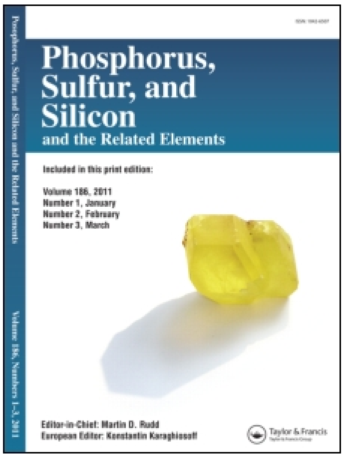

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Donor-Acceptor N ⟶ P Interaction and its Effect on the Phosphorylation of α-Aminoketones

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DONOR-ACCEPTOR N → P INTERACTION AND ITS EFFECT ON THE PHOSPHORYLATION OF α-AMINOKETONES

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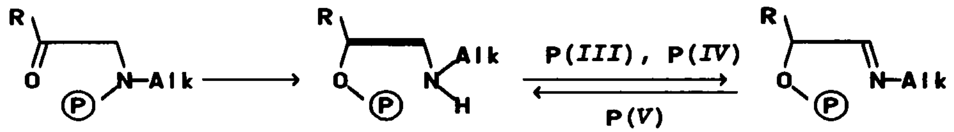
Aminovinylphosphites of Z-configuration $R''_2PO—CR=CH—NR'_2$ are formed in the reaction of α-aminoketones $RCOCH_2NR'_2$ and chlorophosphites with the use of triethylamine as a base. The high stereoselectivity of this process is due to the preliminary coordination of phosphorus chloride to the amino group of the substrate and the following intramolecular rearrangement in the complex with the simultaneous evolution of the salt of hydrogen chloride with triethylamine. A thermodynamic study of the complex formation between reactants in the first stage of the above mentioned process supports this idea.

Key words: α-Aminoketones, aminovinylphosphites, N → P donor-acceptor interaction, thermodynamic parameters.

INTRODUCTION

α-Aminoketones are considered as ambident nucleophiles and in the reactions with halogenated organophosphorus compounds they can form N-, O-[1–3] or N,O-phosphorylated products.[4] The ratio of N,O-isomers, formed in such kind of competitive nucleophile-electrophilic interactions, is dependent on the structure of reagents and conditions of reactions. As a rule, the kinetically-controlled products are N-phosphorylated α-aminoketones **I**, which undergo the rearrangement (sometimes during the reaction) into thermodynamically more stable α-hydroxy imines **III**.

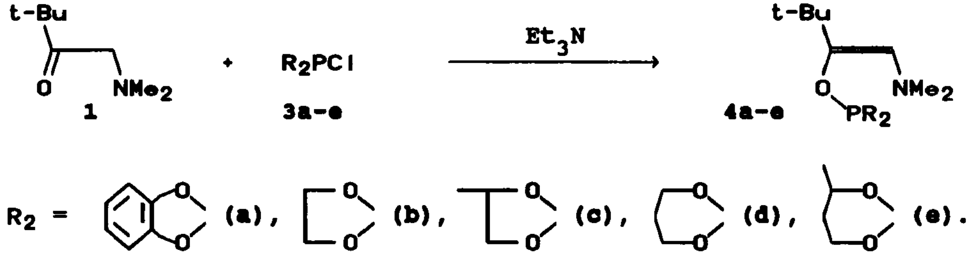


I II III

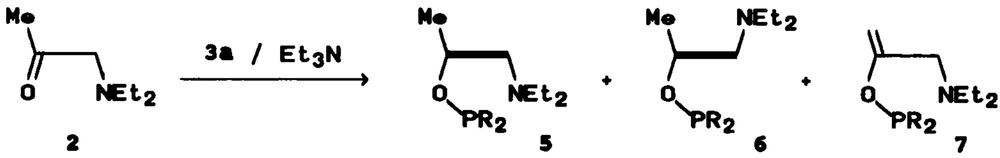
The mentioned regularities were well studied using the substrates with primary or secondary amino groups. α-Aminoketones, having tertiary amino-groups, at first sight can't form P—N-derivatives, however, we have found that the tertiary amino-group takes direct part in the reactions of aminoketones with chlorophosphites and essentially influences the structure and properties of the reaction products.

RESULTS AND DISCUSSION

The reaction of α-aminoketones **1**, **2** and chlorophosphites **3a–e** with the use of triethylamine as a base, in a chloroform solution at room temperature leads to the formation of aminovinylphosphites **4a–e**, **5**, **6**, **7** according to the following reaction schemes I and II:



SCHEME I



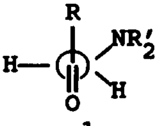
SCHEME II

Dimethylaminopynakolin **1** forms vinyl esters of Z-configuration only. At the same time, diethylaminoacetone **2** forms at 20°C a mixture of three possible isomers (ratio **5**:**6**:**7** = 85:10:5), however, if the reaction temperature is below −10°C, the Z-isomer **5** is the single product of this reaction.

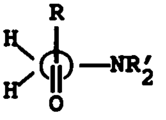
Such high selectivity of the formation of vinyl ester is considered as a nontrivial case in such processes. For example, the silylation-reaction of α-aminoketones even under mild conditions leads, as a rule, to a mixture of products with a various ratio of Z- and E-isomers.[5–7] At the same time, the synthesis of the isomerically pure compounds is an important problem.

In general, the stereoisomeric composition of products of the discussed reaction can be determined, on the one hand, by a conformational rigidity of the starting aminoketones, on the other hand, by the peculiarities of the reaction mechanism.

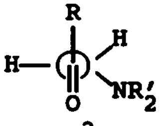
As there are three absorption bands in the IR-spectra of aminoketones, corresponding to the vibrations of the carbonyl group (1700, 1720, 1740 cm^{-1}), probably, these compounds can be considered as a mixture of some conformers φ^1, φ^2 and φ^3.



φ^1



φ^2



φ^3

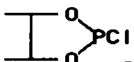
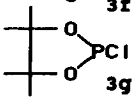
Therefore, the observed stereospecific formation of vinyl ester can not be explained due to the conformational rigidity of the starting aminoketones.

More detailed study of this reaction allowed to state that it passes through the formation of an intermediate substance. This conclusion was made during the study of the reaction of chlorophosphites **3a–e** with aminoketone **1** without triethylamine in the reaction mixture using ^{31}P NMR technique. For example, in the mixture of **3a** and **1** two signals at 171 ppm (starting chlorophosphite **3a**) and 122 ppm (intermediate substance) were detected immediately after mixing. The appearance and growth of the signal corresponding to the reaction product **4a** (120 ppm) was observed during the reaction, at the same time the intermediate substance signal remained small and disappeared simultaneously with the starting chlorophosphite at the end of the reaction. A similar picture was observed for the other reactions of chlorophosphites **3b–e** with aminoketone **1** (Table I).

At the same time, IR-study data of the reaction between **3a** and **1** give evidence about a great reorganization of practically all the bonds of chlorophosphite and aminoketone before the formation of the product. In a hexane solution of **3a**, the following absorption bands were detected: two bands at 480 and 510 cm^{-1} for P—Cl and intensive bands at 860 and 1233 cm^{-1}, corresponding to the P—O—(C) and (P)—O—C fragments. The absorption bands, corresponding to the C=O-group of ketone **1** were noted above. Besides, there are some bands in the region

TABLE I

Spectral and thermodynamic parameters of complex formation between aminoketone **1** and chlorophosphites **3a–g**

phosphites	δ_P	δ_P complex	l_{P-Cl} Å	$-\Delta G^\circ$ $\frac{kJ}{mole}$	$-\Delta H^\circ$ $\frac{kJ}{mole}$	$-\Delta S^\circ$ $\frac{J}{mole \cdot K}$	K_{equil} $\frac{l}{mole}$
3a	171	122	2.106	13.6	77.4	214	242
3b	168	125	2.105	11.9	72.7	185	122
3c	171	129		13.9	80.0	222	277
3d	155	118	2.128	12.4	95.8	280	154
3e	152	116.5		7.0	77.3	370	17
 **3f**				13.8	58.6	150	261
 **3g**			2.093	10.7	70.1	199	77

of 1000–1050 cm^{-1} in spectra of **1** in a hexane solution, which are responsible, to some extent, for the absorption of N—C-bond.

After mixing of diluted hexane solutions, having an equivalent amount of both reactants **3a** and **1**, the spectra of the solution undergoes some changes. Bands at 480 and 510 cm^{-1} decreased three fold in intensity. The band at 860 cm^{-1} (P—O) decreased significantly, but two new bands at 805 and 1360 cm^{-1} appear in the spectra. The absorption of the carbonyl group of compound **1** was detected as a doublet at 1700, 1720 cm^{-1}, and bands, corresponding to the N—C-bond were practically not seen.

All these IR- and NMR-spectra results gave us some possibility to identify such kind of the intermediate substance as a complex of amino ketones and chlorophosphites, formed due to the donor-acceptor N → P bond. Taking into account the IR spectral data one can suggest some participation of the carbonyl group oxygen in the formation of the complex, which can be within the helate type.

The ability of phosphorus halogenides to form donor-acceptor complexes with tertiary amines was detected four decades ago. At the first time the formation of such kind of complexes was postulated by W. R. Trost in 1954.[8] R. R. Holms and co-workers in 1958–1960 studied the similar complex formation, using vapour pressure analysis and ^{31}P NMR-technique. High field shield of the signal in ^{31}P NMR spectra of the mixture PCl_3—Me_3N was explained by the equilibrium formation of the complex between the reagents.[9–11] The first compound, in which the formation of an intramolecular N → P bond was postulated, was a phosphorylated 2-dimethylaminoethanol, as it was shown in 1966 by M. I. Kabachnik.[12]

Interest to complexes of the Nu → P^{III}-type, which may be considered as preliminary compounds in nucleophilic displacement reactions at a tri-coordinated phosphorus atom, increase significantly now.[13–15] However, such kind of complexes has not been detected directly during the reaction of electrophilic derivatives of tri-coordinated phosphorus compounds till our work.

Taking into consideration the above mentioned circumstance, we studied the thermodynamic aspect of the complex formation between aminoketone **1** and chlorophosphites **3a–g** in chloroform solution using the calorimetric titration method.

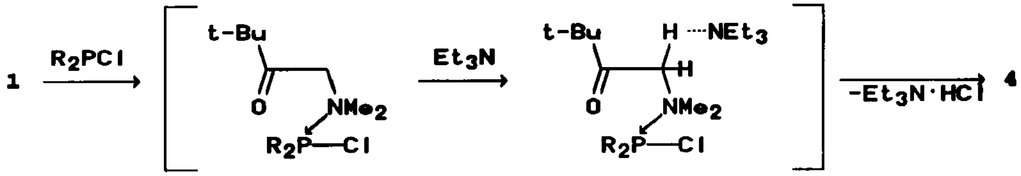
As is seen from the data of Table I, there is a good relationship between enthalpies and entropies of the process of the complex formation (Equation 1):

$$\begin{gathered} \Delta H^0 = (-20.6 \pm 3.1) + (1.105 \pm 0.04)\cdot\Delta S^0 \\ r = 0.994, \quad S_0 = 2.29, \quad n = 7. \end{gathered} \tag{1}$$

The correlative parameters of the equation (1) are in a good agreement with the similar parameters of the equation (2), which was represented in previous work.[16] The latter equation has a good application to about 80 complexes of different types, which were studied in various solvents:

$$\Delta H^0 = -12.9 + 1.41\Delta S^0 \tag{2}$$

Probably, some differences in the values of isoequilibrative temperatures 269 and 337 K, which were calculated from equations (1) and (2) accordingly, are a consequence of the chelate complex formation in our case.



SCHEME III

It is necessary to outline especially the high sensitivity of enthalpy of the complex formation in the distance of P—Cl bond of chlorophosphites. The P—Cl bond has a maximal value for six-membered cyclic phosphite **3d** and the absolute value of the enthalpy term of compound **3d** is maximal too. This fact is well supported by the relationship (Equation 3) between values of enthalpies of the complex formation and distances of P—Cl[17] bonds of compounds **3a, b, d, g**:

$$\Delta H^0 = (1532 \pm 116) - (765 \pm 55) \cdot l_{P-Cl} \qquad r = 0.970, \quad S_0 = 1.40, \quad n = 4. \tag{3}$$

On the contrary, there is no similar relationship between free energies (ΔG^0) and P—Cl bond distances ($r = 0.47$) of the same compounds. Taking into account the analogous data about the similar correlation between the distances of C—Hal bonds and its energies,[18] one may come to the conclusion, that the enthalpy of the complex formation is determined in particular by the energy of the P—Cl bond (or energy of its antibonding orbital).

Thus, the high stereoselectivity of the discussed reaction is connected with the preliminary complex formation between phosphorus chlorides and aminoketones. This complex transforms into vinyl ester by means of simultaneous elimination of hydrogen chloride and intramolecular migration of the phosphorus-containing group from nitrogen to the oxygen of the carbonyl group.

Thus, a great tendency of α-aminoketones to form 1:1 complexes with phosphorus chlorides due to a donor-acceptor bond N → P plays a decisive role in the formation of the structure of the interaction products of aminoketones with chlorophosphites. Such type of complexes may serve as a suitable model for the study of nucleophilic displacement at P^{III}-atom.

EXPERIMENTAL

All experiments were conducted with exclusion of air and moisture under dry argon.

NMR: Bruker Jeminy 200, ^1H (200.13 MHz), ^{31}P (81.02 MHz). Reference substances: ^1H, TMS int., ^{31}P, 85% H_3PO_4 ext. All NMR spectra were recorded in $CDCl_3$ as a solvent. All chemical shift values are listed in ppm. All ^1H NMR spectra are consistent with the structure.

The IR spectra were measured in KBr, on a Carl Zeiss Infracord Spectrometer Model UR 10.

The calorimetric experiments were done at 298 K in a correlation condition of chlorophosphite-aminoketone **1** from 1:1 up to 10:1, concentration of aminoketone (C_0) was 0.021 mol · l^{-1}. Exothermic heat effect of complex formation was registered on the differential automatic calorimeter (volumes of vessels are 3 ml) marked DAC-1-1 and the data were treated with a computer program which was produced according to the recommendations of literature works.[19,20]

Synthesis of vinyl esters **4a–g, 5, 6, 7** *(general method):* The solution of 0.022 mol of aminoketone **1**, 0.02 mol of chlorophosphite **3a–g** and 0.03 mol of triethylamine in 20 ml of chloroform was kept at room temperature till the ^{31}P NMR signal of starting phosphate disappeared (reaction time for **4a**—3 hours, **4b**—7 hours, **4c**—5 days, **4f**—10 days, **4g**—15 days, **5**—12 hours at −15°C, mixture of **5**, **6**, **7**—2 hours at 20°C). The reaction mixture was evaporated under reduced pressure (20 mm Hg), the residue was extracted with pentane. The extract was concentrated by pumping in vacuo (20 mm Hg), the higher boiling residue was fractionally distilled.

1-Dimethylamino-2-(o-phenylenedioxy)phosphinoxy-3,3-dimethyl-1-butene. **4a**: yield 83%; b.p. 95–97°C (0.05 mm Hg); IR spectra (ν, cm^{-1}): 1670 (C=C); PMR spectra: δ 0.90 (s, Me_3C), δ 2.27 (s, Me_2N), δ 5.13 (d, HC=C, $^4J_{PH}$ 1.71), δ 6.9–7.0 (m, H arom); ^{31}P NMR spectra: δ 120 ppm

$C_{14}H_{20}NO_3P$ (281.29)
Anal. found: N 4.91, P 11.07;
calc.: N 4.98, P 11.01.

1-Dimethylamino-2-(ethylenedioxy)phosphinoxy-3,3-dimethyl-1-butene. **4b**: yield 74%; b.p. 65–67°C (0.1 mm Hg); IR spectra (ν, cm^{-1}): 1670 (C=C); PMR spectra: δ 1.03 (s, Me_3C), δ 2.30 (s, Me_2N), δ 3.90–4.25 (m, OCH_2CH_2O), δ 4.90 (d, CH=C, $^4J_{PH}$ 1.40); ^{31}P NMR spectra: δ 122 ppm

$C_{10}H_{20}NO_3P$ (233.24)
Anal. found: N 6.07, P 13.21;
calc.: N 6.01, P 13.28.

1-Dimethylamino-2-(1,2-propylenedioxy)phosphinoxy-3,3-dimethyl-1-butene. **4c**: yield 65%; b.p. 69–70°C (0.1 mm Hg); IR spectra (ν, cm^{-1}): 1670 (C=C); PMR spectra: δ 1.04 (s, Me_3C), δ 1.17 (d, Me—C, $^3J_{HH}$ 5.2), δ 2.29 (s, Me_2N), δ 4.10–4.30 (m, CH_2O), δ 4.45–4.65 (m, CHO), δ 4.89 (d, CH=C, $^4J_{PH}$ 1.40); ^{31}P NMR spectra: δ 127 ppm

$C_{11}H_{22}NO_3P$ (247.28)
Anal. found: N 5.71, P 12.50;
calc.: N 5.66, P 12.52.

1-Dimethylamino-2-(1,3-propylenedioxy)phosphinoxy-3,3-dimethyl-1-butene. **4f**: yield 72%; b.p. 67–69°C (0.1 mm Hg); IR spectra (ν, cm^{-1}): 1670 (C=C); PMR spectra: δ 1.07 (s, Me_3C), δ 1.4–1.6 (m, $OCH_2\underline{CH_2}CH_2O$), δ 2.22 (s, Me_2N), δ 3.7–4.0 (m, OCH_2), δ 4.89 (d, CH=C, $^4J_{PH}$ 1.1); ^{31}P NMR spectra: δ 117 ppm

$C_{11}H_{22}NO_3P$ (247.28)
Anal. found: N 5.73, P 12.48;
calc.: N 5.66, P 12.52.

1-Dimethylamino-2-(1,3-butylenedioxy)phosphinoxy-3,3-dimethyl-1-butene. **4g**: yield 72%; b.p. 71–73°C (0.1 mm Hg); IR spectra (ν, cm^{-1}): 1670 (C=C); PMR spectra: δ 1.03 (s, Me_3C), δ 1.13–1.20 (m, Me—C), δ 1.4–1.6 (m, $OCH\underline{CH_2}CH_2O$), δ 2.21 (s, Me_2N), δ 3.7–4.0 (m, OCH_2), δ 4.3–4.6 (m, OCH), δ 4.89 (d, CH=C, $^4J_{PH}$ 0.8); ^{31}P NMR spectra: δ 116, 118 ppm

$C_{12}H_{24}NO_3P$ (261.30)
Anal. found: N 5.41, P 11.80;
calc.: N 5.36, P 11.85.

1-Diethylamino-2-(o-phenylenedioxy)phosphinoxypropen (Z-isomer). **5**: reaction was carried out at −15°C; yield 78%; b.p. 81–82°C (0.1 mm Hg); IR spectra (ν, cm^{-1}): 1670 (C=C); PMR spectra: δ 0.99 (t, $\underline{CH_3}CH_2N$, $^3J_{HH}$ 7.2), δ 1.38 (d, $\underline{CH_3}$—C=CH, $^4J_{HH}$ 1.1), δ 2.60 (q, $CH_3\underline{CH_2}N$, $^3J_{HH}$ 7.2), δ 4.63 (d q, CH_3—CH=C$\underline{H}$, $^4J_{HH}$ 1.1, $^4J_{PH}$ 1.1), δ 6.7–7.0 (m, H arom); ^{31}P NMR spectra: 123 ppm

$C_{13}H_{18}NO_3P$ (267.27)
Anal. found: N 5.22, P 11.63;
calc.: N 5.24, P 11.59.

1-Diethylamino-2-(o-phenylenedioxy)phosphinoxypropene (E-isomer). **6**: was isolated as a mixture with compounds **5** and **7**, summary yield 74%, contents of **6** 10% (reaction was carried out at 20°C); b.p. 81–85°C (0.1 mm Hg); IR spectra (ν, cm^{-1}): 1670 (C=C); PMR spectra: δ 0.99 (t, $\underline{CH_3}CH_2N$, $^3J_{HH}$ 7.2), δ 1.79 (d, $\underline{CH_3}$—C=CH, $^4J_{HH}$ 1.1), δ 2.43 (q, $CH_3\underline{CH_2}N$, $^3J_{HH}$ 7.2), δ 5.30 (d q, CH_3—C=C$\underline{H}$, $^4J_{HH}$ 1.1, $^4J_{PH}$ 1.1), δ 6.7–7.0 (m, H arom); ^{31}P NMR spectra: 126 ppm.

$C_{13}H_{18}NO_3P$ (267.27)
Anal. found: N 5.29, P 11.52 (for the mixture);
calc.: N 5.24, P 11.59.

3-Diethylamino-2-(o-phenylenedioxy)phosphinoxypropene. **7**: was isolated as a mixture with compounds **5** and **6**, summary yield 74%, contents of **6** 5% (reaction was carried out at 20°C); b.p. 81–85°C (0.1 mm Hg); IR spectra (ν, cm^{-1}): 1670 ($C{=}C$); PMR spectra: δ 0.87 (t, $\underline{CH_3}CH_2N$, $^3J_{HH}$ 7.2), δ 2.26 (q, $CH_3\underline{CH_2}N$, $^3J_{HH}$ 7.2), δ 2.77 (m, $\underline{CH_2}{-}C{=}CH_2$), δ 4.00, 4.38 (m, $CH_2{-}C{=}\underline{CH_2}$), δ 6.7–7.0 (m, H arom); ^{31}P NMR spectra: 116 ppm.

$C_{13}H_{18}NO_3P$ (267.27)
Anal. found: N 5.29, P 11.52 (for the mixture);
calc.: N 5.24, P 11.59.

ACKNOWLEDGEMENTS

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