

Kinetics of the Highly Selective Liquid-Phase Oxidation of Side Chain Alkyl Groups in 2-Methylpyrazine and Picolines by Selenium Dioxide

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Abstract:

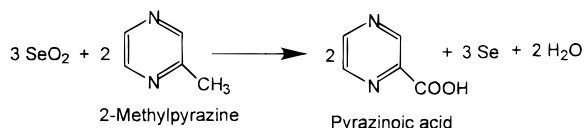
Kinetics of the liquid-phase oxidation of alkyl groups in 2-methylpyrazine and picolines with selenium dioxide at moderate conditions were studied. Thus, 2-methylpyrazine was oxidized to pyrazinoic acid with selenium dioxide in pyridine at 115 °C with 99% selectivity at a 2-methylpyrazine conversion of 100% in 8 h. It was deduced that the reaction follows second-order kinetics and the activation energy was found to be 35 kcal/mol. The same reaction-scheme was found to hold for picolines oxidation to obtain picolinic acids. The byproduct selenium, formed in the reaction, was converted back to selenium dioxide by nitric acid oxidation with 100% selectivity.

Introduction

Pyrazinoic acid and picolinic acids are important pharmaceutical intermediates. They are commonly synthesized by the oxidation of 2-methylpyrazine, 3-picoline, 4-picoline, and 2-picoline, respectively. Different oxidizing agents such as air,^{1–3} nitric acid,^{4,5} and selenium dioxide^{6–11} can be used for this type of oxidation. In air-oxidation the use of costly catalysts and highly corrosive promoters such as bromide salts in acetic acid solvent at elevated temperature makes the process somewhat complicated from both cost and design points of view. In the nitric acid process, the use of higher temperature leads to a higher rate of residue formation. Thus, the separation of the product from the reaction mixture becomes expensive. The molar excess of nitric acid certainly adds to the waste disposal problem. In this aspect it is worth considering the use of the highly selective oxidizing poten-

tiality of selenium dioxide towards these oxidations. Thus, the isolation becomes easier, and the process looks attractive. The selenium dioxide oxidation could be performed in an ordinary stainless steel stirred tank reactor at moderate to low temperatures. Another advantage of using selenium dioxide is that the precipitated selenium metal after the oxidation reaction can be easily recycled back as selenium dioxide after simple oxidation¹² with very high selectivity. Thus, the raw material cost for the expensive selenium dioxide is reduced only to its operational losses plus nitric acid consumption to convert the selenium metal back to selenium dioxide.

Although the chemistry of selenium dioxide oxidation is well-known, the information regarding the kinetics and important process parameters such as initial concentration, temperature, and solvent effect is inadequate and needs to be well-documented. Hence, the present work (Scheme 1) was undertaken to ascertain the suitable process conditions and kinetics for the manufacture of the desired products, pyrazinoic acid and picolinic acids, from the viewpoint of process research and development for large-scale production. The stoichiometric equation of 2-methylpyrazine oxidation is



Experimental Section

The experiments were carried out in an autoclave of 300-mL capacity, made of Hastelloy. The autoclave was equipped with a four-bladed magnetically driven impeller and an internal cooling system. The autoclave was heated externally by a heating element, and the temperature of the reaction was regulated by a temperature indicator controller. The pressure gauge, pressure release valve, and sampling valve were all situated on the reactor cover.

Experimental Procedure

Oxidation of 2-Methylpyrazine and Picolines. Predetermined quantities of starting material, solvent, and selenium dioxide were charged into the autoclave. The reaction temperature was maintained at the desired level by controlling the flow rate of cooling water and the heating rate. A constant temperature was maintained throughout the reaction period.

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Scheme 1. Oxidation of 2-methylpyrazine and picolines by selenium dioxide

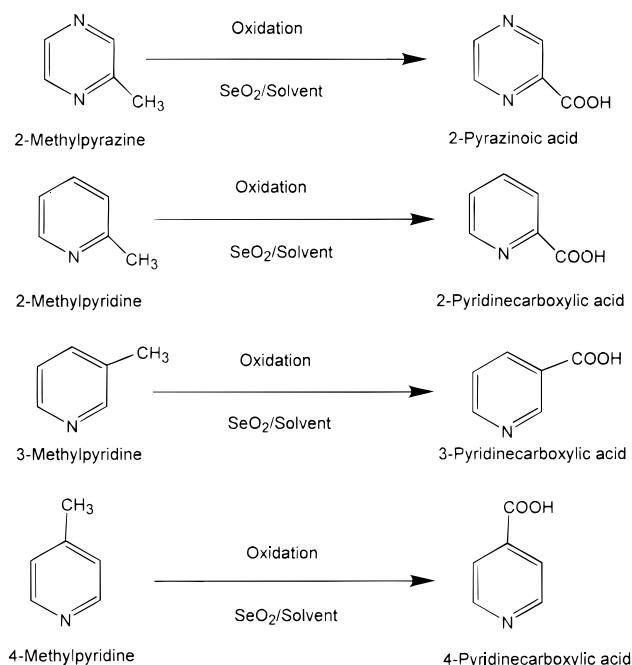


Table 1. Typical reaction of the oxidation of selenium to selenium dioxide by nitric acid

selenium loading	1.26 mol/L
concentration of nitric acid	5.6 mol/L
nitric acid feed	35.3% w/v
reaction temperature	100 °C
reaction time	3 h
reaction volume	1 L
conversion of selenium	98%
selectivity to selenium dioxide	100%

Oxidation of Selenium to Selenium Dioxide. A 2-L borosilicate glass reactor provided with a stirrer, baffles, thermometer pocket, and a reflux condenser was used for this reaction. Predetermined quantities of selenium, nitric acid, and water were added to the reactor, and it was brought to the required temperature. After the stipulated reaction period, the reaction mixture was cooled to room temperature and filtered to remove unreacted selenium. The filtrate was distilled under reduced pressure to isolate the selenium dioxide. The reaction conditions are given in Table 1.

Analysis. Estimation of Unreacted Starting Material. Samples of 1–2 mL, withdrawn at regular intervals of time, were analyzed for unreacted starting material by gas chromatography on a Chemito 8510 instrument equipped with a flame ionization detector, connected to an integrator. A 2-m long, 0.003-m diameter stainless steel column with 10% SE-30 on Chromosorb-W was used. The injector and detector temperatures were maintained at 300 °C, and the oven temperature programming was: 60 °C, 10 °C/min ramp, 200 °C, 20 °C/min ramp, 250 °C, 5 min.

Estimation of Unreacted Selenium Dioxide. A known volume (2 mL) of the reaction mixture was taken after filtration for the determination of selenium dioxide. To this solution, 5 mL of 1.5 M potassium iodide was added followed by 2 mL of 6 N sulphuric acid. The solution was

then promptly titrated with standard sodium thiosulphate solution. When the solution became pale yellow, starch solution was added, and the titration was continued until a sharp change from a turbid brown to transparent red end-point was noted. The free selenium dioxide present in the reaction mixture was calculated from the titre value.

Estimation of Organo Selenium Compounds. Two milliliters of the filtered reaction mixture and 2 mL of concentrated sulphuric acid were heated together. Fuming nitric acid was added dropwise until the mixture became colorless, and heating was continued for about 5 min. The mixture was then cooled and diluted with 5 mL of previously boiled distilled water. Urea was then added to the solution to destroy nitrous acid. The resulting solution was analyzed for selenium dioxide as per the method described earlier. The amount of total selenium dioxide was calculated from the titre value. The amount of free selenium dioxide estimated from the previous method was subtracted from the amount of the total selenium dioxide obtained from this method to account for the selenium in the form of organo selenium compounds.

Isolation of the Desired Product. After the stipulated reaction period, the reaction mixture was filtered to remove precipitated selenium, and the filtrate was distilled under reduced pressure to remove the solvent. The residual mass, after solvent removal, was made basic with 10% sodium hydroxide and filtered to remove any particulate matter. The filtrate was then acidified with 10% formic acid, and the free acids were extracted with toluene. Thereafter, the toluene was removed by distillation under reduced pressure to obtain the solid acids with an isolated yield of 92–96%.

Result and Discussion

Definitions. Conversion. This is the ratio of the number of moles of the reactant reacted to the number of moles of reactant added initially.

Selectivity. This is the ratio of the moles of reactant consumed in the formation of the desired acid to the total number of moles of reactant reacted.

Process Parameter Studies. Effect of Period of Reaction and Initial Concentration of 2-Methylpyrazine on the Rate of Oxidation in Pyridine. It was observed from Figure 1, that with an increase in period of reaction, the conversion of 2-methylpyrazine also increased, as expected.

The reaction was studied over a wide range of initial concentrations, and it was observed that the rate of reaction also increased with the initial concentration (Figure 1).

Effect of Temperature on the Conversion and Selectivity of 2-Methylpyrazine in Pyridine. The oxidation of 2-methylpyrazine in pyridine was studied over a range (105–140 °C) of temperatures. It was found that although the rate of reaction increased with temperature, (Figure 2), the selectivity decreased significantly at higher temperature possibly due to higher rate of formation of organo selenium compounds and decomposition of ring structure leading to residue formation (Table 2).

Effect of Different Solvents on the Rate of Oxidation of 2-Methylpyrazine. In a view to obtain a faster rate and higher selectivity, different alternative solvents such as

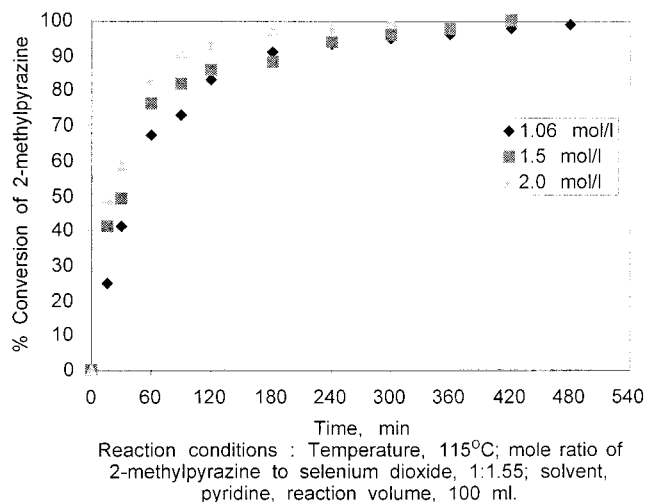


Figure 1. Effect of reaction time and initial concentration on the rate of oxidation of 2-methylpyrazine in pyridine.

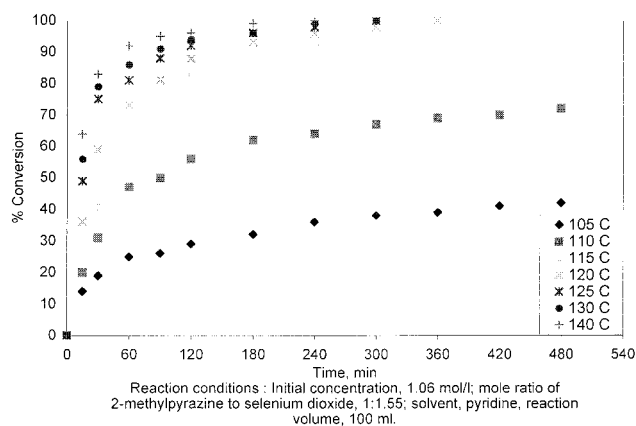


Figure 2. Effect of temperature on the rate of oxidation of 2-methylpyrazine in pyridine.

Table 2. Effect of temperature on the conversion and selectivity to the desired pyrazinoic acid^a

temperature, °C	% conversion of 2-methylpyrazine	% selectivity to pyrazinoic acid
105	29	100
110	56	99
115	83	99
120	88	98
125	92	97
130	94	94
140	96	89

^a Reaction conditions: initial concentration of 2-methylpyrazine, 1.06 mol/L; SeO₂ concentration, 1.65 mol/L; reaction time, 2 h; reaction volume, 100 mL.

pyridine, dibenzyl ether, and 1,4-dioxane were considered for this investigation. The rate of oxidation of 2-methylpyrazine was much slower in 1,4-dioxane compare to other solvents under the identical reaction conditions (Figure 3). This surely indicates that the nature of the solvent plays a critical role in this sort of oxidation.

The Rate of Oxidation of Different Starting Material in Dibenzyl Ether. The rate of oxidation of different starting materials, was examined in dibenzyl ether. It was observed that under identical reaction conditions, the rate of oxidation

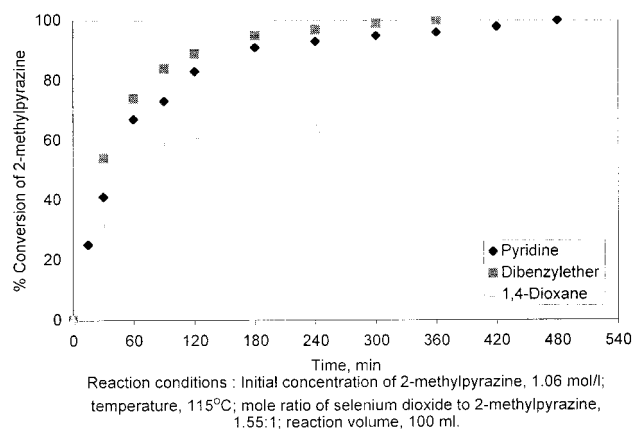


Figure 3. The rate of oxidation of 2-methylpyrazine in various solvents.

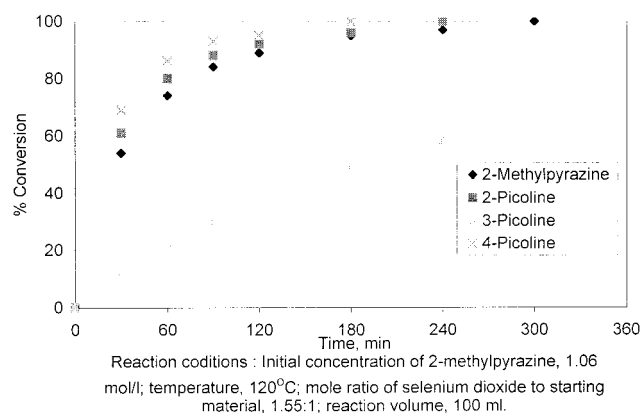


Figure 4. The rate of oxidation of various starting materials in dibenzylether.

Table 3. Product distribution with overall material balance for the oxidation of 2-methylpyrazine with selenium dioxide^a

material	moles of MP accounted for	% MP accounted for	% overall material balance
MP (input)	1.06	100	100
pyrazinoic acid	1.049	99	
organo selenium cmpds	0.0063	0.6	
residue	0.00424	0.4	

^a Reaction conditions: initial concentration of 2-methylpyrazine (MP), 1.06 mol/L; SeO₂, 1.65 mol/L temperature, 115 °C; solvent, pyridine; reaction volume, 1 L.

follows the following order, 4-picoline > 2-picoline > 2-methylpyrazine > 3-picoline (Figure 4). It may be concluded that in the rate-determining step the acidity of the proton of the C–H bond adds to the faster rate of oxidation.

Product Distribution. The product distribution and overall material balance was determined in a 1-L reactor. The complete product distribution with overall material balance on the basis of analytical results is given in Table 3.

Kinetics. Considering the reaction



the rate of disappearance of 2-methylpyrazine or picolines can be expressed as

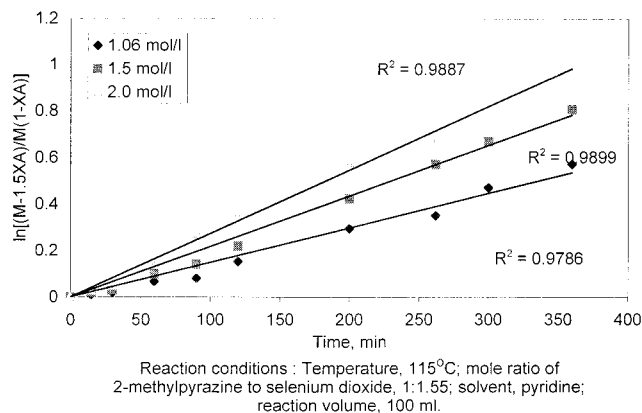


Figure 5. $\ln[(M - 1.5X_A)/M(1 - X_A)]$ vs t at different initial concentrations of 2-methylpyrazine in pyridine.

Table 4. k values at different initial concentrations of 2-methylpyrazine in pyridine^a

initial concentration, mol/L	$k \times 10^2$, L mol ⁻¹ min ⁻¹
1.06	2.8
1.5	4.1
2.0	5.1

^a Reaction conditions: molar ratio of 2-methylpyrazine: SeO₂, 1:1.55; temperature, 115 °C; solvent, pyridine; reaction volume, 100 mL.

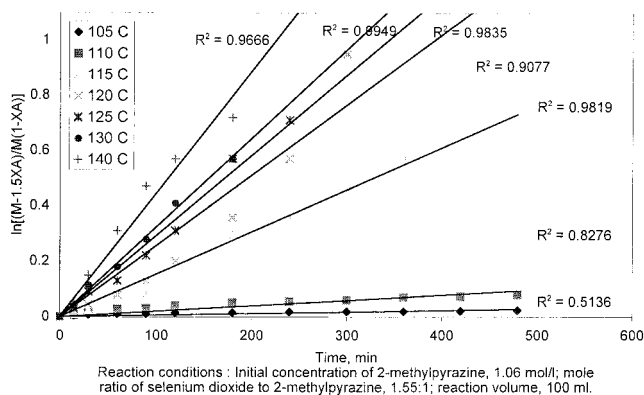


Figure 6. $\ln[(M - 1.5X_A)/M(1 - X_A)]$ vs t at different temperatures for the oxidation of 2-methylpyrazine in pyridine.

$$-r_A = -dC_A/dt = kC_A C_B = C_{A0} dX_A/dt \quad (2)$$

$$C_{A0} dX_A/dt = kC_{A0}(1 - X_A)C_{B0}(1 - X_B) \quad (3)$$

From stoichiometry, for 1 mol of 2-methylpyrazine or picolines, 1.5 mol of selenium dioxide is required.

Thus, at any instant, t

$$1.5C_{A0}X_A = C_{B0}X_B \quad (4)$$

Thus

$$C_{A0}dX_A/dt = kC_{A0}^2(1 - X_A)(M - 1.5X_A) \quad (5)$$

where $M = C_{B0}/C_{A0}$. By integrating and simplification the final form will be where $M \neq 1.5$ and

$$\ln[(M - 1.5X_A)/M(1 - X_A)] = C_{A0}(M - 1.5)kt \quad (6)$$

$$\ln[(M - 1.5X_A)/M(1 - X_A)] = (C_{B0} - 1.5C_{A0})kt \quad (7)$$

Table 5. k values for the oxidation of 2-methylpyrazine at different temperatures in pyridine^a

temperature, °C	$k \times 10^2$, L mol ⁻¹ min ⁻¹
105	0.1
110	0.37
115	2.8
120	4.7
125	5.4
130	6.0
140	8.3

^a Reaction conditions: initial concentration, 1.06 mol/L; SeO₂, 1.65 mol/L; solvent, pyridine; reaction volume, 100 mL.

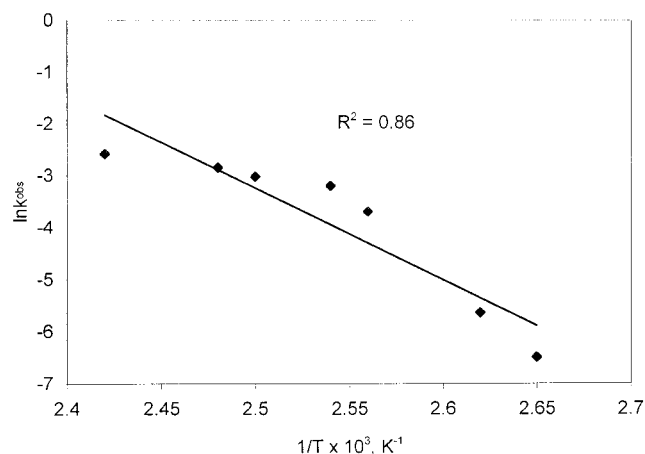


Figure 7. Arrhenius plot.

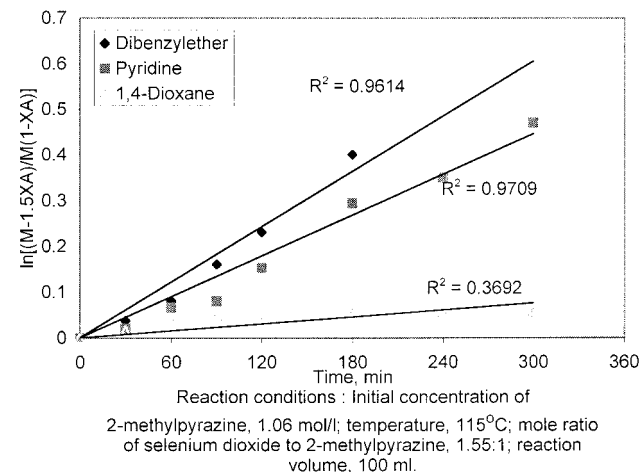


Figure 8. $\ln[(M - 1.5X_A)/M(1 - X_A)]$ vs t with different solvents for the oxidation of 2-methylpyrazine.

A plot of $\ln[(M - 1.5X_A)/M(1 - X_A)]$ vs t at different initial concentrations (Figure 5) shows that the oxidation in pyridine follows second-order kinetics. The k value at different initial concentrations is given in Table 4.

From the respective slopes of the plot of $\ln[(M - 1.5X_A)/M(1 - X_A)]$ vs t at different temperatures in pyridine solvent (Figure 6), k values for the oxidation are determined and given in Table 5. It is observed that at a temperature below 110 °C, the rate of reaction is very slow and the reaction does not follow a second-order rate law.

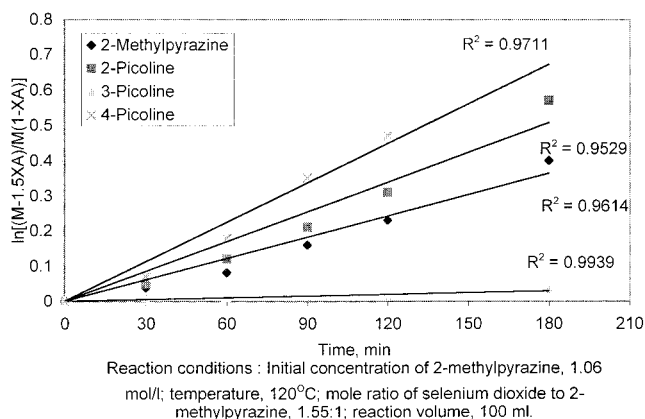


Figure 9. $\ln[(M - 1.5X_A)/(M(1 - X_A))]$ vs t for different starting materials in dibenzylether.

Table 6. k values for different solvents for the oxidation of 2-methylpyrazine^a

solvent	$k \times 10^2, \text{L mol}^{-1} \text{min}^{-1}$
dibenzyl ether	3.8
pyridine	2.8
1,4-dioxane	0.6

^a Reaction conditions: 2-methylpyrazine:SeO₂ ratio, 1:1.55; temperature, 115 °C; solvent, pyridine; reaction volume, 100 mL.

Table 7. k values for the oxidation of different starting materials in dibenzyl ether at 120 °C^a

starting material	$k \times 10^2, \text{L mol}^{-1} \text{min}^{-1}$
2-methylpyrazine	3.8
2-picoline	5.3
3-picoline	0.4
4-picoline	7.0

^a Reaction conditions: initial concentration, 1.06 mol/L; SeO₂, 1.65 mol/L; temperature, 120 °C; solvent, dibenzyl ether; reaction volume, 100 mL.

From the Arrhenius plot, (Figure 7), the energy of activation was found to be 35 kcal/mol ($r^2 = 0.86$).

k values for 2-methylpyrazine oxidation in different solvents and for different starting materials in dibenzyl ether were determined from Figure 8 and Figure 9 and are given in Tables 6 and 7, respectively. Although best-fit lines for a second-order rate equation were obtained for the oxidation of 2-methylpyrazine in pyridine and dibenzyl ether, they were not obtained in dioxane. This means that the solvent has a specific role in this oxidation.

Comparison of this Process with Other Existing Processes. The very high selectivity obtained in this oxidation reaction, permits the simple isolation of the desired products unlike that obtained in air and nitric acid oxidation.

Although air oxidation is commercially preferred to chemical oxidation, the use of costly catalysts and the

complicated bubble column reactor design make it somewhat inferior to selenium dioxide oxidation. The recycling of costly cobalt, manganese, and zirconium acetate catalysts is still problematic in air oxidation, but the selenium can be easily converted to selenium dioxide with very high selectivity, thus reducing the operating cost.

The material of construction is not as exotic as in air or nitric acid oxidation because of the use of a low to moderate reaction temperature and a common noncorrosive solvent.

The major disadvantage of this process-scheme is in the handling of poisonous selenium metal. With proper industrial practice, this problem could be overcome.

Conclusions

The oxidation of 2-methylpyrazine and picolines with selenium dioxide follows second-order kinetics with respect to the starting materials. The activation energy was found to be 35 kcal/mol.

The valuable data obtained in this study could enable one to formulate the optimum process conditions and to design an appropriate reactor for plant level production.

Above all, the high selectivity of this process is an added advantage in comparison to the other processes, but strict precautions must be taken for large-scale production while handling the poisonous selenium metal.

Notations

C_{A_0}	initial concentration of 2-methylpyrazine or picolines at time, $t = 0$, mol/L
C_{B_0}	initial concentration of selenium dioxide at time, $t = 0$, mol/L
C_A	concentration of 2-methylpyrazine or picolines at time, $t = t$, mol/L
C_B	concentration of selenium dioxide at time, $t = t$, mol/L
X_A	fractional conversion of 2-methylpyrazine or picolines at, $t = t$.
$-r_A$	$-dC_A/dt$ = rate of disappearance of substrate
M	molar ratio of the initial concentration of selenium dioxide to the substrate
k	rate constant, $\text{L mol}^{-1} \text{min}^{-1}$
t	time, min

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