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Dedicated to the 90th Anniversary of Corresponding Member of the Russian Academy of Sciences A.N. Pudovik

Kinetics and Mechanism of the Pudovik Reaction in the Azomethine Series:

III.[1] Acid-catalyzed Hydrophosphorylation of Imines

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Abstract—A complex spectral (UV, IR, and ^{31}P NMR), preparative, and kinetic investigation of the mechanism of the noncatalytic variant of the Pudovik reaction in the series of imines was carried out. The reaction proceeds through a four-center cyclic transition state. The transition state is highly labile, which determines its high sensitivity to the structure of the reagents, the nature of the solvent and catalyst, and some other factors. The necessary condition for the hydrophosphorylation of imines to occur is the participation of proton-donor reagents and acidic admixtures, specifically hydrolysis products of dialkyl hydrogen phosphites, such as monoalkyl dihydrogen phosphates and phosphorous acid, which act as acid catalysts. When the starting reagents are thoroughly purified and no such catalysts are present, the Pudovik reaction fails to occur in the imine series.

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Hydrophosphorylation of imines with hydrogen phosphites, the imine variant of the Pudovik reaction, is one of the common methods for preparing α-aminophosphonates, phosphorus-containing analogs of natural amino acids [2]. It is proposed that the reaction involves noncatalyzed addition of hydrophosphoryl compounds by the C=N bond to form a concerted four-center transition state in which the proton-acceptor nitrogen atom acts as an “internal” basic catalyst [3, 4]. However, our ^{31}P NMR study of the hydrophosphorylation of benzalaniline [1] showed that the reaction between Schiff bases and dialkyl hydrogen phosphites thoroughly purified from traces of acidic admixtures does not take place. It proceeds only in the presence of hydrolysis products of dialkyl hydrogen phosphites, implying that the phosphorous acid or its monoalkyl ester formed make the hydrophosphorylation of imines an acid-catalyzed reaction.

In this work we report the results of a kinetic, spectral, and preparative investigation of the role of catalytic processes in the imine variant of the Pudovik reaction with a wider range of unsaturated reagents. For the objects for study we chose *N*-Isoropylarylidenamines **Ia**–**If**, *N*-phenylarylideneamines **IIa**–**IIg**, and *N*-arylbenzylideneamines **IIIa**–**IIIf**. Such choice is motivated by the fact that compounds **I**–**III** react with dialkyl hydrogen phosphites under mild conditions without specially added catalysts. Moreover, by varying substituents in the phenyl ring both of the methylidene and imine fragments of the azomethine one can noticeably vary the electronic situation in the reaction center, i.e. on the carbon and nitrogen atoms of the C=N bond.

N-Arylidenearylamines **IIa**–**IIg** and **IIIa**–**IIIf** were obtained by boiling equimolar mixtures of the staring compounds in benzene with a Dean–Stark trap. The reaction products were isolated from benzene solutions and purified by multiple crystallization. Their yields and melting points are listed in Table 1. The procedures for preparing and physicochemical characteristics of *N*-isopropylbenzylideneamines **Ia**–**If** are presented in [3].

$$R^1C_6H_4CHO + R^2NH_2 \longrightarrow R^1C_6H_4CH{=}NR^2,$$

I, R^1 = 4-Me_2N (**a**), 4-MeO (**b**), H (**c**), 4-Cl (**d**), 4-F (**e**), 4-NO_2 (**g**). **II**, R^1 = 4-Me_2N (**a**), 4-MeO (**b**), H (**c**), 4-Br (**d**), 4-Cl (**e**), 4-F (**f**), 4-NO_2 (**g**); R^2 = Ph. **III**, R^1 = H; R^2 = = 4-MeC_6H_4 (**a**), 4-$CH_3OC_6H_4$ (**b**), 4-IC_6H_4 (**c**), 4-BrC_6H_4 (**d**), 4-ClC_6H_4 (**e**), 4-$NO_2C_6H_4$ (**f**).

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[1] For communication II, see [1].

Table 1. Yields and melting points of *N*-phenylarylideneamines 4-R–C_6H_4CH–NPh **II** and *N*-arylbenzylideneamines C_6H_5CH–N–C_6H_4–R-4 **III**

Comp. no.	Yield, %	mp,°C	Comp. no.	Yield, %	mp,°C
IIa	80	89	**IIIa**	75	27–28
IIb	83	60	**IIIb**	77	68
IIc	75	50	**IIIc**	83	82
IId	76	74	**IIId**	84	66–67
IIe	81	63	**IIIe**	88	53
IIf	76	44	**IIIf**	82	145
IIg	79	89			

The structure of azomethines was confirmed by IR, NMR, and UV spectroscopy, and their purity was controlled by TLC. The IR spectra all contain bands at 1630–1640 cm^{-1} characteristic of C=N stretching vibrations and lack C=O and N–H absorption bands of the starting reagents. The spectra also contain strong absorption bands of the aromatic ring (1468–1475, 1515–1520, 1600–1610, and 3000–3090 cm^{-1}).

Table 2. Apparent rate constants (k_I) of the reaction of benzalaniline **IIc** with diisopropyl hydrogen phosphite in 2-propanol at 298 K at varied procedures for preparing soluions and contents of water and phosphorous acid

Exp. no.	Concentration of reaction components, M			$k_I \times 10^5$, s^{-1}			
				Series I		Series II	
	(i-PrO)$_2$PHO	H_2O	H_3PO_3	A	B	A	B
1	0.2	–	–	3.8 [a]	[b]	2.6	[b]
2	0.2	1×10^{-3}	–	–	–	4.8	[b]
3	0.2	3×10^{-3}	–	–	–	5.6	[b]
4	0.2	1.85	–	–	–	118	3.2
5	–	–	1×10^{-4}	9.2	4.7	–	–
6	0.2	–	1×10^{-4}	23.9	8.6	–	–
7	0.2	1×10^{-3}	1×10^{-4}	–	–	12.7	4.1
8	0.2	3×10^{-3}	1×10^{-4}	–	–	15.4	6.4

[a] In the subsequent experiments the rate constant was 9.6×10^{-5} s^{-1} 30 min after the beginning of the experiment and 11.3×10^{-5} s^{-1} after 2 h. [b] Reaction does not occur.

The reaction progress was followed by UV spectroscopy. Table 1 lists apparent rate constants for two independent series of reactions of azomethine **IIc** with diisopropyl hydrogen phosphite with varied procedures for preparing working solutions and H_3PO_4 and H_2O additives. Data in columns A and B relate to different procedures for preparing working solutions. In procedure A, an aliquote of diisopropyl hydrogen phosphite was taken with a pipet from a receiver directly after distillation and placed into a spectrophotometer cell charged with a solution of the other components in 2-propanol. In this case, the apparent reaction rate constant increased with time. Note that the reaction of imine **II** with diisorpopyl phosphite involves an inductive period of about 5 min. After that the reaction occurred at a rate shown in Table 2 (exp. no. 1). At the same time, under air-proof conditions, in a thoroughly sealed reaction vessel, and at a low moisture content the rate constants were strictly constant. In procedure B, a solution of diisopropyl phosphite in 2-propanol, prepared from a freshly purified sample, was used. Under these conditions, no reaction was observed for 2 and more weeks.

In both series, the reaction rate of azomethine **IIc** with diisoropyl hydrogen phosphate notably increases after addition of phosphorous acid. This fact provides evidence for the catalytic effect of this compound. Addition of water, too, increases the rate constant. The role of water is more significant when the reaction is performed by procedure A (series II, exp. nos. 1–4).

Analysis of the resulting data gives clear evidence to show that pure benzalaniline **IIc** fails to react with diisopropyl hydrogen phosphite in the absence of the above-mentioned additives. It is only acid admixtures, both specially added and formed by partial hydrolysis of dialkyl hydrogen phosphate, that make the reaction possible. Under these conditions, the effect of water is clearly pronounced. On the one hand, increased concentration of water accelerates hydrolysis of dialkyl hydrogen phosphate. On the other, water is evidently involved in the reaction act: Due to its polarity, water can either increase the acidity of the medium or catalyze imine hydrophosphorylation.

For quantitative interpretation of the specific features of the reaction, we have studied its kinetics by means of UV spectroscopy. Since, as we showed in [1], in 2-propanol hydrolysis of dialkyl hydrogen phosphites is supressed or proceeds much slower than in the other solvents, and diisopropyl hydrogen phosphite undergoes no changes in this medium, the main part of our study was performed just in this solvent. The kinetic measurements were carried out under pseudofirst-order conditions with respect to azomethine with a large excess of dialkyl hydrogen phosphite (0.1–1 M).

Previously we [3, 4] and some other authors [5, 6] showed that the order of the reaction of azomethines with dialkyl hydrogen phosphite in the absence of specially added catalysts is one. In our present case, where dialkyl hydrogen phosphites were purified, as commonly accepted, by fractionation without metallic sodium, high-quality linear dependences between the apparent rate constants k_{app} in 2-propanol on the concentration of dialkyl hydrogen phosphite (DAP). As follows from the log dependences of rate constant on phosphite concentration, the reaction is first-order in DAP.

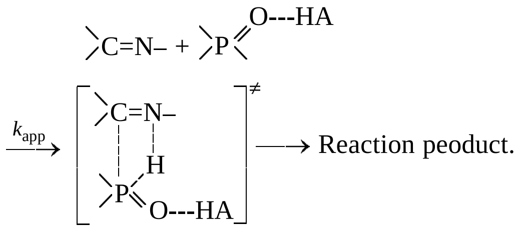
For dimethyl hydrogen phosphite

$$\log k_{app} = (1.039 \pm 0.024)\log [\mathrm{DAP}] - 2.661,$$
$$n\ 8,\ S_0\ 0.012,\ r\ 0.9983.$$

For diisopropyl hydrogen phosphite

$$\log k_{app} = (1.097 \pm 0.036)\log [\mathrm{DAP}] - 2.450,$$
$$n\ 6,\ S_0\ 0.023,\ r\ 0.9978.$$

At the same time, as already mentioned, the Pudovik reaction in 2-propanol fails with thoroughly purified reagents. The reaction proceeds at appreciable rate after short contact of the reagents or reaction mixtures with atmosphere or after addition of water or acidic compounds. It can be suggested that in cases where dialkyl hydrogen phosphites after usual fractionation are used, azomethine reacts with H-complex of dialkyl hydrogen phosphite with acid admixture HA. The role of the latter can be played by water and hydrolysis products of dialkyl hydrogen phosphite whose presence we substantiated previously [1]. In this case, the observed first order in phosphite can be explained by a scheme involving formation of a trimolecular activated complex **IV**.



According to this scheme, the reaction rate should be described by the equation $w = k_{app}[\mathrm{C{=}N}][\mathrm{DAP \cdot HA}]$.

As the concentration of the sufficiently strong phosphite–proton-donor complex is linearly related to the concentration of dialkyl hydrogen phosphite, the order in phosphite is formally determined as one.

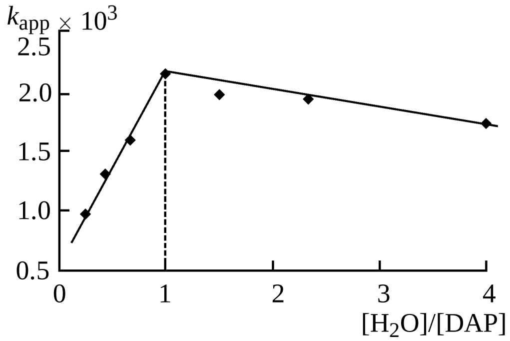


Fig. 1. Dependence of the apparent rate constant of the reaction of diisopropyl hydrogen phosphite (DAP) with benzalaniline (**IIc**) on the ratio of the concentrations of water and phosphite in 2-propanol.

However, when the rate-limiting stage is not formation of complex **IV** but its further transformation to the reaction product, as we previously observed in the reaction of dimethyl hydrogen phosphite with 1-(cyclohexylimino)-2-butene [7], the reaction order in dialkyl hydrogen phosphite becomes zero.

In view of the possible formation of the phosphite–water H-complex, to establish its composition we invoked the isomolar series method [8] with slight modifications, i.e. instead of a parameter relating to the concentration of the complex, we studied changes in apparent rate constant at varied relative concentrations of water and diisopropyl hydrogen phosphite (Fig. 1). As seen from the resulting dependences, the highest apparent rate constant relates to a 1 : 1 diisopropyl hydrogen phosphite: water ratio. This result can be considered evidence to show that the prereaction complex has just the same composition.

In the kinetic experiment by the second procedure, when dialkyl hydrogen phosphite is used as a solution, an inductive period of about 5–10 min is observed; evidently, this time is necessary for absorption of air moisture. Thorough isolation of the reaction mixtures from air moisture can prolong the inductive period to several days. But here, too, the first order of the reaction in dialkyl hydrogen phosphite is preserved, in accordance with high-quality linear correlations for different temperatures.

At 298 K

$$\log k_{app} = (1.018 \pm 0.035)\log [\mathrm{DAP}] - 2.523,$$
$$n\ 5,\ r\ 0.9982,\ S_0\ 0.020,$$

At 308 K

$$\log k_{app} = (0.977 \pm 0.018)\log [\mathrm{DAP}] - 2.354,$$
$$n\ 6,\ r\ 0.9993,\ S_0\ 0.016,$$

At 323 K

$$\log k_{app} = (1.084 \pm 0.086)\log [\mathrm{DAP}] - 2.195,$$
$$n\ 5,\ r\ 0.9906,\ S_0\ 0.063.$$

Table 3. Rate constants at 298 K and activation parameters of the reaction of *N*-isopropylarylidenamines **I** with dimethyl hydrogen phosphite and of azomethines **II** and **III** with diisopropyl hydrogen phosphite in 2-propanol

Comp. no.	$k_2 \times 10^3$, $\mathrm{l\,mol^{-1}\,s^{-1}}$	$\Delta H^{\neq}$, $\mathrm{kcal\,mol^{-1}}$	$-\Delta S^{\neq}$, $\mathrm{kcal\,mol^{-1}\,K^{-1}}$
Ia	0.6	10.9	36.6
Ib	1.8	10.9	34.7
Ic	11.1	9.7	34.6
Id	14.1	6.9	44.1
Ie	13.3	6.1	46.6
If	13.0	4.2	53.1
IIa	13.4	2.9	56.8
IIb	18.1	8.3	38.6
IIc	30.0	4.3	50.9
IId	23.2	5.9	46.2
IIe	28.8	5.0	48.8
IIf	25.0	5.7	46.9
IIg	23.2	4.5	50.9
IIIa	11.1	3.2	56.8
IIIb	6.0	3.6	56.7
IIc	14.1	2.3	59.2
IIIc	12.0	1.1	63.8
IIId	10.9	0.6	65.6

The close-to-one reaction order in dialkyl hydrogen phosphite is also preserved when a specially created fixed concentration of water is used. As the fixed concentration of water is increased, the reaction order in phosphite slightly decreases. As the concentration of diisopropyl hydrogen phosphite decreases, the second-order rate constant decreases ($k_{\mathrm{II}} = k_{\mathrm{app}}/[\mathrm{DAP}]$), which points to a more intricate reaction pathway.

At [H$_2$O] 0.257 M

$$\log k_{\mathrm{app}} = (1.021 \pm 0.104)\log [\mathrm{DAP}] - 2.455,$$
$$n\ 4,\ r\ 0.9897,\ S_0\ 0.062,$$

At [H$_2$O] 0.5 M

$$\log k_{\mathrm{app}} = (0.754 \pm 0.045)\log [\mathrm{DAP}] - 1.980,$$
$$n\ 5,\ r\ 0.9947,\ S_0\ 0.017.$$

The order in water of the reaction of diisoropyl hydrogen phosphite with benzalaniline **IIc** in the temperature range 298–323K, too, is close to one.

At 298 K

$$\log k_{\mathrm{app}} = (1.050 \pm 0.045)\log [\mathrm{H_2O}] - 2.769,$$
$$n\ 5,\ r\ 0.9955,\ S_0\ 0.067,$$

At 308 K

$$\log k_{\mathrm{app}} = (0.924 \pm 0.023)\log [\mathrm{H_2O}] - 2.813,$$
$$n\ 5,\ r\ 0.9991,\ S_0\ 0.028,$$

At 323 K

$$\log k_{\mathrm{app}} = (0.908 \pm 0.035)\log [\mathrm{H_2O}] - 2.383,$$
$$n\ 4,\ r\ 0.9986,\ S_0\ 0.032.$$

The order in water of the reaction with dimethyl hydrogen phosphite is much lower than one. At the concentration of dimethyl hydrogen phosphite of 0.363 M, $\log k_{\mathrm{app}} = (0.357 \pm 0.038)\log [\mathrm{H_2O}] - 3.767$ ($n = 5$, $r = 0.9834$, S_0 0.021), which is evidently connected with the lower hydrolytic stability of dimethyl hydrogen phosphite. As a result, just at the beginning of the kinetic experiment the reaction mixture contains sufficient amount of acidic hydrolysis products, and the contribution of water in this reaction decreases.

To assess the effect of electronic factors on the reactivity of imines in the reaction in question, we have studied the kinetics of the reaction of *N*-isopropylarylideneamines (series I) with dimethyl hydrogen phosphite, and of *N*-phenylarylidenamines (series II) and *N*-arylbenzylidenamines (series III) with diisopropyl hydrogen phosphite in 2-propanol, varying the nature of substituents in the aromatic fragments bound with both the carbon and nitrogen atoms of the C=N bond. The rate constants of the above reactions were found to be temperature-dependent in the range 298–338K (Table 3).

The high-quality linear correlations between activation parameters ($\Delta H^{\neq}$ and $\Delta S^{\neq}$) suggest that the reactions belong to the corresponding common reaction series.

*Reaction of azomethines **Ia**–**If** with dimethyl hydrogen phosphite*

$$\Delta H^{\neq} = (359.8 \pm 42.5)\Delta S^{\neq} + 23084.6\ \mathrm{kcal\,mol^{-1}},$$
$$n\ 6,\ r\ 0.9732,\ S_0\ 717.8,$$

*Reaction of azomethines **IIa**–**IIg** with diisopropyl hydrogen phosphite*

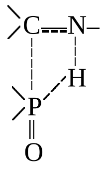
$$\Delta H^{\neq} = (301.1 \pm 10.6)\Delta S^{\neq} + 19819.4\ \mathrm{kcal\,mol^{-1}},$$
$$n\ 7,\ r\ 0.9969,\ S_0\ 144.9,$$

*Reaction of azomethines **IIIa**–**IIIf** with diisopropyl hydrogen phosphite*

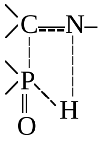
$$\Delta H^{\neq} = (322.6 \pm 23.4)\Delta S^{\neq} + 21604.5\ \mathrm{kcal\,mol^{-1}},$$
$$n\ 5,\ r\ 0.9922,\ S_0\ 168.3.$$

At the same time, the close isokinetic temperatures for the reaction series with azomethines **IIa**–**IIg** and **IIIa**–**IIIf** show that these series belong to the same type of hydrophosphorylation processes having similar mechanisms. The large (in absolute value) negative activation entropies (Table 3) show that the reaction proceeds through a highly organized transition state.

The presence of a well-defined inflection points on the Hammett correlation dependences (Figs. 2–4) where donor and acceptor substituents form separate branches points to lability of the four-center activation complex for which both the nucleophilic (Ad_N addition) and electrophilic (Ad_E mechanism) contributions in the reacting components are important. Therewith, the fact that acceptor substituents increase the reactivity of series I azomethines suggests prevailing contribution of the nucleophilicity of the phosphite into concerted addition with an asymmetric four-center transition state (preference for the Ad_N type). In the other two reaction series, both electron-acceptor and electron-donor substituents in the imine component decelerate the reaction, thus providing further evidence for the rigidity of the activated complex that easily transforms from one type to the other.



Ad_E



AD_N

The same conclusion we drew previously in studying the kinetics of the addition of acid phosphites to Schiff bases, involving no acid catalysts [3]. Note that such a geometric flexibility of activated complexes is characteristic of labile cyclic transition states of concerted reactions. This fact has repeatedly been mentioned in the literature, for example, in relation to addition of hydroxy- and aminophosphonates to phenyl isocyanate [9].

The moderate quality of the correlations presented in Figs. 2–4 can be explained by the complex character of the process, in particular, by the formation of a labile cyclic transition state and the closeness of the isokinetic temperature of the reaction to the experimental temperature.

For the noncatalyzed process, two above-mentioned mechanisms have been discussed in the literature [3]. The first mechanism was offered on the basis of a kinetic study of this reaction, and it involves protonation of the azomethine nitrogen atom by the hydroxyphosphite form with a trivalent phosphorus atom and subsequent attack by the dialkyl phosphite anion [10]:

$$XCH{=}NY + HOP(RO)_2 \longrightarrow \{[XCH{=}\overset{+}{N}HY](RO)_2PO^- \longleftrightarrow [XC^+{-}NH{-}Y][(RO)_2PO^-\} \longrightarrow XCH[P(O)(OR)_2]NHY.$$

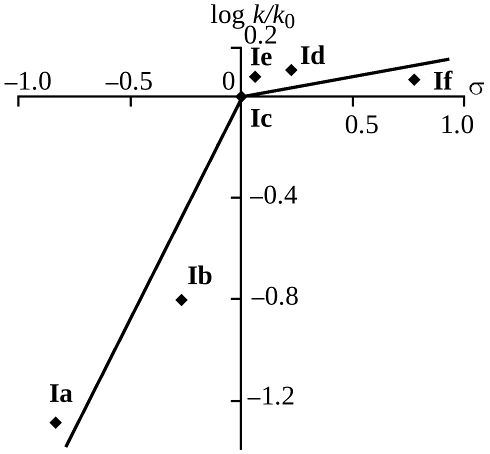


Fig. 2. Dependence of log k/k_0 on Hammett σ constants for the reaction of dimethyl hydrogen phosphite with *N*-isopropylarylidenamines **Ia–If**.

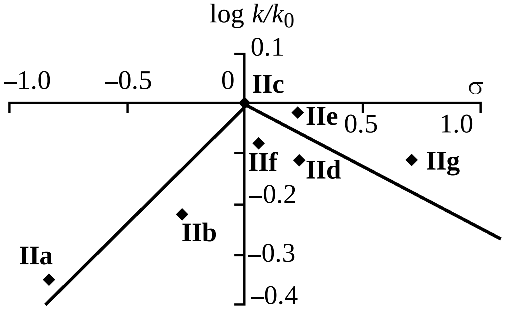


Fig. 3. Dependence of log k/k_0 on Hammett σ constants for the reaction of diisopropyl hydrogen phosphite with *N*-phenylbenzylideneamines **IIa–IIg**.

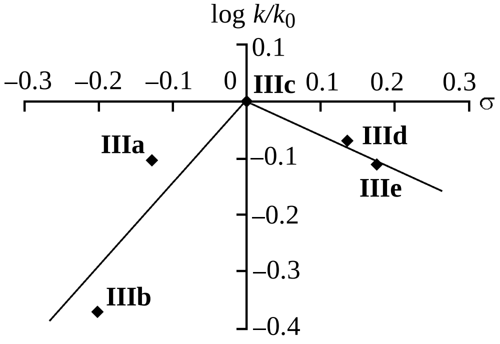


Fig. 4. Dependence of log k/k_0 on Hammett σ constants for the reaction of diisopropyl hydrogen phosphite with *N*-phenylbenzylideneamines **IIIa–IIIe**.

The disadvantage of this mechanism is that it postulates as a reactive species the σ^3-P tautomeric form of dialkyl hydrogen phosphite. This form is often invoked in speculations on the mechanisms of

Table 4. Spectral characteristics of solutions of $(RO)_2PHO$ in the presence of triethylamine a day after their preparation

Exp. no.	R	Dialkyl hydrogen phosphite	Others compounds	Solvent
1	*i*-Pr	5.85 (683.0)	–	Acetonitrile
2	Me	13.09 (699.7)	–	DMSO
3	Me	9.71 (689.3)[a]	$[Et_3NCH_3]^+[(CH_3O)P(H)O_2]^-$[b] 3.89 (605.6) $[Et_3NCH_3]^+_2[HPO_3]^{2-}$[c] 3.39 (595.5)	Triethylamine

[a] 67%. [b] 15%. [c] 18%.

reactions of dialkyl hydrogen phosphites with aliphatic radicals, but no real evidence for its existence has not yet been reported. It is accepted that in this case the equilibrium is almost completely shifted to the isomer with a four-coordinate phosphorus atom [11]. In this connection it is pertinent to mention the recent information on the existence of the hydroxy form of dialkyl(aryl, hetaryl)phosphinous acids with strongly electron-acceptor substituents at the three-coordinate phosphorus atom [12].

The inductive period might be considered to be required for forming and accumulating the three-coordinate form of dialkyl hydrogen phosphite after its purification and putting in solution. But if this were so, this stage would most likely by rate-limiting in the proposed reaction mechanisms.

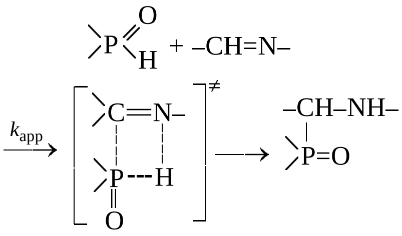
There have been numerous attempts to detect the three-coordinate form of dialkyl hydrogen phosphites. In our turn, we tried to detect this form by ^{31}P NMR spectroscopy. To this end, we measured the spectra of dimethyl and diisopropyl hydrogen phosphites in various solvents [1], but no additional signals characteristic of three-coordinate phosphorus atom were found. To initiate formation of the σ^3-P form and stabilize it, we added to solutions of phosphites in acetonitrile and DMSO triethylamine in an amount comparable with the amount of phosphite. However, in this case, too, no additional signals were detected (Table 4, exp. nos. 1 and 2).

No traces of hydroxyphosphites were found in the spectrum of dimethyl hydrogen phosphite in triethylamine solution (Table 4, exp. no. 3). Along with the phosphite signals, the ^{31}P NMR spectrum displays two new groups of signals assignable to phosphite demethylation products, that is triethyl(methyl)ammonium salts of hydrogen phosphites with preserved P–H bond.

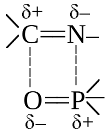
$$(CH_3O)_2PHO + Et_3N$$
$$\rightarrow [Et_3NCH_3]^+[(CH_3O)P(H)O_2]^- + [Et_3NCH_3]^+_2[HPO_3]^-.$$

Based on these results we suggest that the addition reaction invove initial rupture of the P–H bond rather than P(IV)→P(III) isomerization of hydrogen phosphites.

The second mechanism substantiated by kinetic [4, 13] and preparative [14] data suggests formation of a four-membered cyclic transition state.



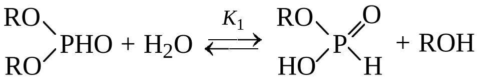
Since dialkyl hydrogen phosphites are not strong proton donors [15, 16], coordination of the P–H bond with C=N can be assumed with a slight reserve. The pK_a of diethyl phosphite, estimated by the transmetalation method in THF and DMSO, is 20.8–22 [17, 18]. Therefore, in our case we consider more probable a complex like **V** formed by dipole–dipole interactions.



V

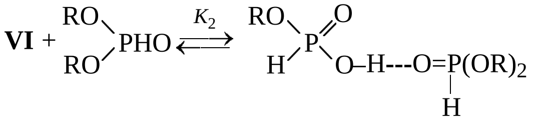
Evidence for this suggestion is provided by the hyprosochromic shift of the absorption band of azomethine after addition of phosphoryl compound in its solution we observed previously [4].

Hence, our results show that the Pudovik reaction in the azomethine series in the absence of a specially added catalyst requires initial hydrolysis of dialkyl hydrogen phosphite to occur.



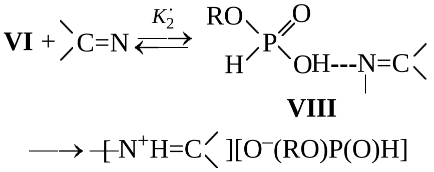
VI

Monoalkyl phosphite **VI** formed by hydrolysis is a fairly strong acid and can react with dialkyl hydrogen phosphite to form a stable adduct **VII** analogous to that described in [19]. As a result, nucleophilic activation of the hydrophosphoryl group takes place, which loosens the P–H bond.



VII

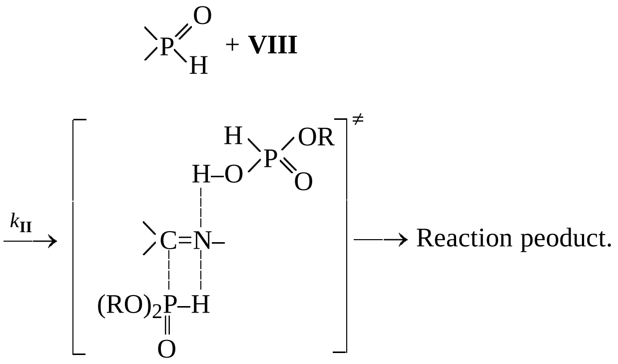
On the other hand, since imine is a strong base and monoalkylphosphorous acid is a pronounced proton donor, the former can also be stabilized in complex **VIII** that can competitively with the *Ad* process convert into salt **IX** whose formation we reported previously [1].



VIII

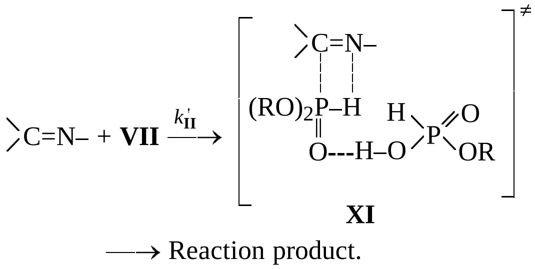
IX

The subsequent formation of aminophosphonate can proceed by two alternative pathways. The first involves reaction of imine H-complex **VIII** with hydrophosphoryl compounds to form a trimolecular activated complex **X**.



X

The second pathway involves reaction of azomethine with dialkyl hydrogen phosphite H-complex **VII**. In this case, the role of the basicity center in trimolecular complex **XI** is played by the phosphoryl oxygen atom of dialkyl hydrogen phosphite; the acidic monoalkyl phosphite exerts electrophilic assistance by hydrogen bonding with the phosphoryl group.



XI

Such a dualism in the behavior of dialkyl hydrogen phosphites (either donor or acceptor of protons) we previously observed in the Kabachnik–Fields reaction [2].

The two pathways of the Pudovik reaction are quite difficult to decide between, since they are kinetically indistinguishable. It should only be mentioned that, as previously observed [1], salt **IX** easily formed in the reaction of azomethine **IIc** with phosphorous acid does not react with dialkyl hydrogen phosphites.

Nevertheless, we attempted to evaluate the relative probability of formation of prereaction and activated complexes by means of quantum-chemical calculations by the semiempirical PM3 method with full geometry optimization. Dimethyl hydrogen phosphite and benzalaniline **IIc** were chosen as model compounds. For acid catalysts we chose methyl dihydrogen phosphite and, for comparison, hydrogen chloride that is considered [4] to be present in dialkyl hydrogen phosphites not specially purified with metallic sodium. The thermodynamic stability of the complexes was measured by the difference between the total energies of formation of these structures and the sum of the total energies of formation of the starting molecules (ΔE). The calculation results are listed in Table 5.

It can be seen that the H-complexes of acid catalysts, HCl (Table 5, no. 1) and methyl dihydrogen phosphite (no. 2), are 5–6 kcal mol^{-1} energetically more favorable than the corresponding complexes of imine (nos. 3, 4). This result implies preferential formation of the former in the acid–base equilibria attendant in the hydrophosphorylation reaction. Therewith, as would be expected, the complexes with HCl, a stronger acid, are 6–7 kcal mol^{-1} more favorable than analogous complexes with methyl dihydrogen phosphite. This is clearly reflected in the lengths of the corresponding hydrogen bonds. Thus, the $P=O\cdots H$ bond length in the complex of dimethyl hydrogen phosphite with HCl (Table 5, no. 1) is 0.95 Å, whereas in the analogous complex with monomethyl phosphite **VII** it is almost double as long (1.80 Å).

The possible formation of sufficiently strong complexes of dialkyl hydrogen phosphites with acidic

Table 5. Relative thermodynamic stability (ΔE, kcal mol^{-1}) of prereaction (PC) and activated (AC) complexes in the reaction of dimethyl hydrogen phosphite with benzalaniline in the presence of HCl and methyl dihydrogen phosphite, calculated by the PM3 method

Run no.	Complexes	ΔE, kcal mol^{-1}
	Prereaction complexes	
1	$(MeO)_2PHO$---HCl	–14.87
2	$(MeO)_2PHO$---HOPH(O)(OMe) (**VII**)	–7.75
3	Ph–CH=N–Ph---HCl	–8.66
4	Ph–CH=N–Ph---HOPH(O)(OMe) (**VIII**)	–2.57
	Activated complexes	
5	$(MeO)_2PHO$---HCl + Ph–CH=N–Ph	–1.31
6	$(MeO)_2PHO$ + Ph–CH=N–Ph---HCl	2.95
7	$(MeO)_2PHO$---HOPH(O)(OMe) + Ph–CH=N–Ph (**XI**)	1.75
8	$(MeO)_2PHO$ + Ph–CH=N–Ph---HOPH(O)(OMe) (**X**)	6.06

reagents, that follows from the calculations, is nicely consistent with experimental data according to which dialkyl hydrogen phosphites cannot be purified from acidic admixtures even by multiple rectification. Pure dialkyl hydrogen phosphites can only be obtained by distillation in the presence of metallic sodium. Such an agreement between the calculation and experimental results point to their correctness and reliability of their implied conclusions.

On the whole the calculation results point to a significant thermodynamic preference for prereaction complexes in which the acidic reagent activates the phosphoryl group of dialkyl hydrogen phosphite. Analogous complexes of acids with imine are much less favorable.

The same tendency follows from the PM3 calculation results for possible structures of the activated complex in the reaction studied. Cyclic four-membered transition states in which the acidic reagent activates the phosphoryl group of dialkyl hydrogen phosphite (Table 5, nos. 5, 7) is favored by about 4 kcal mol^{-1} over the alternative structures with activation by hydrogen bonding with the imine nitrogen atom (Table 5, nos. 6, 8). Therewith, the complexes with HCl are always about 3 kcal mol^{-1} more favorable that analogous complexes with the less acidic methyl dihydrogen phosphite. Moreover, the calculations show that the four-membered concerted transition state is much more favorable than acyclic activated complex, which agrees well with kinetic data, specifically with the high negative value of the activation entropy (–40 to –60 cal mol^{-1} K^{-1}).

The model activated complex **XI** has a much elongated P–H bond, which is consistent with a cyclic four-membered transition state where the imine nitrogen atom plays the role of internal base that facilitates loosening of the P–H bond of dialkyl hydrogen phosphite.

Hence, the quantum-chemical results provide evidence for the conclusion that acidic reagents play a significant role in formation of prereaction complexes and stabilization of the transition state of the reaction. Therewith, the resulting data point to preferential coordination of acidic reagents by the phosphoryl group of dialkyl hydrogen phosphite rather than by the imine nitrogen atom and thus make it possible to decide between the two suggested kinetically indistinguishable reaction mechanisms.

EXPERIMENTAL

The IR spectra were obtained on a Specord M-80 spectrometer for suspensions in mineral oil. The ^{31}P NMR spectra were recorded on a Varian Unity-300 NMR spectrometer (121 MHz) against external 85% phosphoric acid. The synthetic procedures and constants for *N*-isopropylbenzylideneamines **Ia**–**If** are given in [3].

***N*-Phenylarylideneamines II**. A mixture of 0.047 mol of 4-substituted benzaldehyde, 0.047 mol of aniline, and 50 ml of benzene was heated under reflux with a Dean–Stark trap. The solvent was then removed, and the product was crystallized from 2-propanol. The constants and yields of azomethines **IIa**–**IIg** are listed in Table 1. The purity of the products was controlled by IR spectroscopy and TLC on Silufol UV-254 plates (eluent hexane–acetone, 1 : 1; development in iodine vapor).

***N*-Arylbenzylideneamines III.**. A mixture of 0.047 mol of 4-substituted aniline, 0.047 mol of benzaldehyde, and 50 ml of benzene heated under reflux with a Dean–Stark trap. The solvent was then removed, and the products were crystallized from 2-propanol. The constants and yields of azomethines **IIIa**–**IIIf** are listed in Table 1. The purity of the products was controlled by IR spectroscopy and TLC.

Dimethyl and diisopropyl hydrogen phosphites were fractionated 4–5 times in a vacuum under dry argon. Before the third distillation, metallic sodium was added to remove acidic admixtures. 2-Propanol, DMSO, and dioxane for kinetic measurements were purified by the procedure in [20], and toluene and acetonitrile, by the procedure in [21].

Kinetic studies were carried out by spectroscopy on SF-46 and SF-26 spectrophotometers in temperature-controlled cells in the temperature range 293–358 K. Reaction progress was controlled by the decrease of absorbance (or increase of transmittance) of the reaction mixture in the range 280–350 nm at a wavelength corresponding to the maximum change of the optical density of imine and the minimum absorption of reaction products in the course of the reaction.

The kinetic experiments were carried out under pseudofirst-order conditions in azomethines. The concentrations of azomethines were 10^{-5}–10^{-4} M at large excesses of dialkyl hydrogen phosphite (10^{-1}–1 M) and water (10^{-1}–1 M).

Solutions were prepared directly in the working cell by two procedures. According to the first procedure, solutions of purified amines and necessary additives of known concentrations in corresponding solvents were placed in the cell, after which 0.1 ml of individual dialkyl hydrogen phosphite was added (procedure A). According to the second procedure, a necessary amount of a solution of a freshly purified dialkyl hydrogen phosphite in the same solvent (method B) was added last. The resulting solution was stirred and placed in the cell. From this moment time reading and photometry were begun.

The pseudofirst-order rate constants were calculated from the linear dependence of $\ln[1/(D - D_\infty)]$ on t, where D is the current optical density, D_∞ is the optical density measured after the spectral picture no longer changed (usually after a day), and t is the current time (s).

The activation parameters were calculated from the rate constants measured at no less than four different temperatures [21]. The calculated activation parameters are listed in Table 3.

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