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Selective Gas-Phase Oxidation of Pyridine Derivatives with Hydrogen Peroxide

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Abstract—The interfering kinetics of the synchronous reactions of hydrogen peroxide decomposition and the oxidation of pyridine derivatives have been studied experimentally. The regions of the selective oxidation of the pyridine derivatives have been found, and the optimal conditions for the production of 4-vinylpyridine, 4-vinylpyridine *N*-monoxide, 2,2-dipyridyl, and pyridine have been determined. The most probable synchronization mechanism is suggested for hydrogen peroxide decomposition and the free-radical chain oxidation of pyridine derivatives. The $HO_2^{\bullet}$ radical plays the key role in this mechanism. The activation energies are calculated for the elementary steps of 4-ethylpyridine dehydrogenation.

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The wide use of pyridine and its derivatives in the synthesis of medicines, polymers, additives, pesticides, desiccants, and defoliants has stimulated a search for the optimization of their syntheses.

There have been a number of reports detailing the oxidation processes for nitrogen-containing heterocyclic compounds, including pyridine bases [1–3]. However, the role of hydrogen peroxide in the oxidation of nitrogen-containing heterocyclic compounds remains obscure.

There have been reports on the syntheses of the *N*-oxides of pyridine and its derivatives in the presence of hydrogen peroxide. These reactions are catalyzed by acetic acid [4], peracetic acid [5], acetic anhydride [6], and organic acids and their anhydrides [7, 8]. In some cases, enzyme systems are used as catalysts [9, 10].

The hydrogen peroxide–based syntheses of important pyridine bases without employing the above catalysts are of theoretical and applied interest, because it is difficult to completely remove these catalysts and their decomposition products from the desired product.

Investigation of the conjugated oxidation of hydrocarbons with hydrogen peroxide [11, 12] has determined the conditions under which various reaction mechanisms take place. The mechanism of the synchronization of these reactions must involve the free radical $HO_2^{\bullet}$ as a common reactive intermediate [12].

A specific feature of hydrogen peroxide decomposition and hydrocarbon oxidation is that these reactions are parallel and simultaneous or, in other terms, synchronous.

Synchronous chemical reactions can be either (1) parallel or (2) complex interacting reactions. In case (1), the possibility of interaction is ruled out, whereas in case (2) interaction is an essential condition for the existence of the chemical system.

Here, we report the selective oxidative dehydrogenation of 4-ethylpyridine (4-EP) and piperidine, the *N*-monoxidation of 4-vinylpyridine (4-VP), and the dealkodimerization and dealkylation of 2-picoline (2-P) through the synchronization of free-radical hydrogen peroxide decomposition and the oxidation of the pyridine bases.

EXPERIMENTAL

The experiments were performed to determine the kinetics of the homogeneous oxidation of pyridine derivatives with hydrogen peroxide. The experimental setup and procedure used in the study of conjugated oxidation with hydrogen peroxide are detailed elsewhere [11]. The reactions were conducted at atmospheric pressure in a flow quartz reactor of the integral type, whose design allowed undecomposed H_2O_2 to be fed into the reaction zone separately from the hydrocarbon. The volume of the reaction zone was 2 to 5 cm^3. The reaction products were analyzed chromatographically using a capillary column and a flame-ionization detector (column length, 50 m; inner diameter, 0.3 mm; column temperature, 140°C; evaporator temperature, 160°C; detector current, 130 mA; carrier gas, nitrogen; stationary phase, dinonyl phthalate). NMR, IR, and UV spectroscopy and mass spectrometry were also used.

RESULTS AND DISCUSSION

The study of the conjugated oxidative dehydrogenation of 4-EP in the temperature range 520–640°C elucidated the kinetics of this reaction.

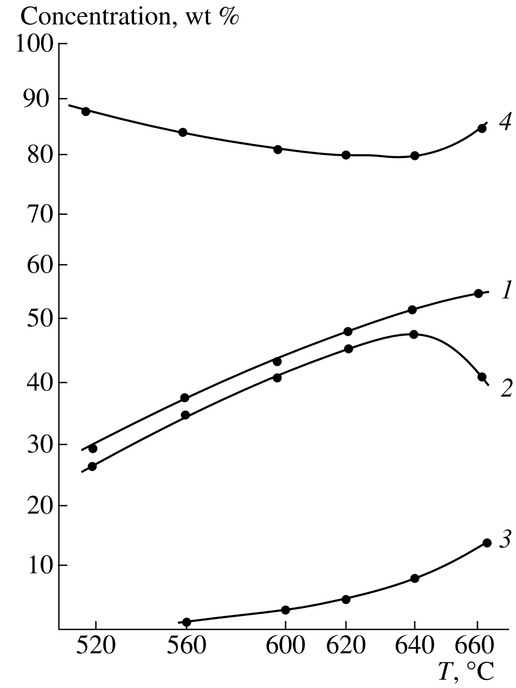


Fig. 1. Temperature dependences of (*1*) 4-EP conversion, (*2*) the 4-VP yield, (*3*) the pyridine yield, and (*4*) the oxygen concentration in the gas phase in 4-EP oxidative dehydrogenation between 520 and 660°C. The concentration of H_2O_2 is 20 wt %, the 4-EP VHSV is 0.065 h^{-1}, and 4-EP/H_2O_2 = 1 : 3 (v/v).

As can be seen in Fig. 1, an increase in temperature from 520 to 640°C causes an increase in the 4-VP yield. This is likely due to the growth of the rate of generation of the active species $HO_2^{\bullet}$ through the thermal decomposition of hydrogen peroxide. This is confirmed by some decrease in the amount of oxygen in the gas phase. A further increase in temperature (above 640°C) results in a dramatic fall of the 4-VP yield and in an increase in the amount of the by-product pyridine. Simultaneously, the oxygen content increases due to the recombination of $HO_2^{\bullet}$ radicals in the bulk. The increase in the pyridine yield above 640°C is due to the dealkylation of 4-EP and 4-VP, as follows from the increase in the carbon dioxide and ethane concentrations in the gaseous reaction products.

The conjugated dehydrogenation of 4-EP was studied in a wide range of process parameters: 4-EP VHSV, 0.045–0.392 h^{-1}; 4-EP/H_2O_2 volume ratio, 1 : 2 to 1 : 5; and H_2O_2 concentration in aqueous solution, 5–25%. The reaction was carried out at various temperatures between 520 and 660°C. The optimal process conditions were found to be the following: T = 620°C; 4-EP VHSV, 0.065 h^{-1}; and the ratio of 4-EP to 20% hydrogen peroxide solution, 1 : 3. Under these conditions, we obtained 44.3% 4-VP with a selectivity of 96% [13, 14].

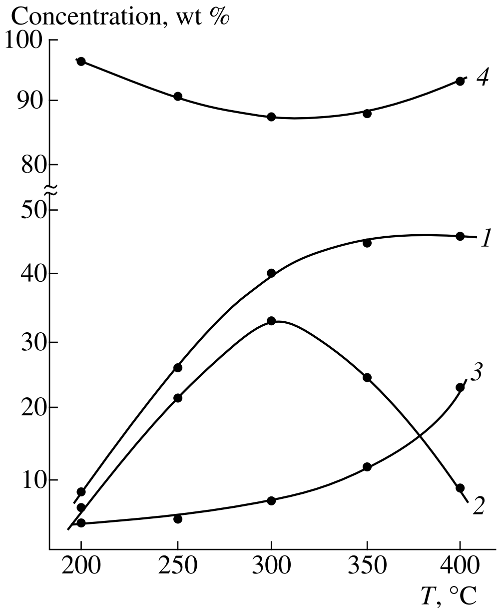


Fig. 2. Temperature dependences of (*1*) 4-EP conversion, (*2*) the 4-VP *N*-monoxide yield, (*3*) the 4-VP yield, and (*4*) the oxygen concentration in the gas phase in 4-EP *N*-monoxidation involving H_2O_2 between 200 and 400°C. The concentration of H_2O_2 is 30 wt %, the 4-VP VHSV is 0.045 h^{-1}, and 4-VP/H_2O_2 = 1 : 3 (v/v).

A decrease in temperature to 200–400°C and changes in some process parameters result in a change in the mechanism of 4-EP oxidation with hydrogen peroxide. In this temperature range, the conjugated *N*-monoxidation of 4-EP to 4-VP *N*-oxide is dominant (Fig. 2). As is seen in Fig. 2 (curve *2*), the highest yield of 4-VP *N*-oxide (33 wt %) is achieved at 300°C. As the temperature is increased from 200 to 300°C, the yield of the desired product increases owing to an increase in the rate of generation of active species through the thermal decomposition of hydrogen peroxide. A decrease in the 4-VP *N*-oxide yield above 300°C at the contact times chosen is likely due to an increase in the concentration of $HO_2^{\bullet}$ radicals, which recombine to form water and oxygen. Indeed, the concentration of oxygen in the gaseous reaction products increases (Fig. 2, curve *4*). The optimal conditions for the *N*-monoxidation of 4-EP (see caption to Fig. 2) were determined by varying the 4-EP VHSV between 0.030 and 0.065 h^{-1}, the 4-EP/H_2O_2 volume ratio between 1 : 2 and 1 : 4, and the H_2O_2 concentration between 20 and 35%. The reaction was carried out at 200, 300, 350, and 400°C [15–17].

Thus, conjugated 4-EP oxidation can be directed to either 4-VP or 4-VP *N*-oxide by controlling the reaction conditions.

The data obtained suggest the following parallel–consecutive mechanism for the *N*-oxidation of 4-EP:

$$\begin{tikzcd} C_2H_5C_5H_4N + H_2O_2 \arrow[r] \arrow[dr, "H_2O_2", "-2H_2O"'] & C_2H_3C_5H_4N + 2H_2O \arrow[d, "H_2O_2"] \\ & C_2H_3C_5H_4NO + H_2O. \end{tikzcd}$$

It seems that, along with direct oxidation, 4-EP is dehydrogenated to 4-VP and the resulting 4-VP is then oxidized to *N*-oxide.

In order to obtain direct evidence for the consecutive mechanism of the *N*-oxidation of 4-EP to 4-VP as the intermediate, we studied the oxidation of 4-VP. Under conditions similar to those for 4-EP oxidation, 4-VP is *N*-monoxidated with hydrogen peroxide to form 4-VP *N*-monoxide (Fig. 3). As is seen in Fig. 3 (curve *1*), the highest 4-VP *N*-monoxide yield of 82 wt % is reached at 300°C. As the temperature is increased from 250 to 300°C, the yield of the desired product somewhat increases due to a slight increase in the number of active species resulting from the thermal decomposition of hydrogen peroxide. The 4-VP N-monoxide yield somewhat decreases above 300°C [18].

The obvious correlation between the desired product yield and oxygen concentration curves (Figs. 1–3) provides reliable evidence for the synchronous occurrence of hydrogen peroxide decomposition and 4-EP or 4-VP oxidation. This correlation is due to the common intermediate, namely, the free radical $HO_2^{\bullet}$ [11, 12].

Based on the experimental data obtained and on the known synchronization mechanism for hydrocarbon oxidation and hydrogen peroxide decomposition [11, 12], we suggested a free-radical chain mechanistic scheme for the conversion of 4-EP to 4-VP and 4-VP *N*-oxide, as well as for the transformation of 4-VP to 4-VP *N*-oxide.

Primary reaction:

$$H_2O_2 \longrightarrow 2OH^{\bullet}$$

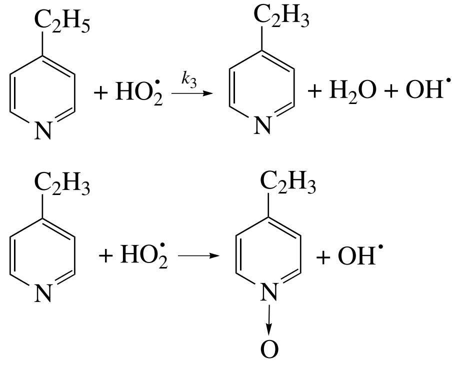
$$\frac{H_2O_2 + OH^{\bullet} \longrightarrow HO_2^{\bullet} + H_2O}{2H_2O_2 = 2H_2O + O_2}$$

Secondary reactions:

Chain initiation $H_2O_2 \xrightarrow{k_1} 2OH^{\bullet}$ (I)

Chain propagation

$H_2O_2 + OH^{\bullet} \xrightarrow{k_2} HO_2^{\bullet} + H_2O$ (II)



(III)

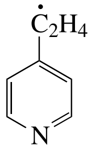
Chain termination

$OH^{\bullet} + \text{wall} \xrightarrow{k_4} OH^{\bullet}(\text{ads})$ (IV)

$HO_2^{\bullet} + \text{wall} \xrightarrow{k_5} HO_2^{\bullet}\ (\text{ads})$ (V)

The peroxide H_2O_2 is simultaneously an actor (A) and an inductor, and the substrate is an acceptor.

In the mechanism of the 4-VP formation, the substitution reaction involving radical $\dot{O}H$, which can produce radical



, is not taken into account. The

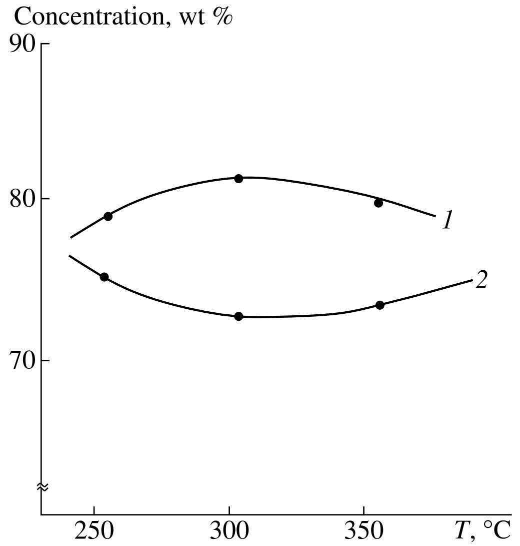


Fig. 3. Temperature dependences of the (*1*) 4-VP *N*-monoxide yield and (*2*) oxygen concentration in the gas phase in 4-VP *N*-monoxidation involving H_2O_2. The concentration of H_2O_2 is 30 wt %, the 4-VP VHSV is 0.045 h^{-1}, and 4-VP/H_2O_2 = 1 : 3 (v/v).

reason for this is that the molecular hydrogen, the products of oxidative cracking, and other compounds that could form upon the formation of such a radical were not detected. In addition, the decomposition of H_2O_2 vapor in the gas phase is among the best known reactions, which occurs via the mechanism involved in the above scheme [19, 20]. As was found by earlier studies [19, 20], the concentration of $HO_2^{\bullet}$ radicals in the gas phase is many orders of magnitude higher than the $OH^{\bullet}$ concentration.

Based on the unbranched chain mechanism of 4-EP and 4-VP conversion, we derived a differential equation taking into account the consumption of the starting compounds and the formation of the reaction products:

$$-\frac{dN_{A_1}}{dV} = k_{eff}C_{A_1}C_{A_2}, \quad k_{eff} = \frac{k_1k_3}{k_4},$$

where A_1 is the actor (4-EP); A_2 is H_2O_2; V is the volume of the reaction zone; N_{A_1} is the current 4-EP molar feed rate, mol/h; and k_1, k_3, and k_4 are the rate constants of the chain initiation, propagation, and termination, respectively. The initial parameters are $V = 0$, $N_{A_1} = N^0_{A_1}$, and $0\ cm^3 \le V \le 2\ cm^3$.

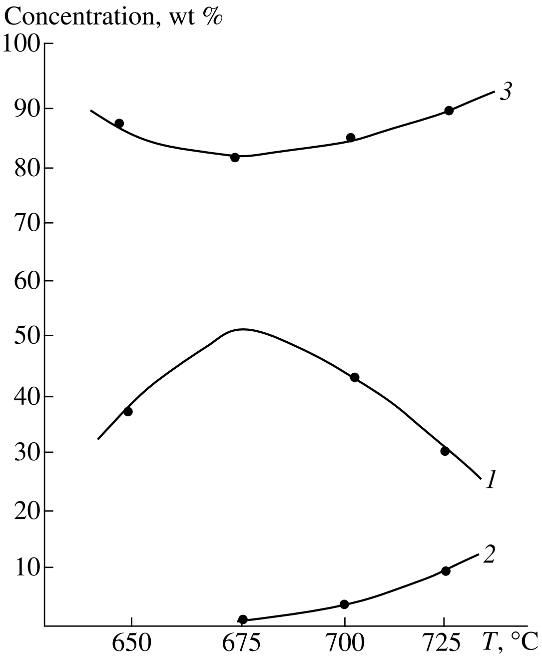


Fig. 4. Temperature dependences of the (*1*) 2,2-DP yield, (*2*) pyridine yield, and (*3*) oxygen concentration in the gas phase in 2-P oxidation with hydrogen peroxide between 650 and 725°C. The concentration of H_2O_2 is 35 wt %, the 2-P VHSV is 0.07 h^{-1}, and 2-P/H_2O_2 = 1 : 3 (v/v).

The activation energies of the elementary steps of 4-EP dehydrogenation were calculated from the rate equation:

Reaction	(I)	(II)	(III)	(IV)	(V)
E, kcal/mol	52.0	5.0	6.2	8.0	7.0

The calculated value of the apparent activation energy is in good agreement with experimental data, the discrepancy being as small as 1 kcal/mol.

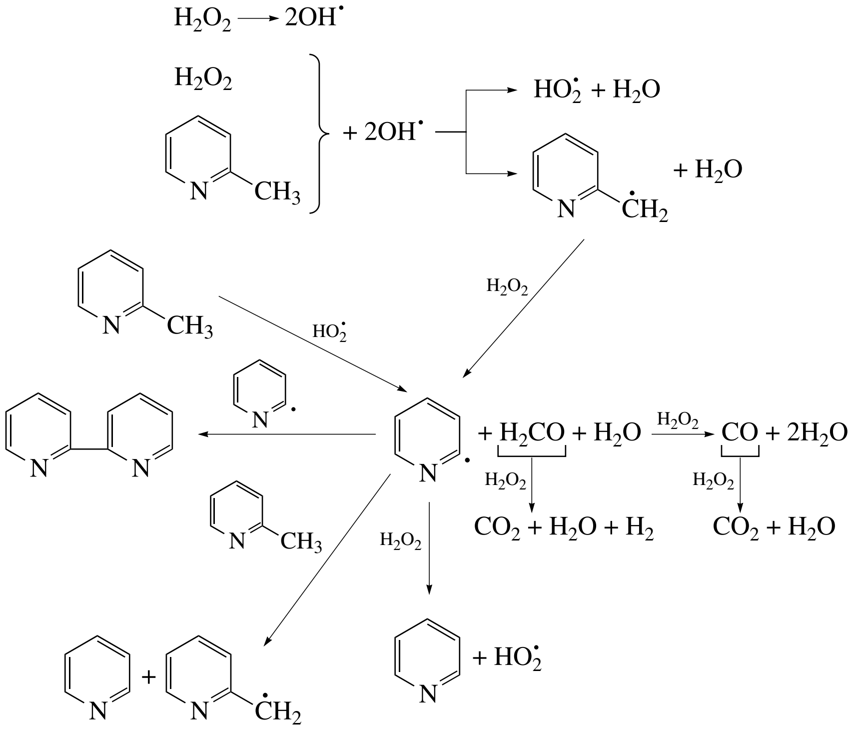
The selective formation of 4-VP during the conjugated oxidative dehydrogenation of 4-EP is observed at 520–640°C, while, at 640°C and above, the dealkylation product, pyridine, forms in significant amounts along with the desired product (Fig. 1). To elucidate the mechanism of the dealkylation of pyridine's alkyl derivatives, the conjugated oxidation of 2-P with hydrogen peroxide was studied in the temperature range 650–725°C [21, 22]. It was found that, under these conditions, 2,2-dipyridyl (2,2-DP) forms from 2-P, passing by the pyridine formation step. The highest yield of 2,2-DP, 52 wt %, was achieved at 675°C, a 2-P VHSV of 0.07 h^{-1}, 2-P/H_2O_2 = 1 : 3 (v/v), and an H_2O_2 concentration of 35 wt % (Fig. 4).

The main product of the 2-P conjugated dealkylation in the presence of hydrogen peroxide at 760–860°C is pyridine (Fig. 5). As the temperature is increased from 760 to 850°C, the pyridine yield increases. Under optimal conditions, pyridine forms in a 42 wt % yield with a selectivity of at least 98% [22].

The correlation between the desired product yield and oxygen content curves (Figs. 4, 5) is evidence of the synchronous occurrence of two complex reactions, specifically, H_2O_2 decomposition and the oxidation of 2-P to 2,2-DP and pyridine.

The most probable stepwise mechanism for the oxidative conversion of 2-P to 2,2-DP and pyridine [11, 12] is the following: The primary reaction, which is H_2O_2 decomposition, is the same as the primary reaction in the above scheme of 4-EP and 4-VP transformations.

Secondary reactions:



It follows from this scheme and earlier data [12, 23] that the observed transformations are due to the interaction of two complex synchronous reactions: hydrogen peroxide decomposition (primary reaction) induces 2-P oxidation to 2,2-DP and pyridine (secondary reactions).

One of the practical applications of the synchronous oxidation reactions can be the conversion of natural compounds for preparative purposes and likely on a larger scale. However, for more complex nitrogen-containing heterocyclic compounds similar in chemical structure to natural compounds, it is necessary to study reactions involving their specific fragments.

For this purpose, we studied the dehydrogenation of piperidine, which is a fragment of many alkaloids. Our experiments have demonstrated that the oxidative dehydrogenation of piperidine affords pyridine in a relatively high yield (65.2 wt %) with a selectivity of at least 98% at 500–540°C, a piperidine VHSV of 0.78 h^{-1}, an H_2O_2 concentration of 25 wt %, and a piperidine : H_2O_2 volume ratio of 1 : 3 [24]. These findings suggest that the piperidine ring can be dehydrogenated under milder conditions than the side hydrocarbon chain and that this method is suitable for the synthesis of alkylpyridines, alkenylpyridines, and *N*-monoxides from the corresponding alkylpiperidines.

The inductive effect of the primary reaction on the secondary, main reaction was evaluated using the determinant equation [11]

$$D = \nu(r_1/r + r_2/r)^{-1},$$

where ν is the stoichiometric coefficient, r_1 and r_2 are the actor (H_2O_2) consumption rates in the primary and secondary reactions, and r is the acceptor (substrate) consumption rate.

The following values of D were obtained for the conditions optimal for the above reactions: 0.21 for 4-EP dehydrogenation, 0.10 for 4-EP *N*-monoxidation, 0.26 for 4-VP *N*-monoxidation, 0.17 for 2-P

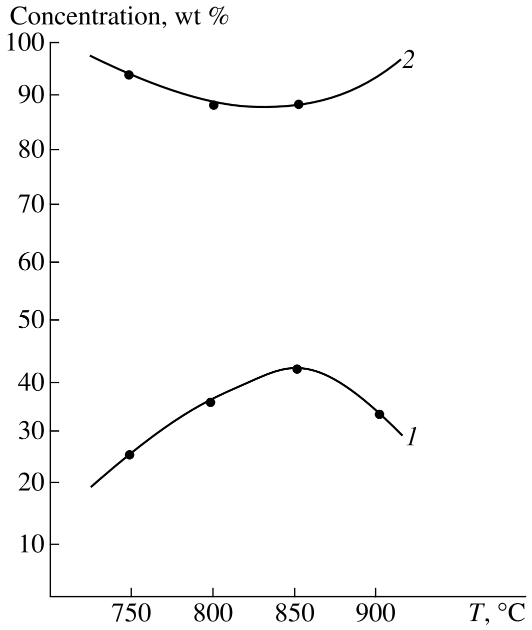


Fig. 5. Temperature dependences of the (*1*) pyridine yield and (*2*) oxygen concentration in the gas phase in 2-P dealkylation in the presence of H_2O_2 between 760 and 860°C. The concentration of H_2O_2 is 35 wt %, the 2-P VHSV is 0.07 h^{-1}, and 2-P/H_2O_2 = 1 : 3 (v/v).

dealkodimerization, and 0.12 for 2-P dealkylation. Based on these values, one can evaluate the efficiency of the inductive effect of the primary reaction according to the determinant equation, bearing in mind that $D \longrightarrow 1$ for the conjugated processes [11, 12].

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