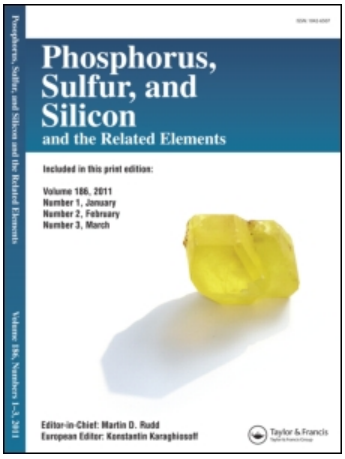


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

H-TETRAOXASPIROPHOSPHORANES AS POSSIBLE INTERMEDIATES IN THE PHOSPHONYLATION BY PHOSPHOROUS ACID/OXIRANES

Svetomir B. Tzokov[ab]; Nikolay G. Vassilev[c]; Rositza T. Momtcheva[a]; Jose Kaneti[d]; Dimiter D. Petkova[a]
[a] Laboratory of BioCatalysis, Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria [b] Department of Chemistry, The University of Sheffield, Sheffield, UK [c] Laboratory of Nuclear Magnetic Resonance, Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria [d] Laboratory of Physical Organic Chemistry, Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria

To cite this Article Tzokov, Svetomir B. , Vassilev, Nikolay G. , Momtcheva, Rositza T. , Kaneti, Jose and Petkova, Dimiter D.(2000) 'H-TETRAOXASPIROPHOSPHORANES AS POSSIBLE INTERMEDIATES IN THE PHOSPHONYLATION BY PHOSPHOROUS ACID/OXIRANES', Phosphorus, Sulfur, and Silicon and the Related Elements, 166: 1, 187 — 196
To link to this Article: DOI: 10.1080/10426500008076540
URL: http://dx.doi.org/10.1080/10426500008076540

Phosphorus, Sulfur and Silicon, 2000, Vol. 166, pp. 187-196
Reprints available directly from the publisher
Photocopying permitted by license only

H-TETRAOXASPIROPHOSPHORANES AS POSSIBLE INTERMEDIATES IN THE PHOSPHONYLATION BY PHOSPHOROUS ACID / OXIRANES

SVETOMIR B. TZOKOV[a*], NIKOLAY G. VASSILEV[b], ROSITZA T. MOMTCHEVA[a], JOSE KANETI[c] and DIMITER D. PETKOV[a]

[a]*Laboratory of BioCatalysis,* [b]*Laboratory of Nuclear Magnetic Resonance and* [c]*Laboratory of Physical Organic Chemistry, Institute of Organic Chemistry, Bulgarian Academy of Sciences 1113 Sofia, Bulgaria*

(Received November 5, 2000; In final form June 19, 2000)

The detailed ^{31}P-NMR study of the mechanism of the ribozymomimetic phosphonylation with phosphorous acid / oxirane revealed consecutive formation of β-hydroxy H-phosphonate monoester, di-(β-hydroxyalkyl) H-phosphonate, alkylene H-phosphonate, β-hydroxyalkyl alkylene phosphite and the corresponding stereoelectronically stabilized pentacoordinated H-tetraoxaspirophosphorane. The equilibrium between the triphosphite and the spirophosphorane shifts towards the β-hydroxyalkyl alkylene phosphite at high temperatures. In the presence of alcohol and controlled amounts of water transesterification of the β-hydroxyalkyl alkylene phosphite to the corresponding alkyl alkylene phosphite, and hydrolysis to β-hydroxyalkyl alkyl H-phosphonate proceed at the elevated temperature. β-Hydroxyalkyl alkyl H-phosphonates are model compounds of the phosphodiester bond and undergo hydrolysis with a diol leaving in the presence of one equivalent of water.

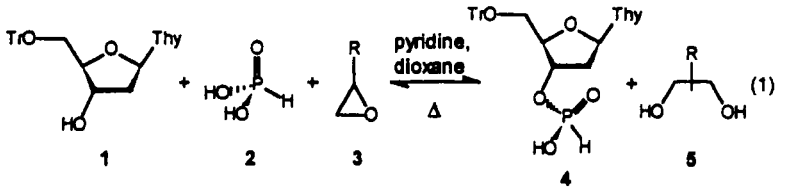
Keywords: phosphonylation; oxiranes; spirophosphorane; 2-hydroxyl group; transesterification; ribozyme

INTRODUCTION

We reported recently the preparation of sugar H-phosphonates, such as the nucleoside H-phosphonate **4**, based on the reaction of phosphonous acid

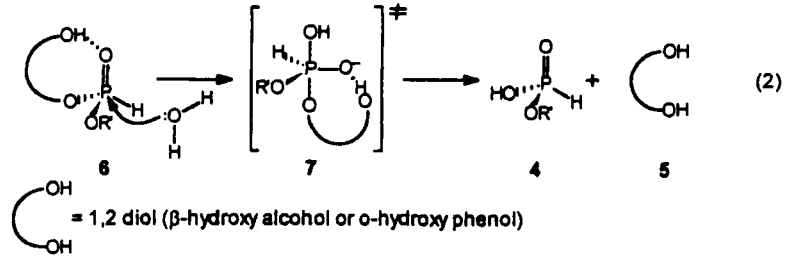
* Current address: Department of Chemistry, The University of Sheffield, Dainton Building, Brook Hill, Sheffield S3 7HF, UK, Email: ch4sbt@sheffield.ac.uk

with the nucleoside **1** in the presence of oxirane **3** as condensation agent[1] (Scheme 1):



SCHEME 1

This reaction was found to proceed via the intermediate formation of several phosphorus compounds. We already described[2] the hydrolysis accompanied by leaving of the diol **5** of the intermediately formed 2-hydroxy H-phosphonate diester in aprotic organic media (Scheme 2) as a model of the reaction catalyzed by the large ribozymes (group I, group II, spliceosomal introns and ribonuclease P)[3].

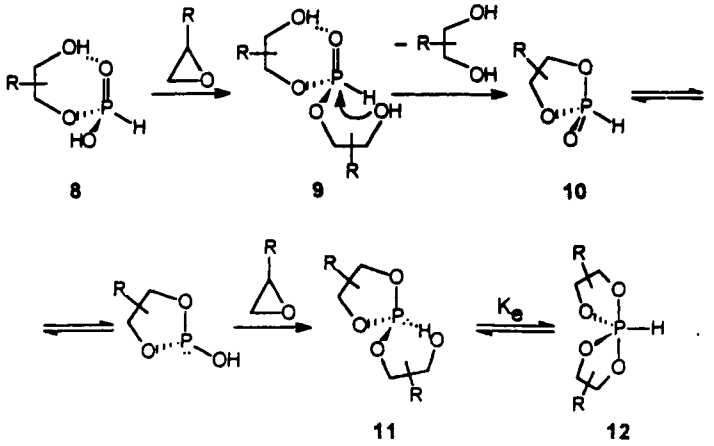


SCHEME 2

However, the detailed mechanism of the total reaction of phosphonylation by phosphorous acid / oxirane, has not yet been described. Here we report the formation of H-tetraoxaspirophosphorane **12** (Scheme 3) and its possible intermediacy in the phosphonylation reaction (1).

RESULTS AND DISCUSSION

By analogy with a similar reaction of phosphinylation by phosphinic acid and oxirane[4],[5], we have tentatively assumed[1] a transient formation of



SCHEME 3

the β-hydroxyalkyl phosphite **8** (Scheme 3) that is further subjected to β-hydroxyl-assisted transesterification by the nucleoside **1**. The isolated **8**, however, proved to be unreactive in the ester exchange reaction suggesting that a higher degree of β-hydroxyalkylation of phosphorous acid by oxiranes provides the phosphonylation agent. Actually, ^{31}P spectra of the reaction mixture of phosphorous acid and oxirane (Figure 1a) indicate the intermediate formation of the esters **9** – **11** and accumulation of the spirophosphorane **12** (Scheme 3).

The acid-catalyzed ring-opening reaction of oxiranes with phosphorous and phosphoric acids has been recently described[6],[7]. Due to the anchimeric assistance of the vicinal hydroxyl group, β-hydroxyalkyl H-phosphonates **8** react faster than phosphorous acid with oxiranes[6] and after heating in dioxane/pyridine signals for di-(β-hydroxyalkyl) H-phosphonate **9** and alkylene H-phosphonate (2-oxo, 1,3,2-dioxaphospholane) **10** appear in the ^{31}P-NMR spectrum (Figure 1) of the reaction mixture. A doublet, characteristic of the ^{31}P resonance of H-tetraoxaspirophosphorane **12** ($\delta\ ^{31}P = -22.9$ ppm and $J_{P\text{-}H} = 850$ Hz)[8] was also found. This suggests further β-hydroxyalkylation of the dioxaphospholane **10** to yield the β-hydroxyalkyl alkylene phosphite (2-(β-hydroxyethoxy)-1,3,2-dioxaphospholane) **11**, known[8] to be in equilibrium with the spirophosphorane **12** (R-derivative of 1,4,6,9-tetraoxa-5λ^5-phosphaspiro[4,4]nonane)

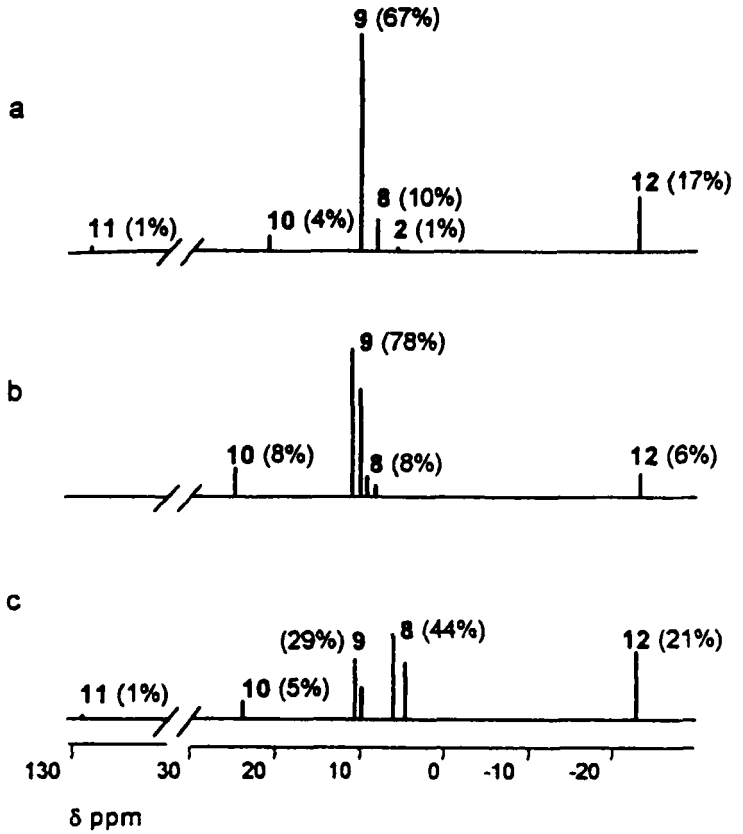


FIGURE 1 Product distribution for the reaction of phosphorous acid with oxirane (R=H) in dioxane 150 minutes after the reaction has started (a), of phosphorous acid with epichlorohydrine ($R=CH_2Cl$) in dioxane 120 minutes after the reaction has started (b), of phosphorous acid with epichlorohydrine ($R=CH_2Cl$) in dioxane / pyridine 120 minutes after the addition of the pyridine (c) as judged from the ^{31}P NMR spectra of the reaction mixtures. For details see EXPERIMENTAL

(Scheme 3). The relative amount of the compounds and the rate of the reaction vary with the change of the oxirane or the solvent (Figure 1).

Spirooxyphosphoranes are stable mimics of the transient pentaoxaphosphorane intermediates or transition states in phosphoryl transfer[9] including phosphoryl transesterification. The spirooxyphosphorane 12 (R=H) is a crystalline compound, stable in aprotic solvents[10] only. The ground

state conformation of this spiranic molecule is probably stabilized stereoelectronically[9] (Figure 2) since the increasing of the reaction temperature shifts the equilibrium in favor of the cyclic triphosphite **11**[11]. The equilibrium constant K_e of the tautomeric equilibrium spirophosphorane / phosphite in (3) is equal to 1 at 100°C and to 10 at room temperature[11]. The equilibrium lies far over in the direction of the tetraoxaspirophosphorane **13** (Chart)[2] in the case of the catechol derivatives and their UV absorption provides a possibility for complete HPLC analysis of the reaction mixture. Therefore, the stable and easily accessible H-tetraoxaspirophosphorane **13** (2λ^5-2,2′-spirobi [1,3,2-benzodioxaphosphole]) has been extensively used in most of our further model experiments.

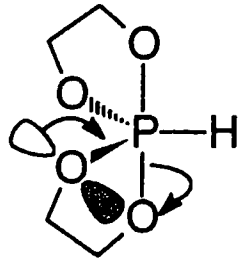
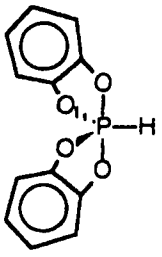


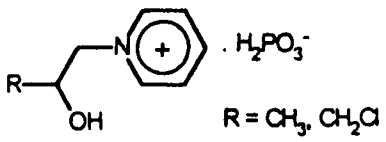
FIGURE 2 An illustration of one of the possible favorable stereoelectronic effects in the spirophosphorane molecule. The other oxygen atoms are able to participate in similar interactions, too

The observation of the formation of spirophosphorane in (3), together with our previously published results[1,2] suggest that the phosphonylation (1) proceeds via the formation of the intermediate H-tetraoxaspirophosphorane (**12**). The latter generates at elevated temperature the triphosphite **11**, reactive in the reaction of transesterification (Scheme 4) and, in the presence of or after addition of an alcohol and a controlled amounts of water, transesterification via the formation of the hexacoordinated intermediate **14** to the alkyl alkylene phosphite **15** takes place. The triphosphites like **15** are readily hydrolyzed in the presence of traces of water to alkyl β-hydroxyalkyl H-phosphonate **6**[12]. In an organic medium, in the presence of one equivalent of water, the H-phosphonate diester **6** undergoes ribozymomimetic hydrolysis with leaving of a diol to the H-phospho-

nate monoester **4** due to the electrophilic participation of the β-hydroxyl group[2]. Our previous results[2] suggest the formation of a strong intramolecular hydrogen bond or dipol-anion interaction in the monoanions of the diols. A similar intramolecular hydrogen bond favors the external nucleophilic attack on **6** leading to the transition state **7** differentially microsolvated by the neighboring hydroxyl group and thus stabilized in organic media by a stronger than in **6** hydrogen bond (Scheme 4, path 4.1). The departure of the leaving diol system to give **4** is then not surprising since 1,2-diols are more acidic than mono-ols[13].



13

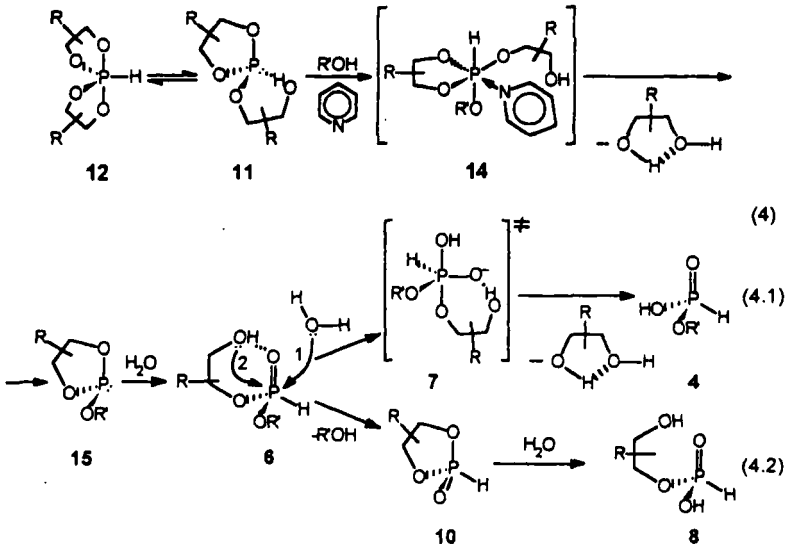


16

CHART

Such a hydrogen bond does not persist in water[14] and the β-hydroxyl is free for the internal nucleophilic attack resulting in the formation of the H-phosphonate **8** (4.2) since aqueous solvation favors the hydrolysis of the cyclophosphite **10**[15].

Therefore, our model experiments suggest that the amount of water present in the reaction mixture is crucial for the effectiveness of the total reaction of phosphonylation (1). On the other hand, the formation of quaternary pyridinium salts **16** (Chart) was found to be a considerable side reaction, a result of the interaction of oxirane with pyridine at high temperatures[16]. This side reaction lowers the effectiveness of the phosphonylation and complicates the purification of the product. The formation of the quaternary pyridinium salt is very intensive in the case of phosphonylation with phosphorous acid / epichlorohydrine ($R=CH_2Cl$)[16]. This side reaction can be easily avoided if the phosphorous acid and the oxirane are allowed to react at 80°C for 90 min to give the active esters and the



SCHEME 4

spirophosphorane **12** (3). The alcohol and pyridine are added then and the reaction mixture has to be heated for an additional 90 min.

In conclusion, the hydrotetraoxaspirophosphoranes are possible intermediates in the reaction of phosphonylation with phosphorous acid / oxirane. They are formed by the interaction of phosphorous acid / oxirane and provide the alkylene β-hydroxyalkyl phosphite, reactive in the phosphonylation reaction. The reaction of the latter with alcohol gives the corresponding alkyl alkylene phosphite, which is further hydrolyzed to alkyl β-hydroxyalkyl H-phosphonates. β-Hydroxyalkyl H-phosphonate diesters are important model compounds in the studies of the ribozyme catalytic mechanism. Our results suggest, that the phosphonylation with phosphorous acid / oxiranes requires meticulously dried solvents and the presence of two equivalents of water in the reaction mixture. It is more easily controlled if the reactions of accumulation of spirophosphorane and of transesterification / hydrolysis are carried out separately.

EXPERIMENTAL

Commercial solvents and reagents were used as received unless otherwise noted. Dioxane was dried over sodium. Pyridine was dried over sodium hydroxide and distilled over calcium hydride before use. ^{31}P NMR spectra were taken on a Bruker DRX-250 spectrometer. ^{31}P chemical shifts are reported in δ(ppm) downfield (+) and upfield (-) from external 85% H_3PO_4. The assignment of the signals is based on literature data.

Reaction of phosphorous acid with oxirane

Fifty milliliters of ethylene oxide (**3**, R = H) were warmed to room temperature and the resulting vapor was dried and bubbled into a solution of phosphorous acid (1.00 g, 11.9 mmol) in 4 ml of dry dioxane. After stirring for 4 hours at room temperature, the resulting mixture was heated at 80°C for 2.5 hours. The reaction mixture was subjected to ^{31}P NMR analysis without further purification. The ^{31}P NMR (100 MHz, dioxane, 25°C, P-H decoupling) spectrum is shown on Figure 1a: δ = 128.0, ethylene β-hydroxyethyl phosphite (2-(2′-hydroxyethoxy)-1,3,2-dioxaphospholane) (**11**, R = H), 1% yield; δ = 21.3, ethylene H-phosphonate (2-oxo, 1,3,2-dioxaphospholane) (**10**, R = H), 4% yield; δ = 10.1, di-(β-hydroxyethyl) H-phosphonate (**9**, R = H), 67% yield; δ = 8.1, β-hydroxyethyl H-phosphonate (**8**, R = H), 10% yield; δ = 5.8, phosphorous acid (**2**), 1% yield; δ = −22.9, 1,4,6,9-tetraoxa-5λ^5-phosphaspiro[4,4]nonane (**12**, R = H), 17% yield.

Reaction of phosphorous acid with epichlorohydrine in dioxane

To a solution of 2.04 g (24.4 mmol) phosphorous acid in 10 ml dioxane 6.00 ml (7.08 g, 76.5 mmol) epichlorohydrine were added dropwise for 30 min. The resulting mixture was stirred for 30 min at room temperature and was heated at 80°C for 2 h. The reaction mixture was subjected to ^{31}P NMR analysis without further purification. The ^{31}P NMR (100 MHz, dioxane, 25°C) spectrum is shown on Figure 1b: δ = 25.1 (dm, $J_{P\text{-}H}$ = 742.1 Hz) and δ = 24.9 (dm, $J_{P\text{-}H}$ = 742.1 Hz), 2-oxo-4-chloromethyl-1,3,2-dioxaphospholane (3-chloro-1,2-propylene H-phosphonate) (**10**, R = CH_2Cl), two multiplets, indicating two groups of spectroscopically distinguishable isomers, 8% yield; δ = 11.1 (dm, $J_{P\text{-}H}$ = 726.2 Hz),

δ = 10.1 (dm, $J_{P\text{-}H}$ = 731.5 Hz), and δ = 9.2 (dm, $J_{P\text{-}H}$ = 737.0 Hz), di-(β-hydroxyl) H-phosphonate diesters (**9**, R = CH_2Cl – di-(3-chloro-2-hydroxypropyl) H-phosphonate, 3-chloro-2-hydroxypropyl 3-chloro-1-hydroxypropane-2-yl H-phosphonate, and di-(3-chloro-1-hydroxypropane-2-yl) H-phosphonate), 78% yield; δ = 9.3 (dt, $J_{P\text{-}H}$ = 702.8 Hz, $J_{P\text{-}O\text{-}C\text{-}H}$ = 9.0 Hz), 3-chloro-2-hydroxypropyl H-phosphonate and δ = 8.3 (dd, $J_{P\text{-}H}$ = 723.0 Hz, $J_{P\text{-}O\text{-}C\text{-}H}$ = 10.0 Hz), 3-chloro-1-hydroxypropane-2-yl H-phosphonate (**8**, R = CH_2Cl), 8% yield; δ= –22.9 (dm, $J_{P\text{-}H}$ = 845.6 Hz), R-derivative of 1,4,6,9-tetraoxa-5λ^5-phosphaspiro[4,4]nonane (**12**, R = CH_2Cl), a group of five closely situated signals indicating five spectroscopically distinguishable isomers, 6% yield.

Reaction of phosphorous acid with epichlorohydrine in pyridine / dioxane

To 0.8 ml of the reaction mixture of phosphorous acid with epichlorohydrine in dioxane were added 1.2 ml pyridine. The resulting mixture was heated at 80°C for 2 h. The reaction mixture was subjected to ^{31}P NMR analysis without further purification. The ^{31}P NMR (100 MHz, pyridine / dioxane, 25°C) spectrum is shown on Figure 1c: δ = 129.0, 3-chloro-1,2-propylene 3-chloro-2-hydroxypropyl phosphite (**11**, R = CH_2Cl), 1% yield; δ = 23.9 (dm, $J_{P\text{-}H}$ = 729.0 Hz) and δ = 23.7 (dm, $J_{P\text{-}H}$ = 729.0 Hz), 2-oxo-4-chloromethyl-1,3,2-dioxaphospholane (3-chloro-1,2-propylene H-phosphonate) (**10**, R = CH_2Cl), two multiplets, indicating two groups of spectroscopically distinguishable isomers, 5% yield; δ = 10.6 (dm, $J_{P\text{-}H}$ = 712.4 Hz) and δ = 9.8 (dm, $J_{P\text{-}H}$ = 707.9 Hz), di-(β-hydroxyl) H-phosphonate diesters (**9**, R = CH_2Cl-di-(3-chloro-2-hydroxypropyl) H-phosphonate and 3-chloro-2-hydroxypropyl 3-chloro-1-hydroxypropane-2-yl H-phosphonate), 29% yield; δ = 6.2 (dt, $J_{P\text{-}H}$ = 625.9 Hz, $J_{P\text{-}O\text{-}C\text{-}H}$ = 9.7 Hz), 3-chloro-2-hydroxypropyl H-phosphonate and δ = 4.8 (dd, $J_{P\text{-}H}$ = 630.9 Hz, $J_{P\text{-}O\text{-}C\text{-}H}$ = 10.4 Hz), 3-chloro-1-hydroxypropane-2-yl H-phosphonate (**8**, R = CH_2Cl), 44% yield; δ = –22.8 (dm, $J_{P\text{-}H}$ = 847.2 Hz), R-derivative of 1,4,6,9-tetraoxa-5λ^5-phosphaspiro[4,4]nonane (**12**, R = CH_2Cl), a group of five closely situated signals indicating five spectroscopically distinguishable isomers, 21% yield.

Acknowledgements

This work was partially supported by the National Research Fund (Project K-625).

References

[1] S. B. Tzokov, I. T. Devedjiev, E. K. Bratovanova, D. D. Petkov, *Angew. Chem. Int. Ed. Engl.*, **33**, 2302 (1994).
[2] S. B. Tzokov; R. T. Momtcheva, N. G. Vassilev, J. Kaneti, D. D. Petkov, *J. Am. Chem. Soc.*, **121**, 5103–5107 (1999).
[3] T. R. Cech, The RNA World, R. Gesteland, J. Atkins, Eds. (Cold Sprin Harbor Laboratory Press, New York, 1993), Chap. 11, pp. 239–269.
[4] S. B. Tzokov, I. T. Devedjiev, D. D. Petkov, *J. Org. Chem.*, **61**, 12 (1996).
[5] I. T. Devedjiev, G. Borisov, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **53**, 37 (1990).
[6] T. Biela, R. Szymanski, P. Kubisa, *Makromol. Chem.*, **193**, 285 (1992).
[7] T. Biela, P. Kubisa, S. Penczek *Makromol. Chem.*, **193** 1147 (1992).
[8] R. Burgada, D. Houlla, R. Wolf, *C. R. Acad. Sci. Ser. C*, **264**, 356 (1967).
[9] G. R. J. Thatcher, R. Kluger, *Adv. Phys. Org. Chem.*, **25**, 99 (1989).
[10] L. V. Nesterov, R. A. Sabirova, N. E. Krepisheva, R. I. Nutalapova, *Dokl. Acad. Nauk*, **148**, 1085 (1963).
[11] D. Bernard, C. Laurenco, R. Burgada, *J. Organomet. Chem.*, **47**, 113 (1973).
[12] E. L. Gefter, *Zh. Obsch. Khim.*, **26**, 1440 (1956).
[13] J. Hine, M. Hine, *J. Am. Chem. Soc.*, **74**, 5266 (1952).
[14] A.J. Kirby, *Acc. Chem. Res.*, **30**, 290 (1977).
[15] A. Dejaegere, X. Liang, M. Karplus, *J. Chem. Soc. Faraday Trans.*, **90**, 1763 (1994).
[16] V. S. Garkusha-Bozhko, O. P. Shvaika, *Khim. Geterotsikl. Soedin.*, 507 (1990).