroacetate ($k$) Ions Concentrations at 20°C and Ionic Strength 0·2

| Anion mol/l | $k_{Cl^-}$ [a] | $k_{Br^-}$ [a] | $k$ | Anion mol/l | $k_{Cl^-}$ [a] | $k_{Br^-}$ [a] | $k$ |
|---|---|---|---|---|---|---|---|
| 0·00 | 11·8 | — | — | 0·12 | 19·4 | 30·4 | — |
| 0·01 | — | — | 104·4[b] | 0·15 | 20·3 | 31·5 | — |
| 0·02 | — | — | 107·4[b] | 0·16 | — | — | 96·0[c] |
| 0·04 | 15·4 | 22·2 | 116·3[b] | 0·20 | — | — | 103·2[c] |
| 0·08 | 17·6 | 27·7 | 76·4[c] | | | | |

[a] pH 4·57, [b] pH 2·45, [c] pH 3·30.

extrapolated to zero buffer concentration. The dependence given in Fig. 1 shows three different regions. At pH < 1 the reaction rate increases with proton concentration, at pH 1–2·5 the rate constant is independent of $[H^+]$, and at higher pH its value gradually decreases to give finally a linear dependence with a slope −1.

On the basis of the mechanism suggested by Challis and coworkers[3] we can explain the dependence of log $k_2$ on pH in the region pH < 2·5 by that a non-catalyzed decomposition of the intermediate formed in a rapid reversible step predominates at pH 2·5–1, whereas a catalyzed decomposition becomes increasingly significant at lower pH. The gradual decrease of $k_2$ at pH > 2·5 is caused by the fact that the decomposition rate of the intermediate into products assumes higher values than the rate of the reverse reaction, so that the formation of the intermediate (having the rate constant $k_1[H^+]$) becomes rate-limiting.

In the pH region 2–2·5 $k_2$ increases linearly with concentration of chloroacetate buffer, whereas at higher pH values (3–3·5) this dependence is not linear and the slope somewhat decreases with increasing buffer concentration. Therefrom it follows that, besides the non-catalyzed and proton-catalyzed decompositions of the intermediate into products, also the reaction with $ClCH_2CO_2^-$ becomes kinetically significant (splitting off of the proton from the intermediate).

The dependence of the rate constant on the base concentration can be explained by that both the formation and decomposition of the intermediate can act as rate-determining step. The curvature of this dependence is caused by the fact that the decomposition of the intermediate is rate-limiting at low base concentrations, whereas with the increasing base concentration its formation begins to become rate-limiting. At a sufficiently high buffer concentration the rate constant would not depend on base concentration at all. The bimolecular rate constant $k_2$ is thus defined by Eq. (*1*).

$$k_2 = k_1[H^+](k_0 + k_H[H^+] + k_B[B])/(k_{-1}[H^+] + k_0 + k_H[H^+] + k_B[B]) . \quad (1)$$

Even at pH > 2·5 the rate constant depends on the first power of $[HNO_2]$, which excludes $N_2O_3$ as nitrosating agent. The species $NO^+$ and $H_2NO_2^+$ can be considered as nitrosating agents[7], the latter being more probable with respect to the high value of $k_1[H^+]$. In the pH region where the formation of the intermediate becomes rate-limiting, *i.e.* nitrosation of 3-methoxyphenol, the reaction rate should increase in the presence of chloride and bromide ions, as further reactive agents NOCl and NOBr are formed (Table I). Addition of bromide ions had a greater effect than that of chloride ions in accord with the fact that the equilibrium concentration of NOBr is higher than that of NOCl. In this case the rate constant $k_2$ should approach to the value $10^2$ corresponding to a situation where the rate of formation of the intermediate is so large that its transformation into products becomes again rate-limiting. In fact, these rate constants approached to 2–3 times smaller values. The reason of this difference is not yet clear to us.

The linear dependence of log $k$ *vs* pH having the slope $-1$ suggests that 3-methoxyphenol (and not its anion) is significant kinetically up to pH 5. The value of the rate constant $k_2 = 5 \cdot 10^3\ \mathrm{l\ mol^{-1}\ s^{-1}}$ is comparable with the values of maximum rate constants of the acid catalyzed reactions of $HNO_2$ with nucleophiles[7] and approaches obviously the values of diffusion-controlled reactions (the value given for the dissociation constant of $H_2NO_2^+$ is $10^{-7}$ mol/l). This would also explain why 3-methoxyphenolate anion does not make itself felt kinetically. The protonated nitrous acid is so reactive, that it does not substantially differentiate between various nucleophiles, and the concentration of nucleophile is decisive.

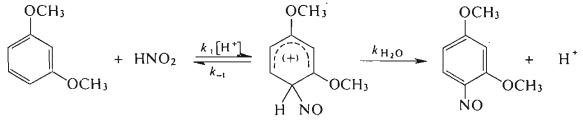
*Nitrosation Kinetics of Resorcinol*

The course of resorcinol nitrosation is very similar to nitrosation of 3-methoxyphenol, the only substantial difference being in that the rate is higher, *viz.* about 3 times higher at pH $< 2{\cdot}5$ and about 2 times higher at pH $> 2{\cdot}5$. The main reason is obviously that there are two equivalent positions capable of nitrosation in resorcinol In addition to it, the nitroso derivative formed primarily can react in the acid medium with a further molecule of nitrous acid to give the dinitroso derivative, so that the experimental constant has a higher value than it should correspond to the formation of mononitroso derivative. As it can be seen from Fig. 1, the values of rate constants $k_2$ of nitrosation of 3-methoxyphenol and resorcinol approach to those of phenol. Whereas in the case of 3-methoxyphenol at pH 5 nitrosation is rate-limiting, $k_2$ of phenol nitrosation is pH-independent which means that the decomposition of the intermediate into the products is rate-limiting. It is very probable that even in the case of phenol a further increase of pH would result in a change of the rate-determining step, and that the rate constants $k_1$ are comparable (and close to constants of diffusion-controlled reactions) for all the three compounds. The difference in the overall nitrosation rates is thus caused, first of all, by the ratio $k_0/k_{-1}$ being far greater for 3-hydroxy- and 3-methoxyphenols than that for phenol. This is perhaps a consequence of the fact that 3-hydroxy and 3-methoxy groups stabilize the oxime more than the starting phenol (and, hence, also the activated complex of oxime formation).

*Nitrosation Kinetics of* 1,3-*Dimethoxybenzene*

The nitrosation of 1,3-dimethoxybenzene was 1. order in nitrous acid, whether the reaction was followed directly spectrophotometrically or by decreases of nitrous acid. The position of maximum and the overall characteristic appearance of spectra was the same as in the nitrosation of 3-methoxyphenol, although the nitroso compounds and oximes have entirely different spectra[8]; it means that the hydrolysis of the primary nitroso derivative into oxime took place many times more rapidly than the proper nitrosation. In contrast to resorcinol and 3-methoxyphenol, the

nitrosation rate of 1,3-dimethoxybenzene (in the pH range −0·3 to 1·5) is inversely proportional to $[H^+]$, and the rate constant is many times smaller (Fig. 1). The assumption, that the linear dependence of the rate constant on $[H^+]$ is caused by the nitrosation of 1,3-dimethoxybenzene being the rate-determining step, is very unprobable. The difference in the rate constants $k_1$ would be about 5 orders of magnitude, which is much more than it was found with couplings and iodinations, although




SCHEME 2

the both respective agents are less reactive and, hence, more selective[9]. In analogy with phenol nitrosation we can suggest the following mechanism (Scheme 2) for the nitrosation of 1,3-dimethoxybenzene, the expression for $k_2$ being $k_2 = (k_1[H^+].k_{H_2O})/(k_{-1} + k_{H_2O})$. From the Scheme it can be seen that the overall reaction rate must depend on $[H^+]$ without respect to which of the steps is rate-limiting. It can be expected that the rate constant $k_1$ of nitrosation will have a comparable value with $k_1$ of phenol nitrosation. A far smaller overall nitrosation rate is due to the unfavourable ratio $k_1/k_{H_2O}$, because the primary nitroso derivative is far less stable than oxime, and, hence, the activated complex of the second reaction step is also far less stable than in the analogous reactions of phenols.

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