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

Experimental and Theoretical Investigation of Intramolecular Transformations of Silicon-containing (Haloalkyl)phosphorylated Ureas and Acylamides

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Abstract — Silicon-containing chloromethylphosphorylated ureas undergo transformation involving evolution of chlorotrimethylsilane and formation of 1,3,4-oxazaphospholes. Their analogs, silicon-containing phosphorylated acylamides, transform in another way, viz. by β-cleavage to form the corresponding siloxyphosphonates. Quantum-chemical investigation of thermodynamic characteristics of these processes was carried out.

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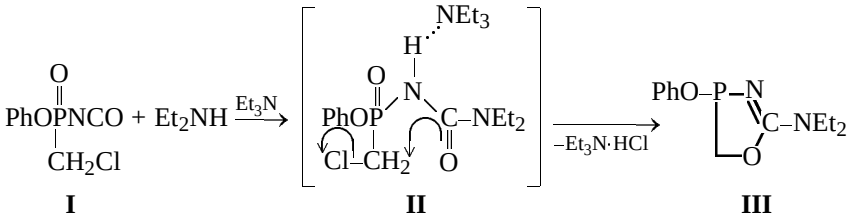
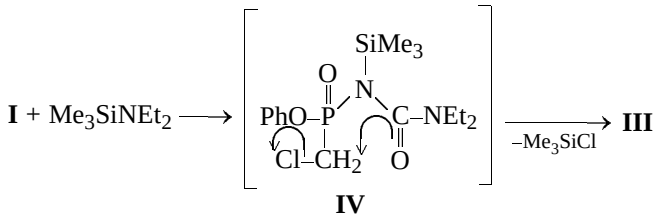
We previously showed that phenyl (chloromethyl)-phosphonoisocyanatidate (**I**) easily takes up dialkylamines to give chloromethylphosphorylated ureas **II**. In the presence of equimolar amount of a base (primary, secondary, or tertiary amine), the latter undergo cyclization leading to 1,3,4-oxazaphospholes **III**. The role of the base is to form initially an H-complex including the amine molecule and the proton of the secondary amido group, which is accompanied by weakening or cleavage of the N–H bond. The subsequent nucleophilic attack of the carbonyl oxygen atom on the chloromethyl carbon atom leads to separation of amine hydrochloride and formation of oxazaphosphole **III** [1].



I **II** **III**

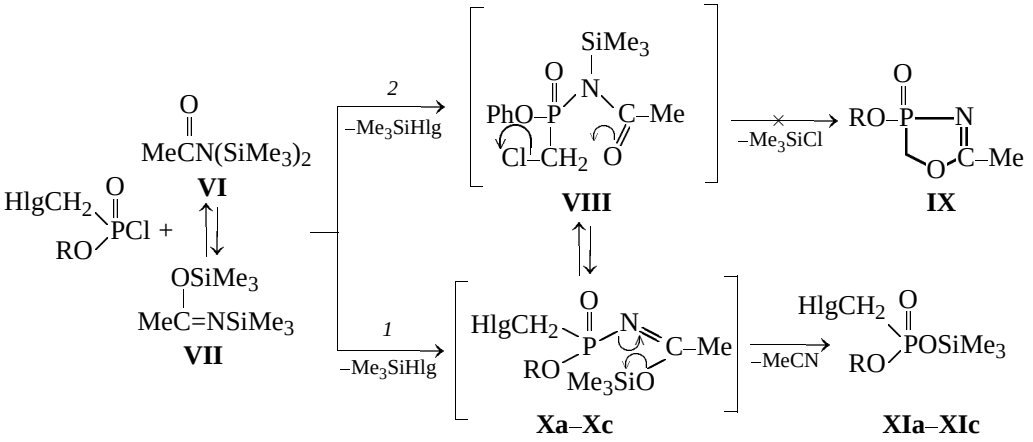
We suggested an that analogous synthetic result can be obtained by cyclization of silicon-containing phosphorylated ureas. This approach seemed preferred, since it excluded the necessity of using solvents and amines and involved no filtration and solvent removal stages. To verify this suggestion, we studied the reaction of isocyanate **I** with diethyl(trimethylsilyl)-amine.



IV

Actually, heating of equimolar amounts of isocyanate **I** and silylamine is accompanied by evolution of chlorotrimethylsilane and formation of 1,3,4-oxazaphosphole **III**. Its physicochemical characteristic are identical to those of the previously obtained sample. The reaction involves initial addition of silylamine by the isocyanato group with intermediate formation of phosphorylated silicon-containing urea **IV**. The subsequent nucleophilic substitution by the halomethyl carbon atom results in formation of final product **III** and evolution of chlorotrimethylsilane.

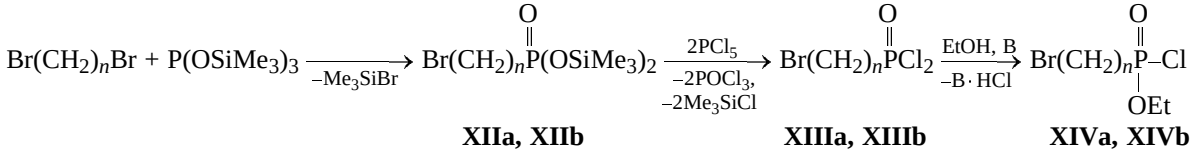
It was reasonable to suggest that the developed synthetic approach to substituted oxazaphospholes can be extended to obtain silicon-containing (haloalkyl)-phosphorylated acylamides. We planned to synthesize the latter via reaction of (halomethyl)phosphonochloridates **Va**–**Vc** with *N*,*O*-bis(trimethylsilyl)acetamide (**VI**). The subsequent cyclization of acylamidophosphonate **VIII** by the mentioned scheme was expected to give C-alkyl-substituted phosphole **IX**. But it occurred that the reaction involve liberation of acetonitrile along with chlorotrimethylsilane and yields trimethylsilyl (halomethyl)phosphonates **XIa** and **XIb**.

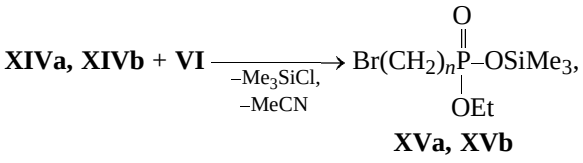


V, X, XI, Hlg = Cl, R = Ph (**a**), Et (**c**); Hlg = Br, R = Ph (**b**).

It follows from published data that disilylated acylamides **VI** undergo reversible 1,3-N⇄O trimethylsilyl migration and thus can exist in the amide and imide forms. Bis(trimethylsilyl)acetamide (**VI**), according to spectral data, exists mainly in imide form **VII** [2]. The obtained experimental data show that phosphonochloridates **Va, Vb** react with the imide form of silylated acetamide **VII**, and the process takes pathway *1*. Pathway *2* suggests phosphorylation of amide form **VI** to form intermediate **VIII** that undergoes 1,3-N⇄O trimethylsilyl migration yielding intermediate **XI**; finally, the latter decomposes to give product **XI**.

To assess the effect of the length of the haloalkyl substituent in phosphonochloridates on the synthetic result of their reaction with silylacetamide **VI**, we prepared ethyl (bromoethyl)- and ethyl (bromopropyl)-phosphonochloridates (**XIVa, XIVb**). The reactions of dibromoethane or dibromopropane with tris(trimethylsilyl) phosphite produce (bromoalkyl)phosphonates **XIIa, XIIb**. Their chlorination with phosphorus pentachloride allowed us to prepare phosphonic dichlorides **XIIIa, XIIIb** whose partial esterification gives target phosphonochloridates **XIVa, XIVb**. It was found that the reaction of phosphonates **XIVa, XIVb** with silylacetamide **VI** provides the same synthetic result, i.e. it yields trimethylsilyl (bromoalkyl)phosphonates **XV**.



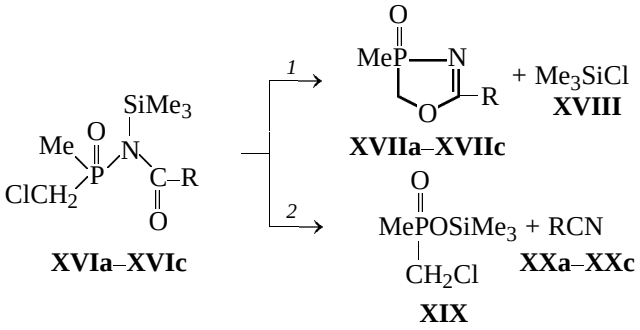


XVa, XVb

XII–**XV,** n = 2 (**a**), 3 (**b**).

Note that silicon-containing phosphorylated ureas and amides, while only slightly differing in structure (diethylamino instead of methyl group), transform by different pathways to give linear or cyclic products.

To find out why compounds **IV** and **VIII** transform by different pathways, we perfomed quantum-chemical calculations of structures **XVIa**–**XVIc, XVIIa**–**XVIIc, XVIII, XIX,** and **XXa**–**XXc** that model the structures of phosphorylated ureas, acylamides, and possible reaction products.



XVIa–**XVIc**

XVIIa–**XVIIc**

XVIII

XIX

XXa–**XXc**

XVI, XVII, XX, R = NMe_2 (**a**), Me (**b**), Ph (**c**).

Table 1. Energetic characteristics of compounds studied [a]

Comp. no.	ΔH_f^0, kcal mol^{-1}	DFT method, 3z basis	
		$-E_0$, au	$-G_{298}$, au
XVIa	–187.7	1745.298823	1745.353284
XVIb	–181.8	1572.270776	1572.318654
XVIc	–144.1	1763.780334	1764.832403
XVIIa	–106.8	876.322270	876.364350
XVIIb	–99.7	703.294807	703.328888
XVIIc	–63.8	894.806456	894.845689
XVIII	–87.4	868.982914	869.015525
XIX	–203.8	1439.687305	1439.731474
XXa	23.0	305.602517	305.635833
XXb	23.3	132.591641	132.615700
XXc	58.5	324.100669	324.131106
XXIa	–189.2	1745.302642	1745.359137
XXIb	–182.6	1572.270008	1572.319580
XXIc	–148.5	1763.786152	1764.840506

[a] (ΔH_f^0) Enthalpy of formation of the molecule in the standard state; (E_0) total energy including zero-point energy; and (G_{298}) Gibbs energy.

The calculations were carried out by the semiempirical PM3 method using the MOPAC 6 program package [3], and by the density functional method (DFT/PBE/3z) using the PRIRODA program [4].

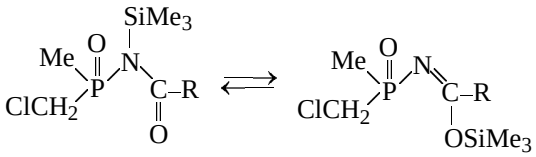
As follows from the calculation results listed in Tables 1 and 2, the processes that take place in practice are thermodynamically favorable. Therewith, with dimethylamino derivative **XVIa**, β-decomposition (pathway *2*) is thermodynamically unfavorable and does not take place. With methyl derivative **XVIb**, both pathways are thermodynamically favorable, and the energy gap between pathways *1* and *2* is not large. The reason that β-decomposition is the only pathway to be realized is probably explained by specific features of reaction mechanisms, that is by kinetic factors. A qualitatively analogous picture would be observed at R=Ph (compound **XVIc**). Such structural factors as the highest negative charge on oxygen, the highest located HOMO, the weakest (longest) C–Cl bond, and the strongest N–Si bond in compound **XVIa** compared to its analogs **XVIb** and **XVIc** (Table 3) argue in favor of the intramolecular cyclization of dimethylamino derivative **XVIa** into **XVIIa**, that evidently

Table 2. Energetic characteristics of cyclization, β-decomposition, and rearrangement by the results of PM3[a] and DFT[b] calculations

Parameter	Cyclization			β-Decomposition			Rearrangement		
	XVIa → **XVIIa**	**XVIb** → **XVIIb**	**XVIc** → **XVIIc**	**XVIa** → **XXa**	**XVIb** → **XXb**	**XVIc** → **XXc**	**XVIa** → **XXIa**	**XVIb** → **XXIb**	**XVIc** → **XXIc**
$\Delta\Delta H_f^0$	–6.4	–5.3	–7.1	7.0	1.3	–1.5	–1.5	–0.9	–4.4
ΔE_0	–4.0	–4.5	–5.7	5.6	–5.3	–4.8	–2.4	0.4	–3.6
ΔG_{298}	–16.7	–16.2	–18.1	1.0	–18.3	–19.1	–3.7	–1.0	–5.1

[a] $\Delta\Delta H_f^0 = \Sigma\Delta H_f^0$(prod.) – ΔH_f^0(reag.). [b] $\Delta E_0 = \Sigma\Delta E_0$(prod.) – ΔE_0(reag.), $\Delta G_{298} = \Sigma\Delta G_{298}$(prod.) – $\Sigma\Delta G_{298}$(reag.).

involves nucleophilic attack of the carbonyl oxygen on the chloromethyl carbon. All tables list data for the most stable conformers of the compounds under study. The possibility of the reversible N → O trimethylsilyl migration in compounds **XVIa, XVIb** to form imido derivatives **XXIa, XXIb** should also be mentioned.



XVIa–**XVIc** **XXIa**–**XXIc**

XVI, XXI, R = NMe_2 (**a**), Me (**b**), Ph (**c**).

As seen from Table 2, the calculation methods used show that rearrangement is always thermodynamically favorable, but with the dimethylamino- and phenyl derivatives it is much more preferred than with the methyl derivative.

EXPERIMENTAL

The ^{1}H NMR spectra were registered on a Bruker WM-250 (250.13 MHz) spectrometer against residual proton signals of deuterated solvents (chloroform-*d* and acetone-d_6). The ^{31}P NMR spectra were obtained on a Bruker MSL-400 (161.97 MHz) spectrometer against external 85% phosphoric acid.

2-(Diethylamino)-4-phenoxy-4,5-dihydro-1,3,4λ^5-oxazaphosphole-2,4-dione (III). A mixture of 2.3 g of phosphonoisocyanatidate **I** and 1.45 g of diethyl(trimethylsilyl)amine was kept for 2 h at 120°C. Fractionation of the reaction mixture gave 1.6 g (60%) of compound **III**, bp 219–220°C (0.02 mm Hg), n_D^{20} 1.5383 [5]. ^{31}P NMR spectrum: δ_P 51.50 ppm.

Phenyl (bromomethyl)phosphonochloridate (Vb). Heating of equimolar amounts of (bromomethyl)phosphonic dichloride with phenol for several hours gave 70% of compound **Vb**, bp 106°C (0.09 mm Hg). ^{31}P NMR spectrum: δ_P 26.1 ppm. Found, %: P 11.17. $C_7H_7BrClO_2P$. Calculated, %: P 11.50.

Table 3. Principal geometric and electronic characteristics of compounds **XVIa**–**XVIc** by the results of DFT calculations

Comp. no.	$-q_O$	$-\varepsilon_{HOMO}$, au	l_{C-Cl}, Å	l_{N-Si}, Å
XVIa	0.2573	0.2148	1.810	1.826
XVIb	0.2409	0.2247	1.800	1.851
XVIc	0.2318	0.2252	1.807	1.849

Phenyl trimethylsilyl (chloromethyl)phosphonate (XIa). A mixture of 2.25 g of (chloromethyl)-phosphonate **Va** and 2.05 of bis(trimethylsilyl)acetamide (**VI**) was kept for 2 h at 100°C. Fractionation of the resulting mixture gave 2.0 g (73%) of compound **XIa**, bp 75°C (0.02 mm Hg), n_D^{20} 1.5249 [6]. ^{31}P NMR spectrum: δ_P 5.15 ppm. Found, %: P 9.60. $C_{10}H_{16}BrO_3PSi$. Calculated, %: P 9.91.

Phenyl trimethylsilyl (bromomethyl)phosphonate (XIb). A mixture of 4.05 g of chlorophosphonate **Vb** and 3.0 g of silylacetamide **VI** was heated for 1 h at 140°C. Fractionation of the resulting mixture gave 2.8 g (58%) of compound **XIb**, bp 116°C (0.08 mm Hg), n_D^{20} 1.5040. ^{31}P NMR spectrum: δ_P 7.09 ppm. Found, %: P 9.60. $C_{10}H_{16}BrO_3PSi$. Calculated, %: P 9.91.

Ethyl trimethylsilyl (chloromethyl)phosphonate (XIc) was prepared analogously from 3.54 g of chlorophosphonate **Vc** and 4.06 g of silylacetamide **VI**. Yield 2.6 g (56%), bp 59°C (0.06 mm Hg), n_D^{20} 1.4319. ^{31}P NMR spectrum: δ_P 10.22 ppm. Found, %: P 12.96; Si 11.71. $C_6H_{16}ClO_3PSi$. Calculated, %: P 13.44; Si 12.14.

Bis(trimethylsilyl) (2-bromoethyl)phosphonate (XIIa). A mixture of 45 g of tris(trimetylsilyl) phosphite and 61 g of dibromoethane was kept for 2 h at 160°C. Fractionation of the resulting mixture gave 30 g (59%) of compound **XIIa**, bp 78–79°C (0.08 mm Hg), n_D^{20} 1.4437. ^{31}P NMR spectrum: δ_P 7.28 ppm. Found, %: P 9.39; Si 16.96. $C_8H_{22}BrO_3PSi_2$. Calculated, %: P 9.30; Si 16.81.

Bis(trimethylsilyl) (3-bromopropyl)phosphonate (XIIb). A mixture of 15 g of tris(trimetylsilyl) phosphite and 40 g of dibromopropane was heated for 2 h at 170°C. Bromotrimethylsilane and dibromopropane were distilled off, and the residue was fractionated in a vacuum to give 9.5 g (55%) of compound **XIIb**, bp 115°C (0.1 mm Hg), n_D^{20} 1.4508. ^{31}P NMR spectrum: δ_P 11.58 ppm. Found, %: P 8.22; Si 15.76. $C_8H_{24}BrO_3PSi_2$. Calculated, %: P 8.93; Si 15.76.

(2-Bromoethyl)phosphonic dichloride (XIIIa). A mixture of 24.5 g of phosphonate **XIIa**, 0.3 g of copper monochloride, and 41.7 g of phosphorus pentachloride was kept for 1 h at 100°C. Fractionation of the reaction mixture gave 15.4 g (68%) of compound **XIIIa**, bp 108–110°C (10 mm Hg) [7]. ^{31}P NMR spectrum: δ_P 44.21 ppm. Found, %: P 13.39. $C_2H_4Br \cdot Cl_2OP$. Calculated, %: P 13.72.

(3-Bromopropyl)phosphonic dichloride (XIIIb). Phosphonate **XIIb**, 18 g, was heated to 150°C, and 22.5 g of phosphorus pentachloride was added in portions. The resulting mixture was kept for 2 h at 20°C and fractionated to give 10.5 g (87%) of compound **XIIIb**, bp 153–156°C (20 mm Hg) [8]. ^{31}P NMR spectrum: δ_P 48.81 ppm.

Ethyl (2-bromoethyl)phosphonochloridate (XIVa). A solution of 4.5 g of phosphonic dichloride **XIIIa** in 15 ml of chloroform was treated with 0.92 g of anhydrous ethanol, and the resulting solution was kept for 1 day. Fractionation gave 1.8 g (38%) of compound **XIVa**, bp 75°C (0.1 mm Hg). ^{31}P NMR spectrum: δ_P 36.11 ppm. Found, %: Br 34.44; Cl 15.31; P 12.79. $C_4H_9BrClO_2P$. Calculated, %: Br 33.97; Cl 15.07; P 13.16.

Ethyl (3-bromopropyl)phosphonochloridate (XIVb). To a solution of 7.2 g of phosphonic dichloride **XIIIb** in 30 ml of diethyl ether, a mixture of 1.5 g of ethanol and 3.0 g of triethylamine was added at –30°C. After 10 h, amine hydrochloride was filtered off, and the residue was fractionated in a vacuum to give 2.4 g (32%) of compound **XIVb**, bp 104°C (0.08 mm Hg), n_D^{20} 1.4872. ^{31}P NMR spectrum: δ_P 42.21 ppm. Found, %: P 12.12. $C_5H_{11}BrCO_2P$. Calculated, %: P 12.42.

Ethyl trimethylsilyl (2-bromoethyl)phosphonate (XVa). A mixture of 7.0 g of chloride **XIVa** and 6.0 g of silylacetamide **VI** was kept for 20 h at 20°C. Fractionation gave 4.2 g (49%) of compound **XIIIa**, bp 85°C (0.1 mm Hg), n_D^{20} 1.4413. ^{1}H NMR spectrum, δ, ppm: 0.18 (Me_3Si). ^{31}P NMR spectrum, δ_P 17.26 ppm. Found, %: P 10.89; Si 9.63. $C_7H_{18}BrO_3 \cdot SiP$. Calculated.%: P 10.72; Si 9.68.

Ethyl trimethylsilyl (3-bromopropyl)phosphonate (XVb). A solution of 5.0 g of phosphonochloridate **XIV** in 30 ml of anhydrous diethyl ether was mixed with a solution of 4 g of silylacetamide **VI** in 20 ml of diethyl ether. The resulting mixture was kept for 2 days at 20°C. Fractionation gave 3.4 g (57%) of compound **XVb**, bp 92°C (0.06 mm Hg), n_D^{20} 1.4500. ^{1}H NMR spectrum, δ, ppm: 0.17 (Me_3Si). ^{31}P NMR spectrum: δ_P 21.13 ppm. Found, %: C 31.44; H 6.22; P 10.19. $C_8H_{20}BrO_3PSi$. Calculated, %: C 31.68; H 6.60; P 10.23.

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