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## RETRO ABRAMOV VS. REARRANGEMENT PATH COMPETITION IN HYDROXYPHOSPHONATE DECOMPOSITION

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1-hydroxyphosphonates 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<sup>1</sup>. They have been shown to inhibit the enzymes renin<sup>2</sup>, ESPS synthase<sup>3</sup>, HIV protease<sup>4</sup>, and PTPase<sup>5</sup>, antiviral compound<sup>6</sup>. In addition, 1-hydroxyphosphonates are attractive 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<sup>7-12</sup>.

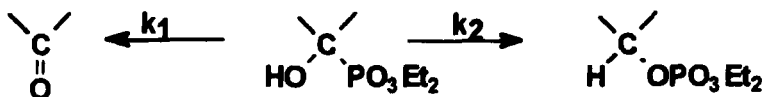
One of the most general method of their synthesis is the Abramov reaction and its Pudovik's modification<sup>13-17</sup>.

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

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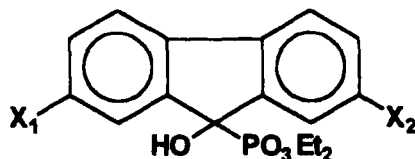
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Recently we have published the results of our studies on the reversibility of hydroxyphosphonate formation<sup>20,21</sup>. It was shown that in basic media there are two possible ways of hydroxyphosphonate decomposition. The first one, called retro-Abramov 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<sup>21</sup>. 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.



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<sup>20</sup>.

The kinetic of hydroxyphosphonate decomposition was studied<sup>21</sup> 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<sup>21</sup> 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	$k_1/k_2$		
	Quinuclidine	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 electron-donating 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<sup>20</sup> 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 <sup>31</sup>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.

<sup>31</sup>P NMR technique allows more detailed analysis of the above process. Monitoring of the concentration changes of different species in the <sup>31</sup>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

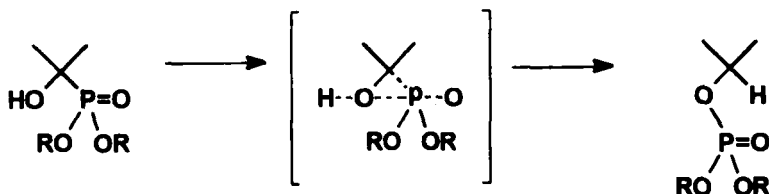
The observed reaction rates for Retro Abramow ( $k_1$ ) and rearrangement ( $k_2$ ) obtained by <sup>31</sup>P-NMR are collected in Table II.

TABLE II The observed reaction rates for Retro Abramow ( $k_1$ ) and rearrangement ( $k_2$ ) obtained by <sup>31</sup>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<sup>21</sup> that the more electron-donating 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 membered cyclic intermediate was proposed for the rearrangement of hydroxyphosphonate to phosphate<sup>22</sup>.



If the reaction proceeds 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.

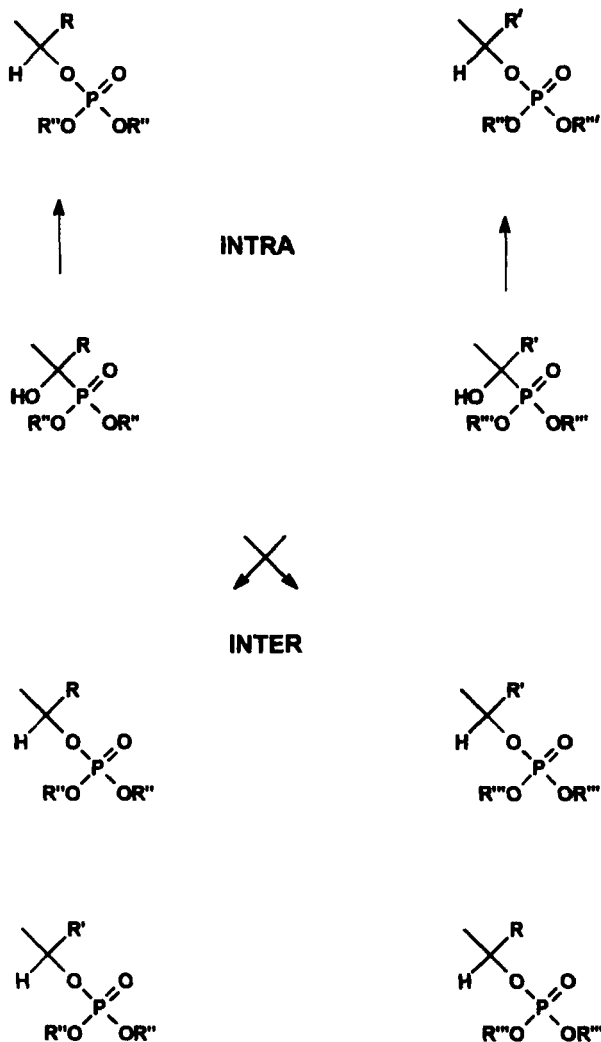
To confirm the intramolecular mechanism of the rearrangement we set up another experiment in which we have monitored the kinetics of the decomposition of the mixture of two different hydroxyphosphonates of similar rearrangement reaction rates for them. The reactions were run in chloroform in the presence of butylamine and the change of the  $^{31}\text{P}$ -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<sup>20</sup>, 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 supported by comparison of the reaction rates in the presence of  $BuNH_2$  and TEA in methylene chloride and ethanol<sup>20</sup>. In chloroform, the reaction with TEA was about 50 times slower than that for  $BuNH_2$  ( $1.79 \pm 0.05$  and

$82 \pm 0.47 \times 10^{-5}$ , respectively) whereas only about 10 times slower when ethanol was used as a solvent ( $29.9 \pm 0.03$  and  $370 \pm 0.03 \times 10^{-5}$ ). 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 basicity and steric factors of the amines used. This explains also the low value of enthalpy 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

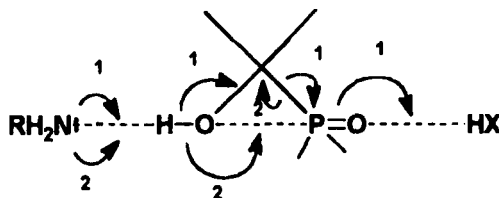
	$CH_3$	$C_2H_5$	$iC_3H_7$
$k_1$	0.117	0.0538	0.00078
$k_2$	0.022	0.0134	0.00054
$k_2/k_1$	5.5	4	1.44

## CONCLUSIONS

Low and negative reaction enthalpy as well as the results of the cross reaction experiment strongly indicates that phosphonate phosphate rearrangement 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 explains why the presence of the electronegative substituents or carbanion stabilizing groups on the carbon side of the P-C bond facilitates the rearrangement 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<sup>23</sup>. 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 shall 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  $^{31}\text{P}$ ,  $^1\text{H}$ -NMR spectra were taken at certain time. During the whole kinetic experiment the tube resided in the NMR instrument.

### *Acknowledgements*

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