*Russian Journal of General Chemistry, Vol. 72, No. 7, 2002, pp. 1067–1070. Translated from Zhurnal Obshchei Khimii, Vol. 72, No. 7, 2002, pp. 1141–1144.*
*Original Russian Text Copyright © 2002 by Sobanov, Zolotukhin, Galkin, Cherkasov, Pudovik.*

# Kinetics and Mechanism of the Pudovik Reaction in the Azomethine Series: I. Addition of Dimethyl Hydrogen Phosphite to *N*-Isopropylbenzalimines

**A. A. Sobanov, A. V. Zolotukhin, V. I. Galkin, R. A. Cherkasov, and A. N. Pudovik**

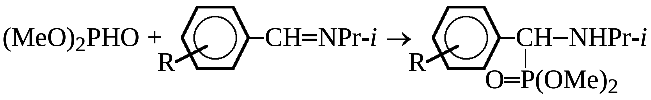
*Kazan State University, Kazan, Tatarstan, Russia*

Received June 28, 1999

**Abstract**—For a series of phenyl-substituted *N*-isopropylbenzalimines, the effect of substituent on their capability to add dimethyl hydrogen phosphite was studied qualitatively in the condensed phase (DTA) and quantitatively (with determination of the kinetic and activation parameters) in 2-propanol solutions with spectrophotometric monitoring of the reaction. A reaction mechanism was proposed, involving formation of a highly organized four-membered transition state.

One of the main routes to α-amino phosphonates is the Pudovik reaction consisting in addition of dialkyl hydrogen phosphites to compounds containing a C=N bond [1]. Despite numerous publications on the synthetic aspect of the Pudovik reaction and applications of its products, kinetic data on this reaction are few and sometimes contradictory. The first attempt to quantitatively study this reaction, catalyzed with a sodium alcoholate, was made by Pudovik and Korchemkina [2]. They suggested a chain mechanism involving formation of the dialkyl phosphite anion followed by its attack of the electrophilic carbon atom of the C=N bond. This mechanism was subsequently supported in [3, 4]. Kinetic studies of the reactions of azomethines with dialkyl hydrogen phosphites in the presence of HCl [5, 6] led to a conclusion that the acid catalyst not only enhances the electrophilicity of the azomethine carbon atom owing to protonation of the nitrogen atom, but also increases the relative content of the P(III) form of dialkyl hydrogen phosphonate, responsible, as believed in [5, 6], for the addition. However, the kinetic method chosen in [5, 6], namely, alkali titration of unchanged dialkyl hydrogen phosphite, seems to be unsuitable for obtaining reliable quantitative characteristics. A $^1$H NMR study of the kinetics of α-amino phosphonate formation in the absence of catalysts [7–9] showed that this is a second-order reaction. Introduction of electron-withdrawing substituents into the benzene ring of both aldehyde and amine fragments decelerates the reaction. Based on this result, an electrophilic mechanism was proposed, involving initial protonation of the imine nitrogen atom with the P(III) form of dialkyl hydrogen phosphite. On the contrary, our spectrophotometric study of the kinetics of addition of dialkyl hydrogen phosphites to 1-cyclohexylimino-2-butene in the absence of catalysts led to a conclusion that the reaction is nucleophilic [10]. The reaction is preceded by fast formation of a complex (presumably from dialkyl hydrogen phosphite and imine), as suggested by a considerable bathochromic shift of the imine absorption maximum. Subsequent transformation of the complex into the reaction product is a monomolecular process. Later we found [11] that the complex is formed with the participation of hydrogen chloride present in the initial dialkyl hydrogen phosphite as impurity, despite repeated distillation. Therefore, in the subsequent experiments dialkyl hydrogen phosphites were purified by adding a small amount of sodium metal prior to distillation. On mixing the reactants, solvation complexes are formed, probably via donor–acceptor interactions of the phosphoryl group rather than H bonding. The complex formation is reflected in the reaction kinetics.

The goal of this study was to elucidate the reaction mechanism, with the reaction of dimethyl hydrogen phosphite with a series of substituted *N*-isopropylbenzalimines (see below) as example.



**Ia–If** **IIa–IIf**

R = 4-$Me_2N$ (**a**), 4-MeO (**b**), H (**c**), 4-Cl (**d**), 4-F (**e**), 3-$NO_2$ (**f**).

1070-3632/02/7207-1067 $27.00 © 2002 MAIK “Nauka/Interperiodica”

**Table 1.** Yields, boiling points, refractive indices, and relative densities of *N*-isopropylbenzalimines **Ia**–**If** and amino phosphonates **IIa**–**IIf**

| Comp. no. | Yield, % | bp, °C (*p*, mm Hg), or mp, °C | $n_D^{20}$ | $d_4^{20}$ |
|---|---|---|---|---|
| **Ia** | 79 | 153 (8) | 1.5940 | 0.9619 |
| **Ib** | 83 | 135 (16) | 1.5440 | 0.9818 |
| **Ic** | 81 | 91 (18) | 1.5262 | 0.9241 |
| **Id** | 80 | 110 (12) | 1.5442 | 1.0485 |
| **Ie** | 76 | 88 (15) | 1.5070 | 0.9981 |
| **If** | 70 | 42 | – | – |
| **IIa** | 71 | 73 | – | – |
| **IIb** | 92 | 56 | – | – |
| **IIc** | 44 | 72 | – | – |
| **IId** | 67 | 58 | – | – |
| **IIe** | 65 | 49 | – | – |
| **IIf** | 89 | 51 | – | – |

**Table 2.** Rate constants and activation parameters of the reaction of *N*-isopropylbenzalimines **Ia**–**If** with dimethyl hydrogen phosphite in 2-propanol

| Comp. no | $k \times 10^2$, l mol$^{-1}$ s$^{-1}$ | | | | $\Delta H^{\neq}$, kJ mol$^{-1}$ | $-\Delta S^{\neq}$, J mol$^{-1}$ K$^{-1}$ |
|---|---|---|---|---|---|---|
| | 25°C | 35°C | 45°C | 55°C | | |
| **Ia** | 0.058 | 0.113 | 0.212 | 0.342 | 45.6 | 153.1 |
| **Ib** | 0.176 | 0.308 | 0.584 | 1.027 | 45.2 | 145.2 |
| **Ic** | 1.110 | 2.161 | 3.672 | 5.491 | 40.7 | 144.8 |
| **Id** | 1.410 | 2.001 | 3.052 | 4.432 | 28.7 | 184.5 |
| **Ie** | 1.330 | 2.004 | 2.853 | 3.746 | 25.5 | 195.0 |
| **If** | 1.301 | 1.410 | 2.128 | 2.608 | 17.6 | 222.2 |

*N*-Isopropylbenzalimines **I** were prepared by condensation of the corresponding substituted benzaldehydes with isopropylamine. The composition and structure of the imines were confirmed by elemental analysis and by IR, NMR, and UV spectroscopy. The IR spectra of these compounds contain bands at about 1640 cm$^{-1}$, characteristic of the C=N bond. The constants of the imines are listed in Table 1.

The imines react with dimethyl hydrogen phosphite on heating in the absence of catalyst to give the corresponding aminophosphonates **II**. The DTA curves of equimolar mixtures of the reactants exhibit similar exoeffects (their maxima are given below) assignable to addition of dimethyl hydrogen phosphite across the C=N bond:

| Comp. no | **Ia** | **Ib** | **Ic** | **Id** | **Ie** | **If** |
|---|---|---|---|---|---|---|
| $T_{max}$, °C | 80 | 89 | 93 | 93 | 95 | 109 |

By workup of the contents of Stepanov vessels after passing the exothermic maximum, we isolated the corresponding amino phosphonates **II**; their yields and constants are listed in Table 1.

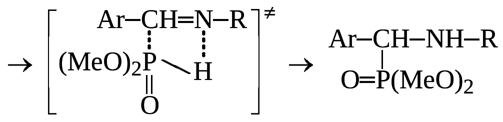
The structures of products **II** were confirmed by NMR and IR spectroscopy. Their IR spectra contain bands at 3270 [ν(N–H)], 1240 [ν(P=O)], and 1030–1060 [ν(POC)] cm$^{-1}$. The phosphorus chemical shift in the $^{31}$P NMR spectra is about 25 ppm, which is typical of phosphonates.

The trend in variation of the temperatures of the endoeffects ($T_{max}$) for the reactions of imines **I** with dimethyl hydrogen phosphite clearly shows that the reactivity tends to decrease on introducing electron-withdrawing substituents into the aromatic ring of the imines, which, at first glance, suggests the electrophilic mechanism of the reaction involving the initial proton transfer from dialkyl hydrogen phosphite to the nitrogen atom. This result is nicely consistent with the kinetic data obtained by $^1$H NMR [7–9]. However, it is not quite correct to make definite conclusions on the reaction mechanism from such data, because in the absence of a solvent or at high concentrations of the reactants the polarity of the medium and other factors affecting the reaction rate appreciably change in going from one reaction to another.

Therefore, a quantitative study of this reaction was performed in 2-propanol in the absence of catalyst. The reaction was monitored spectrophotometrically at 298–328 K. We found that the reaction has the total second order (first order with respect to each of the reactants). From the temperature dependence of the rate constants, we determined the activation parameters (Table 2). The kinetic data show that, in going from electron-donating to electron-withdrawing substituents in the aromatic ring of imines **I**, the rate constant increases by an order of magnitude, which suggests the nucleophilic mechanism of the addition.

Considerable negative activation entropies, similar to those obtained for the reaction with 1-cyclohexylimino-2-butene [11], suggest that the reaction occurs via a highly organized four-membered transition state:

$$(MeO)_2PHO + Ar{-}CH{=}N{-}R$$



In this transition state, the hydrogen atom acting as an internal base loosens the P–H bond and assists the nucleophilic attack of the imine carbon atom by the phosphorus atom.

Analysis of the compensation correlations between the activation enthalpies, $\Delta H^{\neq}$, and entropies, $\Delta S^{\neq}$, shows that the experimental points form two different straight lines, one of which corresponds to isopropylbenzalamine and imines containing electron-withdrawing substituents, and the other, to imines with electron-donating substituents: *p*-methoxy and *p*-dimethylamino groups. This fact suggests that the mechanisms of the reactions with the substrates containing donor and acceptor substituents in the aromatic ring have certain specific features. We believe that these features are related to certain geometric distortions of the activated complex (within the framework of the common concerted mechanism with a four-membered transition state) toward larger contribution of the electrophilic assistance in the presence of donor substituents.

It should be noted that such geometric distortions of the activated complex are typical of labile cyclic structures; they were noted in numerous papers, e.g., for addition of hydroxy and amino phosphonates to phenyl isocyanate [12].

In the subsequent paper, we will analyze in detail our kinetic data and consider on the quantitative level the reactivity of *N*-arylazomethines.

Thus, the whole set of the results obtained unambiguously indicates that the reaction, on the whole, occurs by the nucleophilic (with respect to the organophosphorus reagent) mechanism via a four-membered labile cyclic transition state whose geometry is very sensitive to the electronic effects of substituents.

A certain inconsistency of the kinetic data with the DTA data and data of [7–9] may be largely due to appreciably different reaction media.

## EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 spectrophotometer (thin films or mulls in mineral oil), and the $^{31}$P NMR spectra, on an RYa-2303 spectrometer (8 MHz, external reference 85% $H_3PO_4$).

The TLC analysis was performed on Silufol UV-254 plates, eluent hexane–acetone, 1 : 1. The chromatograms were developed by treatment with iodine vapor.

The kinetics of the reactions of *N*-isopropylbenzalimines with dimethyl hydrogen phosphite were studied spectrophotometrically with an SF-46 spectrophotometer in temperature-controlled cells at 298–328 K. Into a cell containing 3 ml of a 0.1 M solution of dimethyl hydrogen phosphite in 2-propanol, kept at the required temperature, we added 1–2 drops of a $(2–3) \times 10^{-2}$ M solution of appropriate imine in 2-propanol. After mixing, the spectrophotometric monitoring was started. The pseudo-first-order rate constants were calculated from the linear dependences of $\ln (D - D_\infty)$ on time. We monitored a decrease in the absorption of imines at the following wavelengths (nm): **Ia**, 320; **Ib**, 300; **Ic**, 278; **Id**, 292; **Ie**, 288; and **If**, 296. The optical densities $D_\infty$ were measured after the reaction was *a fortiori* complete (1 day).

2-Propanol was pretreated as described in [13]. Dimethyl hydrogen phosphite was fractionated four times in a flow of dry argon; the third fractionation was performed with an addition of sodium metal to remove HCl [11].

***N*-Isopropylbenzalimines I.** A mixture of 0.042 mol of isopropylamine and 0.04 mol of substituted benzaldehyde was kept at room temperature for 2 days and then fractionated several times in a vacuum. The constants of the products are listed in Table 1. *N*-Isopropyl-*m*-nitrobenzalimine **If** was recrystallized two times from 2-propanol. The purity of the products was checked by IR spectroscopy and TLC.

**Thermographic studies** were performed in sealed Stepanov vessels on a custom-made installation using a two-coordinate potentiometer and a linear heating sensor. Mineral oil was the reference; the temperature was monitored with a Chromel–Alumel thermocouple; the heating rate was 4–5 deg min$^{-1}$. A Stepanov vessel was charged with 0.55 mg of an equimolar mixture of dimethyl hydrogen phosphite and an imine. After passing the exoeffect maximum, the recording was stopped, and the mixture was recrystallized from hexane with an addition of diethyl ether. The constants and yields of the resulting amino phosphonates **II** are listed in Table 1.

## ACKNOWLEDGMENTS

The study was performed within the framework of the scientific and technical program “Russian Universities—Basic Research” and of joint program of CRDF and Ministry of Education of the Russian Federation “Basic Research and Higher Education” (grant REC-007).

## REFERENCES

1. Pudovik, A.N., *Dokl. Akad. Nauk SSSR*, 1952, vol. 83, no. 6, p. 865.
2. Pudovik, A.N. and Korchemkina, M.V., *Izv. Akad.*

*Nauk SSSR*, *Otd. Khim. Nauk*, 1952, no. 5, p. 940.

3. Henderson, W.M. and Shelver, W.H., *J. Pharm. Sci.*, 1969, vol. 58, no. 1, p. 106.
4. Horkins, L.V., Vicik, L.P., and Sheller, M.N., *J. Pharm. Sci.*, 1972, vol. 61, no. 3, p. 1114.
5. Kozlov, N.S., Pak, V.D., and Levashov, I.N., *Dokl. Akad. Nauk Bel. SSR*, 1970, vol. 14, no. 3, p. 243.
6. Levashov, I.N., Kozlov, N.S., and Pak, V.D., *Zh. Obshch. Khim.*, 1974, vol. 44, no. 5, p. 1112.
7. Pak, V.D., Kozlov, N.S., Balykova, I.A., and Gartman, G.A., *Zh. Obshch. Khim.*, 1976, vol. 46, no. 3, p. 497.
8. Gartman, G.A., Pak, V.D., and Kozlov, N.S., *Zh. Obshch. Khim.*, 1978, vol. 48, no. 7, p. 1504.
9. Gartman, G.A., Pak, V.D., and Kozlov, N.S., *Zh. Obshch. Khim.*, 1979, vol. 49, no. 10, p. 2375.
10. Galkin, V.I., Bakhtiyarova, I.V., Sobanov, A.A., Cherkasov, R.A., and Pudovik, A.N., *Dokl. Akad. Nauk SSSR*, 1985, vol. 285, no. 3, p. 634.
11. Ovchinnikov, V.V., Sobanov, A.A., and Pudovik, A.N., *Dokl. Ross. Akad. Nauk*, 1993, vol. 333, no. 1, p. 48.
12. Sayakhov, R.D., Galkin, V.I., Cherkasov, R.A., Mironov, A.V., and Kutyrev, G.A., *Zh. Obshch. Khim.*, 1993, vol. 63, no. 11, p. 2476.
13. Gordon, A.J. and Ford, R.A., *The Chemist's Companion. A Handbook of Practical Data, Techniques, and References*, New York: Wiley, 1972.