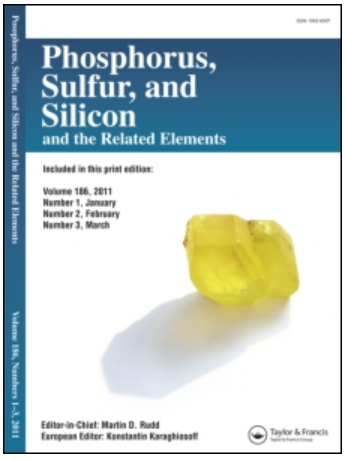

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ON THE NATURE OF THE NUCLEOPHILE IN THE MIXTURE OF PHOSPHITES AND AMINES

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ON THE NATURE OF THE NUCLEOPHILE IN THE MIXTURE OF PHOSPHITES AND AMINES

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It is now commonly accepted that in the presence of strong bases (like metal alcoholates) an equilibrium between phosphite and phosphonate forms of dialkyl phosphites exists and that the phosphite form is highly reactive in the reaction with carbonyl compounds. There is a controversy on the structure of the active form of the phosphite when the addition is catalyzed by amines. We have found that aliphatic amines and dialkyl phoshites form a complex which is a reactive species. Its stoichiometry depends on the nature of the solvent.

Keywords: Phosphite-phosphonate equilibrium; amine-dialkylphosphite complex

INTRODUCTION

The addition of dialkyl phosphite anions to aldehydes (known as the Pudovik reaction) is well known[1] and several mechanistic studies with catalytic amounts of sodium ethanolate have been carried out[2–5], ^{1}H-NMR and IR spectroscopic studies of the alkali metal salts of dialkyl phosphites suggest that the predominant form for the phosphite anion is trivalent (P-O-M) not (M-P=O).[6–7] The negative charge of the anion is associated with the phosphoryl oxygen, and the metal cation is strongly chelated by it. Several other bonding modes, however, have been proposed for the complexes containing anions of dialkyl phosphites.[8–9] Various aggregation states in various solvents were also postulated.[10]

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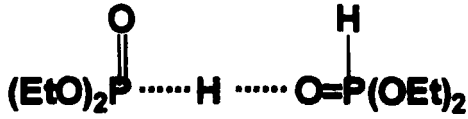
Springs and Haake studied the reaction of dimethyl phosphite with chloroacetone catalyzed by amine.[11] In their opinion, based on the reaction kinetics and determination of the reaction order, the dialkyl phosphite in the presence of triethylamine in methanolic solution behaves as the tautomeric form A (scheme 1).

SCHEME 1

In benzene, the form of the nucleophile is more complex, since aggregation effects may be important; for example, hydrogen-bonded complexes may participate in the reaction (scheme 2).

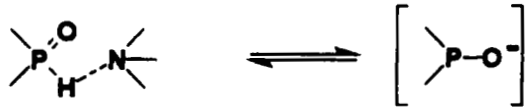


SCHEME 2

A polymeric form of dialkyl phoshite was also postulated.[11]

The structure of phosphonic acid and its esters (phosphonate vs. phosphite) was a rather controversial issue in early days of phosphorus chemistry. Nowadays, phosphonate structure B (scheme 1) is commonly accepted. Even though a true equilibrium between the phosphite and phosphonate apparently exists, as can be inferred from various chemical reactions and from kinetic studies[12–13], the amount of the former is believed to be below detection level of any spectroscopic method.[14] However some thermodynamic data made it possible to calculate the equilibrium constant for the tautomerization.[15–16] For diethyl phosphite the estimated pKa value is 13–14,6.[15–16]

Krutikov and Co.[17] have studied the equilibrium between amines and dialkyl phosphites. Based on the ^{31}P-NMR they have postulated the following equilibrium for aliphatic amines:



SCHEME 3

and another one for the aromatic amines:

SCHEME 4

This postulate is contrary to what has been stated in earlier works, that the concentration of the phosphite form is so small that it cannot be seen by any spectroscopic method. In addition, the statement that amine in the presence of phosphite can act as an acid seems to be rather strange.

RESULTS AND DISCUSSION

We decided to repeat the experiments done by Krutikov. We have measured the change of the phosphorus chemical shift for the dialkyl phosphite, in the presence of various amines, by means of titration experiments monitored by ^{31}P-NMR. Details of the method are given in the experimental part. We have found that the ^{31}P chemical shift difference for aromatic amines were in the range of the experimental error. The observed small changes should be attributed rather to the change of the nature of the solvent after addition of aromatic amine, than to the change of equilibrium in the amine-phosphite system. Similar chemical shifts were obtained when

benzene was added instead of amine. For the aliphatic amines the changes were significant though small. (Fig. 1)

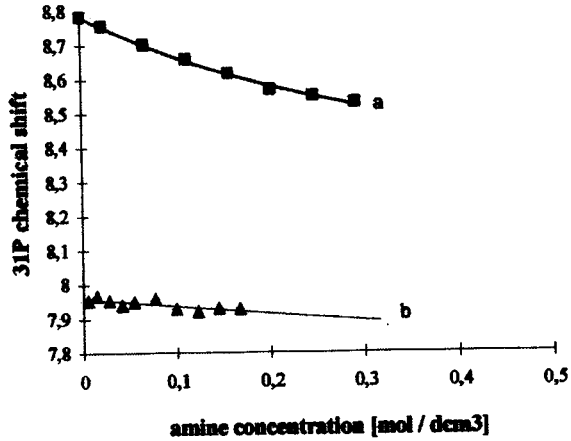


FIGURE 1 ^{31}P chemical shift changes for the dialkyl phosphite in the presence of n-butylamine a. in ethanol solution b. in methylene chloride solution

Observed chemical shift can be expressed as a function of the concentration of complexed and uncomplexed dialkyl phospite and their chemical shifts.

$$\delta_{obs} = \frac{\delta_P \cdot C_P + \delta_{NP} \cdot C_{NP}}{C_P + C_{NP}} \tag{1}$$

The unknown chemical shift for the complex and its concentration can be found by the regression analysis. The equilibrum constant can be then calculated:

$$K = \frac{C_P \cdot C_N}{C_{NP}} \tag{2}$$

Calculated values are given in table I.

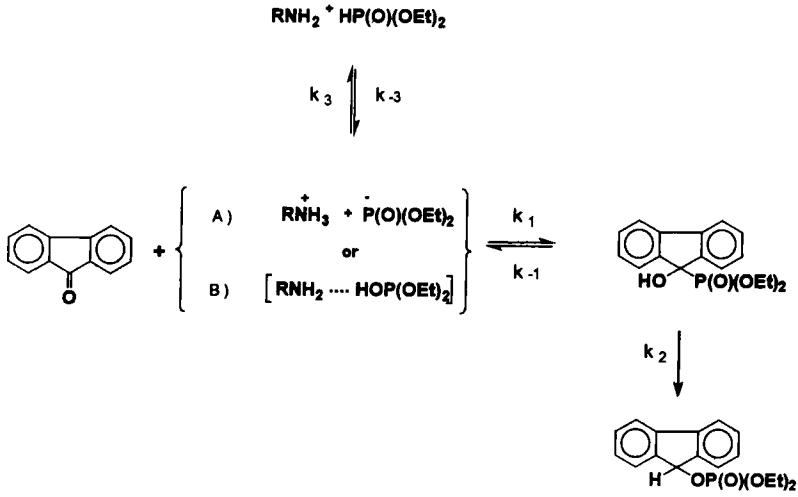
TABLE I Calculated equilibrium constants of amine-phosphite complex formation

	CH_2Cl_2	*EtOH*
K	0.28	2.29
δ_{NP}	7.96	8.79

The presence of the "active form" of phosphite has been measured independently by the kinetic studies with carbonyl compound. For this experiment we have chosen a fluorenone and its derivatives for a few reasons:

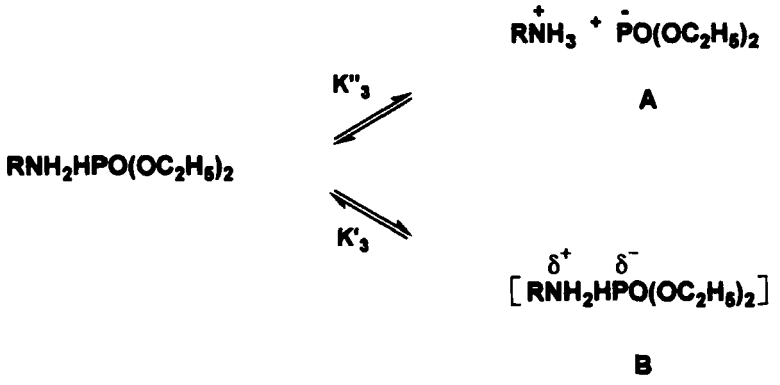
- these ketones in the applied conditions are completely unreactive towards amines,
- their concentration can be very easily monitored since these ketones are yellow and all the products are colorless,
- the reaction proceeds with reasonable rate,
- these ketones do not react with phosphite under the experimental condition in the absence of amine.[18–19]
- the reaction is first order with respect to the ketone.

Scheme (5) shows all possible reactions that can take place in that system.



SCHEME 5

Two different species can be taken into account as a phosphite "active form": free anion A or a complex B. The corresponding equilibrium constants are K''_3 or K'_3



SCHEME 6

If we mark the concentration of the reaction species as:

[F]-fluorenone, [N]- amine, [P]- diethyl phosphite, [NP]- amine-phosphite complex, [HOP]-hydroxyphosphonate, [HP]- phosphite anion, $[P^-] - (C_2H_5)_2PO^-$, $[NH^+]$- RNH_3^+, then:

$$K_3' = \frac{k_3'}{k_{-3}'} = \frac{[NP]}{[N]\cdot[P]} \quad (3) \qquad K_3'' = \frac{k_3'}{k_{-3}''} = \frac{[NH^+]\cdot[P^-]}{[N]\cdot[P]} \quad (4)$$

Equimolar concentration of the amine and phosphite was used, beeing at least 100 fold greater than the concentration of the ketone to provide the pseudo first order kinetics. Thus the total concentration of the amine, phosphite and all active species formed from them were assumed to be constant within the whole experiment.

Reaction with fluorenone can follow route A or B in scheme 5. For model B we can write:

$$\frac{d[F]}{dt} = -k_1\cdot[F]\cdot[NP] + k_{-1}\cdot[HOP] \quad (5)$$

Since the concentrations of the amine and phosphite was equal ([N]=[P]), the initial concentration of phosphite $[P_O]$=[P]+[NP], [NP] can be calculated as : (6)

$$[NP] = P_0 + \frac{1}{2K_3'}\left(1 - \sqrt{1 + 4P_0K_3'}\right) \quad (6)$$

Since amine and phosphite were used in a great excess, the concentration of NP remains constant throughout the whole experiment. The reverse reaction was found to be much slower than the forward one[18] and slower than the irreversible rearrangement of the hydroxyphosphonate to the phosphate. Therefore the equation (5) to (7) can be simplified to:

$$\frac{d[F]}{dt} = -k_1 \cdot [F] \cdot [NP] = -k_{1obs}[F] \tag{7}$$

where:

$$k_{1obs} = k_1 \cdot [NP] \tag{8}$$

For two concentrations values of amine and phosphite two different rate constant could be obtained

$$(k_{1obs})_1 = k_1 \cdot [NP]_1 \tag{9}$$

and

$$(k_{1obs})_2 = k_1 \cdot [NP]_2 \tag{10}$$

their ratio equals

$$\frac{(k_{1obs})_1}{(k_{1obs})_2} = \frac{[NP]_1}{[NP]_2} \tag{11}$$

and depends on the value of K_3. For different systems, for example various amines or solvents, rate constants will change according to the equations (12) or (13).

$$\frac{(k_{1obs})_1}{(k_{1obs})_2} = \lim_{K_3' \to 0} \frac{[NP]_1}{[NP]_2} = \left(\frac{[P_0]_1}{[P_0]_2}\right)^2 \tag{12}$$

$$\frac{(k_{1obs})_1}{(k_{1obs})_2} = \lim_{K_3' \to \infty} \frac{[NP]_1}{[NP]_2} = \frac{[P_0]_1}{[P_0]_2} \tag{13}$$

Thus if the concentration of amine and phosphite is lowered by a factor of 2, then the observed change in the ratio of the observed rate constants should lower by a factor 2–4. The exact value depends upon the K_3 equilibrium constant which was shown to be linearly dependent on the pK of the amine. For more basic amines the ratio is closer to 2, whereas for the less basic amines – closer to 4.

Similar consideration can be used for model A:

$$\frac{d[F]}{dt} = -k_1 \cdot [F] \cdot [NP] = -k_{1obs}[F] \tag{14}$$

where:

$$k_{1obs} = k_1 \cdot [P^-] \tag{15}$$

$$[P^-] = P_0 \frac{1}{\left(1 + \sqrt{\frac{1}{K_3''}}\right)} \tag{16}$$

In this case the ratio of the observed rate constants is equal to the ratio of the initial concentrations of the amine and phosphite despite the pK of the used amine.

$$\frac{(k_{1obs})_1}{(k_{1obs})_2} = \frac{([P^-])_1}{([P^-])_2} = \frac{([P_0])_1}{([P_0])_2} \tag{17}$$

Thus changing the concentration by the factor 2, the ratio should be exactly 2. In this way we can differentiate between the model A or B from scheme 5.

Table II presents data obtained in methanol.

TABLE II Observed reaction rates for hydroxyphosphonate formation in methanol. For details see text

amine	k_{obs} [sek^{-1}]×10^2	*pK of amine*	$(k_{obs})_1/(k_{obs})_2$
Morpholine	0.046±0.003	8.33	3.28
Tributylamine	0.057±0.0014	–	2.89
n-butylamine	1.064±0.025	10.77	2.47
n-propylamine	1.212±0.017	10.71	2.38
t-butylamine	1.672±0.036	10.83	2.33
benzylamine	0.332±0.0035	9.33	2.21
isopropylamine	1.457±0.011	–	2.20
triethylamine	0.295±0.0012	11.01	2.17
diisopropylamine	0.939±0.0057	10.96	1.95
diethylamine	0.841±0.0013	10.49	1.71
piperidine	0.778±0.010	11.12	1.71
dibutylamine	0.676±0.0010	–	1.64

The values of $(k_{obs})_1/(k_{obs})_2$ differ from 2 by more than the statistical experimental error, except for secondary amines. They are within the range 2–4, so we believe that model B is applicable in this case. The situa-

tion is not clear for secondary amines since the observed $(k_{obs})_1/(k_{obs})_2$ ratio is significantly lower than the limiting value of 2. We have no explanation for that.

The situation is different in methylene chloride solution (Table III).

TABLE III Observed reaction rates for hydroxyphosphonate formation in methylene chloride. For details see text

amine	$k_{obs}\ [sek^{-1}]\times 10^2$	*pK of amine*	$(k_{obs})_1/(k_{obs})_2$
butylamine	$6.68\cdot10^{-5}\pm1.4.10^{-6}$	10.77	9.72
diethylamine	$1.61\cdot10^{-6}\pm4.0.10^{-7}$	11.01	11.15
triethylamine	$7.37\cdot10^{-5}\pm5.7.10^{-7}$	10.49	7.60

At the very first glance one can see that changing of the amine and phosphite concentration by a factor of 2 does not change the ratio of the observed rate constants within the range 2–4. This means that the data fit neither model A nor model B. They seem to fulfill the equation (18)

$$\frac{dc}{dt} = \nu = k_1 \cdot [F] \cdot [NP]^2 \tag{18}$$

This correlation is shown on a Figure 2.

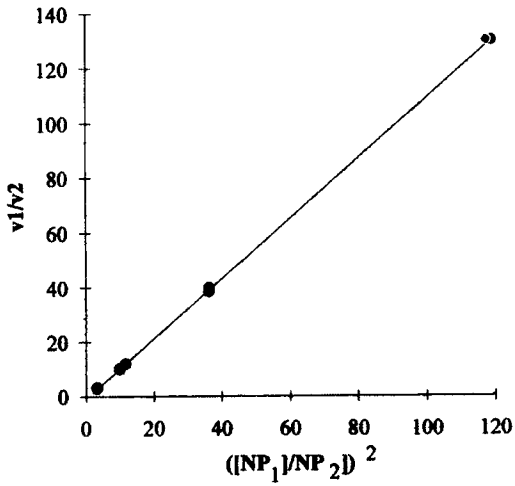


FIGURE 2 The changes of the reaction rates as a function of reactants concentration

In a serie of separate experiments, in which only the concentration of fluorenone was varied, we have proved that the reaction is first order with respect to ketone. Thus the observed changes must be attributed to the formation of the "active form" of phosphite.

In order to study it more carefully we set up a kinetic experiment in which the ratio of reagents - fluorenone : amine : diethyl phosphite was in the range 1:200:200 – 1:800:800. Reaction is much slower when methylene chloride is used as a solvent than in the case of methanol, thus the higher excess of amine and phosphite is necessary in order to be in an observable range of reaction kinetics. We have tried to fit the data obtained for butylamine to a mathematical model expressed by equation (19). Table IV presents both data – obtained (numbers in parentheses) and calculated for the assumed model.

$$\frac{\nu_1}{\nu_2} = a \cdot \left[\frac{[NP_1]}{[NP_2]}\right]^2 + b \tag{19}$$

TABLE IV The changes of the reaction rate as a function of the reactant concentration change. All data are given with respect to the rate constant for the reactant concentration 1:200:200

	$[HP(O)(OEt)_2]$ / [Fluorenone]		
$[BuNH_2]$ / [Fluorenone]	200	400	800
200	1.0	3.47 (3.26)	10.70 (10.2)
400	3.47 (3.10)	12.26 (12.2)	38.84 (40.0)
800	10.70 (10.21)	38.84 (38.37)	128.81 (130)

Similar calculations were also done for the diethylamine and triethylamine. With this model we were able to calculate the equilibrium constants K for the formation of the "active form" of phosphite. Results are summarized in Table V.

TABLE V Equilibrium constants K calculated according to a model expressed by equation (19)

Amine	*K*	*r*	*a*	*b*
Butylamine	0.23	0.9998	1.10±0.02	−0.86±0.50
Diethylamine	0.67	0.9998	0.908±0.005	0.28+0.17
Triethylamine	0.60	0.9974	1.14±0.14	−0.16±10.20

From Table V one can see that the best fit was obtained when coefficient a is close to 1 and coefficient b is statistically insignificant. This means that the reaction rate correlates very strongly with the squares of the "active form".

$$\nu \approx [NP]^2 \tag{20}$$

That in turn supports the prediction expressed in equation (18), that the reaction is second order with respect to the "active form" of a nucleophile. The active form of a nucleophile can be attributed to any species which is stoichiometrically a one to one complex or a compound of an amine and phosphite, for example (EtO)P(O)NHR.[20]

We have also tried to fit the obtained data to a logarithmic model, since in this case the coefficient corresponding to the reaction order could be calculated from linear regression analysis.

$$\log\left(\frac{\nu_1}{\nu_2}\right) = m \cdot \log\left(\frac{[NP_1]}{[NP_2]}\right) + b' \tag{21}$$

The model however is not numerically stable. The minimization of the residuals in the regression analysis drops down very quickly to a small sum of residuals but then it slowly drifts down. The explanation of this fact is as follow. In models expressed by equation (19) and (20) the sum of $(\text{residuals})^2$ and $(\log(\text{residuals})^2$ are minimized correspondingly. In this case only the first one converge unambiguously. Approximate data however we have got, are similar to those calculated before.

EXPERIMENTAL PART

NMR spectra were recorded on AMX 300 MHz Bruker instrument, operating at 300.13 MHz (^{1}H) and 121.499 (^{31}P). Measurements were made in

$CDCl_3$. The details of the synthesis and spectral characteristic of the used compounds which are not commercially available are given in the literature.[21] Other compounds were bought from Aldrich. IR spectra and elemental analysis were performed in the Institute of Organic Chemistry, Biochemistry and Biotechnology. The kinetic experiments were performed on Biochrome Bio-4060 spectrometer in an absolute methanol or dichloromethane solution. The concentration of the carbonyl compound was $2 \cdot 10^{-3}$ mole/dcm^3. To get the pseudo first order kinetics at least a 100 fold excess of amine and a 100 fold excess of diethyl phosphite were used. The use of absolute solvents was necessary to avoid the hydrolysis of diethyl phosphite.

Titration experiment

Butylamine was added to a 0.1M solution of diethyl phosphite in $CDCl_3$ to get the molar ratio of butylamine : diethyl phosphite in the range 0.1 – 10. For each concentration of butylamine the separate ^{31}P-NMR spectrum was recorded with H_3PO_4 as an external standard.

Calculations

All calculation were done by a computer program written especially for particular model in Pascal or using the standard procedures in commercially available programs (Statgraphics, Excel). The fit was performed by minimizing the sum of squared differences between experimental and calculated values.

Acknowledgements

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