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Effect of the Nucleophile Structure and Basicity on Pyridine-Catalyzed Formation of Thiosemicarbazides

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Abstract—The kinetics of pyridine-catalyzed reaction of *O,O*-diaryl hydrazidothiophosphates with phenyl isothiocyanate in benzene at 25°C were studies. Pyridine was found to exhibit a considerable catalytic effect in the formation of phosphorus-containing thiosemicarbazides. A correlation between the reactivity of phosphorus hydrazides in the catalytic reaction and their structure was revealed. The catalytic activity of pyridine increases as the basicity of hydrazide decreases. The effects of the substituents in the aromatic rings and the basicity of hydrazides weaken in going from the noncatalytic to catalytic process. The catalysis by pyridine conforms to the general base catalysis pattern.

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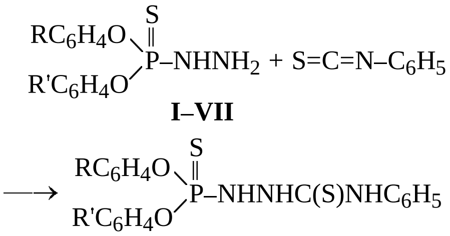
Catalytic activity of organic bases (B) in reactions of hydrazine derivatives with isocyanates and isothiocyanates originates from their ability to form hydrazide–base associates via N–H···B hydrogen bonding [1, 2]. In this respect, pyridines attract considerable interest as substances possessing a strong nucleophilic center (nitrogen atom). Pyridine and its derivatives might be expected to exhibit catalytic effect in the formation of thiosemicarbazides. It is known that the catalytic activity depends both on the structure of reagents and catalyst and on the reaction conditions (properties of the medium and reaction temperature). Studies on such relations will be useful from the practical viewpoint, specifically for selection of most active catalysts and elucidation of the catalysis mechanism.

The present work was aimed at studying the kinetic relations holding in the reaction of *O,O*-diaryl hydrazidothiophosphates **I**–**VII** with phenyl isothiocyanate in the presence of pyridine in benzene at 25°C. It was also important to elucidate the mechanism of catalysis by pyridines in this reaction. Therefore, the effects of the hydrazide structure and basicity on the rate of the catalytic reactions were examined, and the sensitivity (ρ) of the catalytic process to electronic nature of the substituents in the hydrazides **I**–**VII** was compared with that intrinsic to the corresponding noncatalytic reaction.

The results of special experiments showed that *O,O*-diaryl hydrazidothiophosphates **I**–**VII** quantitatively and irreversibly react with phenyl isothiocyanate in benzene both in the presence and in the absence of pyridine according to the scheme given below.



I–VII

For R and R', see Table 1.

The reaction rate of *O,O*-diaryl hydrazidothiophosphates (initial concentration *a*, M) with phenyl isothiocyanate (initial concentration *b*, M) in the presence of pyridine (concentration *m*, M) at $a = b$ is described by Eq. (1).

$$dx/dt = k_0(a - x)^2 + k_b(a - x)^2 m. \qquad (1)$$

Here, k_0 ($\mathrm{l\,mol^{-1}\,s^{-1}}$) and k_b ($\mathrm{l^2\,mol^{-2}\,s^{-1}}$) are, respectively, the rate constants of the noncatalytic and pyridine-catalyzed reaction; x ($\mathrm{mol\,l^{-1}}$) is the amount of unreacted phenyl isothiocyanate at a moment t (s). As follows from Eq. (1), the catalytic process is accompanied by noncatalytic reaction. The apparent rate constant (overall process) is given by Eq. (2).

$$k = k_0 + k_b m. \qquad (2)$$

The apparent rate constants k ($\mathrm{l\,mol^{-1}\,s^{-1}}$) were calculated from the experimental data using the

Table 1. Effect of the structure and basicity of *O,O*-diaryl hydrazidothiophosphates **I**–**VII** on the rate of their pyridine-catalyzed reactions with phenyl isothiocyanate in benzene at 25°C

Comp. no.	R	R'	$k_0 \times 10^3$, $\mathrm{l\,mol^{-1}\,s^{-1}}$	k_b, $\mathrm{l\,mol^{-1}}$	k_b/k_0, $\mathrm{l\,mol^{-1}}$	$\mathrm{p}K_{\mathrm{BH^+}}$ [3]	$\Sigma\sigma^{\Phi}$
I	*p*-CH_3	*p*-CH_3	0.390 ± 0.024	4.54 ± 0.26	11641	2.76	–0.28
II	*p*-CH_3	H	0.239 ± 0.017	2.63 ± 0.21	11004	2.74	–0.20
III	*m*-CH_3	*m*-CH_3	0.248 ± 0.019	3.55 ± 0.12	14315	2.73	–0.18
IV	H	H	0.0958 ± 0.0029	3.21 ± 0.10	33507	2.70	–0.12
V	H	*p*-Cl	0.0920 ± 0.0025	2.09 ± 0.08	22717	2.68	0.01
VI	*p*-Cl	*p*-Cl	0.0465 ± 0.0014	1.82 ± 0.15	39140	2.63	0.14
VII	*m*-Cl	*m*-Cl	0.0372 ± 0.0011	1.36 ± 0.11	36559	2.58	0.24

Table 2. Apparent (k) and catalytic (k_b) rate constants for the reactions of *O,O*-diaryl hydrazidothiophosphates **I**–**VII** with phenyl isothiocyanate in benzene at different pyridine concentrations at 25°C [a]

Comp. no.	Pyridine concentration, M	k, $\mathrm{l\,mol^{-1}\,s^{-1}}$	k_b, $\mathrm{l\,2\,mol^{-2}\,s^{-1}}$
I	0.001	0.00485 ± 0.00024	4.46
	0.0015	0.00714 ± 0.00030	4.50
	0.002	0.00971 ± 0.00038	4.66
II	0.001	0.00295 ± 0.00015	2.72
	0.0015	0.00414 ± 0.00023	2.60
	0.002	0.00536 ± 0.00035	2.56
III	0.001	0.00382 ± 0.00018	3.57
	0.0015	0.00562 ± 0.00020	3.58
	0.002	0.00723 ± 0.00022	3.49
IV	0.001	0.00333 ± 0.00010	3.23
	0.0015	0.00484 ± 0.00016	3.16
	0.002	0.00657 ± 0.00023	3.23
V	0.001	0.00221 ± 0.00013	2.12
	0.0015	0.00318 ± 0.00017	2.06
	0.002	0.00430 ± 0.00022	2.10
VI	0.001	0.00181 ± 0.00008	1.76
	0.0015	0.00278 ± 0.00012	1.82
	0.002	0.00380 ± 0.00018	1.88
VII	0.001	0.00135 ± 0.00005	1.31
	0.0015	0.00216 ± 0.00011	1.40
	0.002	0.00287 ± 0.00016	1.37

[a] Initial reactant concentration 0.00125 M.

second-order kinetic equation and taking into account reaction stoichiometry, for the reciprocal of the current concentration was linear in time at a constant concentration of the catalyst. The rate constants did not change during the process up to a conversion ~80%. The apparent second-order rate constants were linearly related to the catalyst concentration provided that the latter was relatively low (Table 2). Tables 1 and 2 contain the catalytic rate constants k_b calculated by Eq. (2) and rate constants of noncatalytic reactions k_0 [4], which were used to calculate the former.

Addition of a small amount of pyridine to the reaction mixture sharply accelerates the process. The data in Tables 1 and 2 show that pyridine is a highly effective catalyst in the formation of thiosemicarbazides. The catalytic process is strongly influenced by the nucleophile structure. The rates of both catalytic and noncatalytic reactions increase with rise in the electron-donor power of the substituents in the aromatic rings of hydrazides **I**–**VII**. However, within the above series, the catalytic rate constants k_b change by a factor of 3, while the range of variation of the noncatalytic rate constants k_0 is equivalent to an order of magnitude. This means that the catalytic activity of pyridine (which is defined as the ratio of the rate constants of the catalytic and noncatalytic reactions, k_b/k_0), increases as the substrate reactivity decreases. The effect of substituents on the rate of pyridine-catalyzed reactions of *O,O*-diaryl hydrazidothiophosphates with phenyl isothiocyanate is well described by Hammett equation using σ^{Φ} constants (for substituents attached to a phosphorus atom [5]:

$$\log k_b = (0.357 \pm 0.023) - (0.899 \pm 0.126)\Sigma\sigma^{\Phi}, \quad (3)$$

n 7, r 0.954, s 0.059.

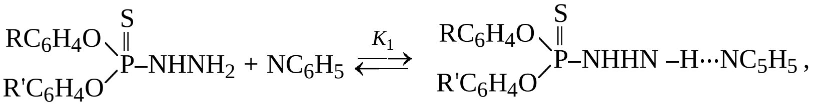
The ρ_{k_b} value equal to –0.899 is more than twice lesser than the corresponding parameter for the noncatalytic reaction in benzene ($\rho_{k_b} = -1.94$ [4]). These values indicate the reaction sensitivity to electonic nature of substituents decreases as the reactivity of the system increases.

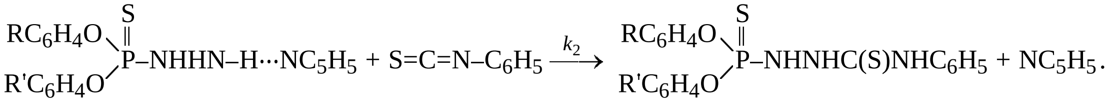
The effect of the nature of hydrazine derivatives in the catalytic process is closely related to the above stated. The results of the present study showed that both catalytic (k_b) and noncatalytic rate constants (k_0)

considerably increase as the basicity of the hydrazides rises (Table 1). On the other hand, the catalytic effect characterized by the ratio k_b/k_0 changes in the opposite direction. Therefore, the catalytic and noncatalytic processes are characterized by different sensitivities to the hydrazide nature (β). Increase of k_b/k_0 as the basicity of the hydrazide decreases suggests stronger catalytic effect of pyridine toward less basic phosphoric hydrazides. The logarithms of the catalytic rate constants are related to the basicity constants of the hydrazides through Brønsted Eq. (4).

$$\log k_b = (-3.18 \pm 0.34) + (1.15 \pm 0.13)\mathrm{p}K_{\mathrm{BH}^+}, \quad (4)$$
$$n\ 7,\ r\ 0.969,\ s\ 0.047.$$

The value of β_{k_b} is equal to 1.15; i.e., it is lower by a factor of >5 than the corresponding parameter for the noncatalytic reaction (β_{k_0} = 5.91 [4]). It is reasonable to presume that significant reduction of the β value in going from the noncatalytic reaction to catalytic is determined by the mechanism of the pyridine-catalyzed reaction. Insofar as pyridine is a Brønsted base, it can favor proton transfer in the catalytic act of a catalytic reaction. On the basis of the results given above and published data on the catalytic activity of pyridines [1, 2, 6], the mechanism of catalysis in the system under study may be represented by schemes (5) and (6).


(5)


(6)

The catalytic process includes two steps. In the first of these [scheme (5)], preliminary association of the catalyst and nucleophile leads to formation of an H-bonded hydrazide–pyridine complex. The H-complex formation is a fast and reversible process characterized by the equilibrium constant K_1 (l mol^{-1}). The second step [scheme (6)] is the rate-determining reaction of the complex with phenyl isothiocyanate to give the final product, phosphorus-containing thiosemicarbazide; it is accompanied by regeneration of the catalyst. Here, the reaction rate is determined by the bimolecular rate constant k_2 (l mol^{-1} s^{-1}). The apparent rate constant for the catalytic reaction (k_b) is expressed by Eq. (7).

$$k_b = K_1 k_2. \quad (7)$$

The sensitivity constant β_{k_b} for the catalytic reaction is an apparent quantity given by formula (8).

$$\beta_{k_b} = \beta_{K_1} + \beta_{k_2}. \quad (8)$$

Thus the β_{k_b} value given above (1.15) reflects the effect of the hydrazide basicity both in the first equilibrium step (β_{k_b}) and in the second step (β_{k_0}), i.e., $\beta_{k_b} = \beta_{K_1} + \beta_{k_2} = 1.15$.

Therefore, decrease in the absolute value of β in going from the noncatalytic process (β_{k_0}) to catalytic (β_{k_b}) originates from the opposite effects of the hydrazide basicity on K_1 and k_2. More basic hydrazides are less prone to form hydrogen bond with the nucleophilic pyridine nitrogen atom [scheme (5)], as compared to less basic hydrazides, and β_{K_1} is negative. In the reaction between the H-complex and phenyl isothiocyanate [scheme (6)], the sensitivity should remain almost unchanged, i.e., $\beta_{k_b} \approx \beta_{k_0}$. Thus, taking into account negative value of β_{K_1} for the equilibrium step and positive β_{k_b} in the rate-determining step, the effective absolute value of β_{k_b} for the catalytic reaction should be lower than β_{k_0} for the noncatalytic process, as is observed in the system under study. Assuming $\beta_{k_b} \approx \beta_{k_0}$, calculation of β_{K_1} by Eq. (8) gives a value of –4.76 which indicates that the equilibrium constant K_1 is more sensitive to the hydrazide basicity than the bimolecular rate constant k_2 by a factor of >4.

A conclusion may be drawn that the sensitivity constant should decrease in absolute value in going from noncatalytic process to catalytic, the latter following the general base catalysis mechanism with preliminary association of the catalyst with nucleophile. The described character of variation of the β parameter in going from noncatalytic to catalytic reaction may be used as a criterion ensuring determination of the catalysis mechanism.

EXPERIMENTAL

The progress of the reactions was monitored following the concentration of unreacted phenyl isothiocyanate [7]. The kinetic measurements were performed in benzene at 25°C. The initial concentrations of phosphorus-containing hydrazides **I**–**VII** and phenyl isothiocyanate were 0.00125 M, and that of pyridine was 0.001 to 0.002 M. The results were processed by the least-squares procedure, the accuracy being characterized by meansquare deviation with a confidence probability of 0.95 [8].

Benzene for kinetic measurements was prepared as described in [9]. *O*,*O*-Diaryl hydrazidothiophosphates **I**–**VII** were synthesized from the corresponding chlorothiophosphates and hydrazine hydrate and were purified by the procedures reported in [10, 11]. Phenyl isothiocyanate was distilled under reduced pressure to use. Pyridine was purified by known method [12]. The physical constants of the reagents used were consistent with those reported in the literature. Reaction solutions in anhydrous benzene were prepared from freshly purified chemicals in an amount necessary for a single series of kinetic experiments.

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