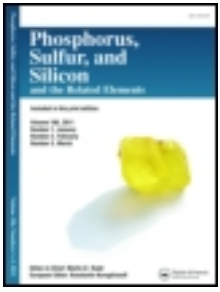


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

RETRO ABRAMOV VS. REARRANGEMENT PATH COMPETITION IN HYDROXYPHOSPHONATE DECOMPOSITION

Roman Gancarz [a] , Irena Gancarz [b] & Agnieszka Deron [a]

[a] Institute of Organic Chemistry, Biochemistry and Biotechnology, Wybrże Wyspiańskiego 27, 50-370, Wroczaw, Poland

[b] Institute of Organic Technology and Plastics, Technical University of Wrochw, Wybrże Wyspiańskiego 27, 50-370, Wroczaw, Poland

Version of record first published: 04 Oct 2006

To cite this article: Roman Gancarz, Irena Gancarz & Agnieszka Deron (2000): RETRO ABRAMOV VS. REARRANGEMENT PATH COMPETITION IN HYDROXYPHOSPHONATE DECOMPOSITION, Phosphorus, Sulfur, and Silicon and the Related Elements, 161:1, 61-69

To link to this article: http://dx.doi.org/10.1080/10426500008042095

Phosphorus, Sulfur and Silicon, 2000, Vol. 161, pp. 61-69
Reprints available directly from the publisher
Photocopying permitted by license only

RETRO ABRAMOV VS. REARRANGEMENT PATH COMPETITION IN HYDROXYPHOSPHONATE DECOMPOSITION

ROMAN GANCARZ[a*], IRENA GANCARZ[b] and AGNIESZKA DERON[a]

[a]*Institute of Organic Chemistry, Biochemistry and Biotechnology and* [b]*Institute of Organic Technology and Plastics, Technical University of Wrocław, Wybrzeże Wyspiańskiego 27. 50–370 Wrocław, Poland*

(Received August 24, 1999; In final form September 21, 1999)

1-hydoxyphosphonates in the presence of aliphatic amine undergo two competitive processes: retro Abramov reaction and intramolecular hydroxyphosphonate-phosphate rearrangement. Both reaction rates and their ratio strongly depend on the nature of the substituent on a alpha carbon atom. Kinetic experiments indicate that two reactions proceed via common transition state.

Keywords: phosphonic acids and derivatives; rearrangement; mechanisms

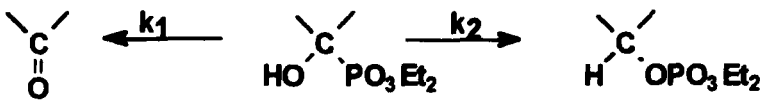
1-Hydroxyalkanephosphonic acids and their esters are compounds of significant biological and pharmaceutical interest[1]. They have been shown to inhibit the enzymes renin[2], ESPS synthase[3], HIV protease[4], and PTPase[5], antiviral compound[6]. In addition, 1-hydroxyphosphonates are atractive as substrates for synthesis of various derivatives of other substituted phosphonates and phosphonic acids. Their usefulness in the recovery and separation processes of some metal ions is also well known[7–12].

One of the most general method of their synthesis is the Abramov reaction and its Pudovik's modification[13–17].

Methods, where the addition of phosphite to carbonyl compound is catalysed by the aluminium oxide, potassium fluoride or both of them are also used[18,19].

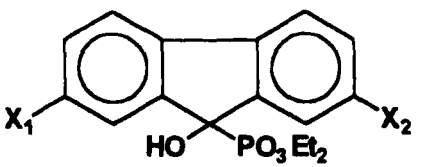
* Correspondence Author

Recently we have published the results of our studies on the reversibility of hydroxyphosphonate formation[20,21]. It was shown that in basic media there are two possible ways of hydroxyphosphonate decomposition. The first one, called retro-Abramov reaction, gives as a result carbonyl compound and dialkyl phosphite. In the second one the rearrangement to the phosphate takes place. Both reactions are shown in the scheme below.



The aliphatic hydroxyphosphonates decompose almost exclusively to the carbonyl compound (route 1) whereas the aromatic ketones undergo almost quantitatively the rearrangement towards the corresponding phosphates (route 2).

In order to study these two competitive processes more carefully and to determine why the reaction proceeds sometimes in one and sometimes in other direction, we have done basic kinetic experiments on the model compounds[21]. Since it is the continuation of the studies which have been published in polish journal, some of the major conclusions from the last one are summarized below.



$X_1, X_2 = H, Br, MeO, NO_2$

9-hydroxy-9-fluorenylphosphonates were chosen as model compounds for several reasons. The whole molecule is relatively rigid and the conformational changes around the reaction center for two different substituents could be neglected. The substituents are relatively far away from the reaction center thus they should not influence the course of the reaction, so the steric effects could be ruled out. Thus we can assume that all observed kinetic changes are caused by the electronic effect of the substituents. Last but not least, all compounds were readily available[20].

The kinetic of hydroxyphosphonate decomposition was studied[21] by monitoring the changes of the absorption of the carbonyl group of the corresponding ketone, produced from the hydroxyphosphonate. Knowing the extinction coefficient of the pure ketone, its concentration in the reaction mixture could be estimated as the ratio of the extinction observed (E_{obs}) and the one calculated assuming complete conversion of the hydroxyphosphonate ester to the ketone($E_{100\%}$). These calculations are valid only if the absorption in the visible part of the spectrum come solely from the ketone (fluorenone).

$$c_{ketone} = \frac{E_{obs}}{E_{100\%}}$$

Three different amines were used as catalysts: triethylamine, butylamine and quinuclidine. In the applied conditions the Abramov reaction i.e. formation of hydroxyphosphonate from the ketone and phosphite is very slow[21] and can be neglected. In most cases the saturation curves were observed. It meant that part of the hydroxyphosphonate was converted to the phosphate and the other part decomposed to the carbonyl compound. No further changes appeared in the reaction mixture even after several days. Thus amount of the ketone formed in the reaction mixture is connected to the ratio of the rate constants k_1 and k_2(on the scheme) according to the equation:

$$\frac{k_1}{k_2} = \frac{E_{obs}}{E_{100\%} - E_{obs}}$$

The ratios k_1/k_2 calculated from the saturation curves are presented in the Table I.

TABLE I The ratios k_1/k_2 calculated from the saturation curves

Fluorene derivative	k_1/k_2		
	Quinucklidine	*Butylamine*	*Triethylamine*
2,7-dimethoxy	0.68	0.37	0.23
2-methoxy	0.45	0.23	0.21
not substituted	0.33	0.17	0.17
2,7-dibromo	0.13	0.03	0.02

The retro-Abramov reaction is preferred when the electrondonating substituents appear in the fluorene molecule and when stronger amines were used (Table I). This is in a good agreement with the previously obtained data[20] showing that aliphatic hydroxyphosphonates almost exclusively undergo retro-Abramov reaction whereas aromatic hydroxyphosphonates decompose mainly to phosphates.

In the present paper we repeated some of the above experiments, monitoring the reaction by ^{31}P-NMR This was especially important for the bromo and nitro compound, since in this case the absorption in the visible part of the spectrum did not come from the ketone only.

^{31}P NMR technique allows more detailed analysis of the above process. Monitoring of the concentration changes of different species in the ^{31}P-NMR spectra one can easily measure not only the ratio of k_1 and k_2 but also their absolute values (Table II).

RESULTS AND DISCUSSION

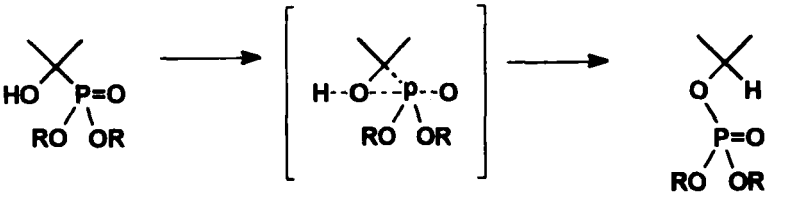
The observed reaction rates for Retro Abramow (k_1) and rearrangement (k_2) obtained by ^{31}P-NMR are collected in Table II.

TABLE II The observed reaction rates for Retro Abramow (k_1) and rearrangement (k_2) obtained by ^{31}P-NMR

	CH_3O,CH_3O	*H,H*	*H,Cl*	*H,NO_2*
k_1	0.000216	0.0144	0.00505	0.0098
k_2	0.000499	0.0558	0.0720	0.9802
k_1/k_2	0.43	0.20	0.07	>0.01

Data from the table II supports earlier conclusion[21] that the more electrondonating group, the faster the total decomposition of the hydroxyphosphonate and the greater the ratio of rearrangement reaction rate with respect to retro -Abramow is observed.

The intramolecular mechanism via three memebered cyclic intermediate was proposed for the rearrangement of hydroxyphosphonate to phosphate[22].



If the reaction proceds via a three membered ring intermediate it should be characterised by negative reaction entropy.

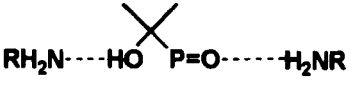
We have run the kinetics in three different temperatures for the 2-nitro compound. This allowed us to estimate the enthalpy and entropy of activation. Values of −1,36 eu. for the Retro-Abramov and −11,91 eu. for the rearrangement reaction were found. Enthalpy of the reaction was 19.73 and 15.77 kcal/mol for the route 1 and 2 respectively. High negative entropy values for the rearrangement reaction indicates that the reaction is intramolecular indeed. Low entropy of activation for the retro Abramov reaction suggests that it is probably a second order reaction.

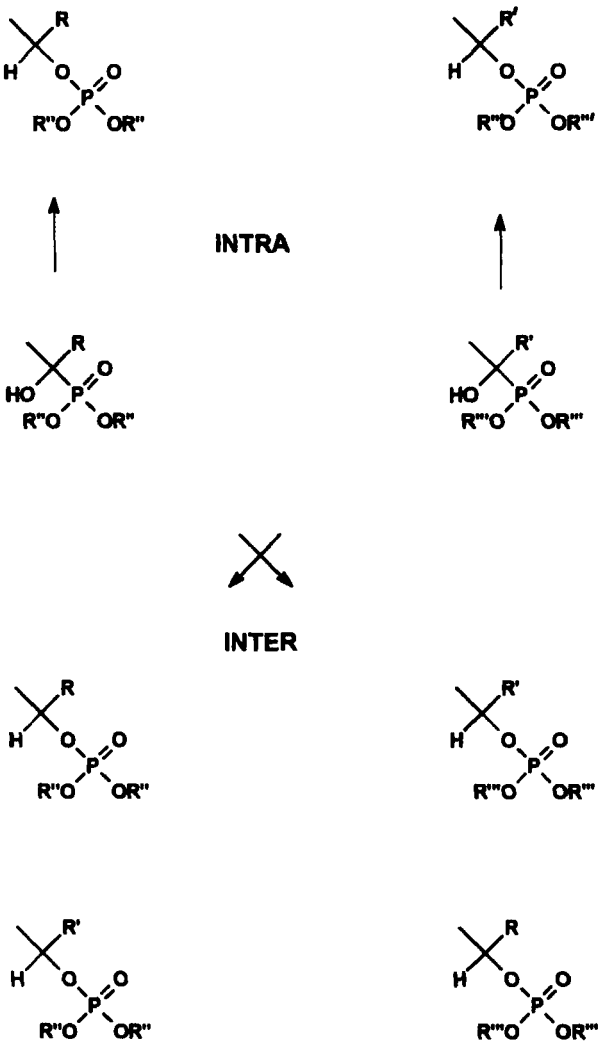
To confirm the intramolecular mechanism of the rearrangement we set up another experiment in which we have monitored the kinetics of the decomposition of the mixture of two different hydroxyphosphonates of similar rearrangement reaction rates for them. The reactions were run in chloroform in the presence of butylamine and the change of the ^{31}P-NMR signals were monitored.

For the intramolecular reaction one should observe the formation of only two phosphates, one from each hydroxyphosphonate. In other case we should observe two additional mixed phosphates (See Scheme on the next page).

Since we did not observe even traces of mixed phosphates the conclusion is that within the limits of the accuracy of NMR technique, the reaction is intramolecular.

We have postulated previously[20], that hydrogen bonds on both hydroxyl and phosphoryl group may increase the polarization of the bonds and thus facilitate the rearrangement reaction via the postulated intermediate.





The hypothesis of the great role of hydrogen bonds was suported by comparison of the reaction rates in the presence of $BuNH_2$ and TEA in methylene chloride and ethanol[20]. In chloroform, the reaction with TEA was about 50 times slower than that for $BuNH_2$ (1.79±0.05 and

$82\pm0.47x10^{-5}$, respectively) whereas only about 10 times slower when ethanol was used as a solvent (29.9 ± 0.03 and $370\pm0.03x10^{-5}$). Triethylamine can act only as a base and contrary to butylamine is not able to form a hydrogen bond with the phosphoryl oxygen. In ethanol, the activation of the phosphoryl group is realised mainly by the solvent, thus the differences in the reaction were due to basisity and steric factors of the amines used. This explains also the low value of enthropy for the retro Abramov reaction.

We have also found that the reaction rate is strongly depended on the size of substituents at the phosphorus atom. Table III presents kinetics data for three different esters of the same 9-hydroxyfluorene-9-phosphonic acid. The striking changes are observed when the methyl or ethyl group is replaced by the sterically demanding isopropyl group.

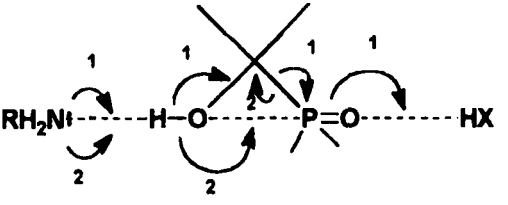
TABLE III Reaction rates as a function of the size of substituents at the phosphorus atom

	CH_3	C_2H_5	iC_3H_7
k_1	0.117	0.0538	0.00078
k_2	0.022	0.0134	0.00054
k_2/k_1	5.5	4	1.44

CONCLUSIONS

Low and negative reaction enthropy as well as the results of the cross reaction experiment strongly indicates that phosphonate phosphate rearrrangement induced by the amines is intramolecular. The three membered ring transition state, proposed in the literature, should yield a highly crowded molecule so the steric factors should be important. Our results are consistent with such a situation (Table III). Replacing the methyl group by ethyl, decreases the reaction rate by a factor close to 2 while the decomposition of sterically hindered diisopropyl esters is thousand times slower. It is unexpected and very important in consideration of the reaction mechanism that the steric factors slowed down both reactions-retro Abramov and the rearrangement one – by a similar degree. This may suggest that both reactions proceed via the same transition state. The differences of the reaction rates in protic and aprotic solvents with "protic" and "aprotic" amines of

comparable basicity, as described above, suggest that the transition state or intermediate forms hydrogen bonds with other solution components. The negative entropy term for retro Abramov elimination indicates that this reaction proceeds via a highly organised structure, probably a pentacoordinated transition state or intermediate. All above experimental facts allows us to propose the following structure of the transition state:



Decomposition of that transition state can follow the route 1 (retro Abramov) or 2 (rearrangement). Route 2 will predominate if the stability of the resulting carbanion like structure is relatively stable. It explaines why the presence of the electronatracting substituents or carbanion stabilizing groups on the carbon side of the P-C bond facilitates the rearrangment reaction over the retro Abramov.

Route 2 is a nucleophilic substitution at the phosphorus atom. The generally accepted mechanism for this type of reaction is S_N2 in line process[23]. A classic S_N2 mechanism requires the linear arrangement of nucleophile, P, and leaving group and also entering and leaving group are simultaneously apical. This is not possible because the reaction was found to be intramolecular. Thus an addition-elimination process with a pentacovalent intermediate undergoing one or several pseudorotation is probably involved in this case. The studies on the mechanism of this reaction will be continued and the results shell be a subject of separate publications.

EXPERIMENTAL PART

All spectra were taken on a Bruker Avance DRX 300MHz instrument. Hydroxyphosphonates were prepared by a method described earlier.

Kinetic experiments

Kinetic experiment were performed in a NMR tube. To a mixture of hydroxyphosphonate in the appropriate solvent the amine was added by the microsyringe and after mixing the reactants, the tube was placed in the NMR instrument and the 31P, 1H-NMR spectra were taken at certain time. During the whole kinetic experiment the tube resided in the NMR instrument.

Acknowledgements

This work was supported by a grant from Komitet Badań Naukowych.

References

1. T. Nagase, T. Kawashiwa, N. Inamato, Chem. Lett., 1997 (1984).
2. D.V Patel, K. Rielly-Gauvin, D.E. Ryono, Tetrahedron Lett., **31**, 5587 (1990).
3. D.V. Patel, K. Rielly-Gauvin. D.E. Ryono, Tetrahedron Lett., **31**, 5591 (1990).
4. J.A. Sikorski, M.J. Miller, D.S. Braccolino, D.G. Cleary, S.D. Corey, J.L Font, K.J. Gruys, C.Y. Han, K.C. Lin, P.D. Pansegrau, J.E. Ream, D. Schnur, A Shah, M.C. Walker, Phosphorus, Sulfur, and Silicon, **76**, 115 (1993).
5. B. Stowasser, K.H. Bundt, L. Jian-Qi, A. Peyman, D. Ruppert, Tetraedron Lett., **33**, 6625 (1989).
6 T.R. Burke, J.J. Barchi, C. George, G. Wolf, S.E. Shoelson, X.J. Yan, Med. Chem., **38**, 1386 (1995).
7. E.K. Baylis, Eur. Pat. Appl. EP 614, 900 (1994).
8. J.C. Martin, Nucleoside Analogues as Antiviral Agents; ACS Symp. Ser. No. 401. Am. Chem. Soc. Washington, DC, (1989).
9. F. Hammershmidt, H. Vollenkle, Liebigs Ann. Chem., 577 (1989).
10. T. Yokomatsu, S. Shibuya, Tetrahedron: Asymmetry **3**, 377 (1992).
11. P.G. Baraldi, M. Guarneri, F. Moroder, G.P. Pollini, D. Simoni, Synthesis. 653 (1992).
12. L. Maier, Phosphorus, Sulfur, and Silicon, **76**, 119 (1993).
13. E. Ohler, S. Kotzinger, Synthesis. 497 (1993).
14. C.K. McClure, P.K. Mishra, C.W. Grote, J. Org. Chem. **62**, 2437 (1997).
15. V.S. Abramov, Zh. Obshch. Khim. **22**, 647. (1952).
16. A.N. Pudovik, I.V. Konovalova, Synthesis, 81 (1979).
17. H. Wynberg, A. Smaardijk, Tetrahedron Lett. **24**, 5899 (1983).
18. F. Texier-Boullet, A. Foucaud, Synthesis, 916 (1982).
19. F. Texier-Boullet, A. Foucaud, Synthesis, 165 (1982).
20. R. Gancarz, I. Gancarz, U. Walkowiak, Phosphorus, Sulphur and Silikon **104**, 45 (1995).
21. R. Gancarz, Scientific Papers of the Institute of Organic Chemistry, Biochemistry and Biotechnology of the Wrocław University of Technology. No 39. Oficyna Wydawnicza Politechniki Wrocławskiej, Wrocław (1997).
22. V.S. Abramov, Y.A. Bochkova, A.D. Polyakova, Zhur. Obsch. Khim. **23**, 1013 (1953).
23. J. Li, P. Beak, J. Am. Chem. Soc. **114**, 9206 (1992), and references cited therein.