On the mechanism of solvolysis of orthophosphoramidates

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The data on the solvolysis of orthophosphoramidates are collected and rationalized into two groups: a mechanism involving a unimolecular decomposition of the compounds where nitrogen contains a positive charge, and a bimolecular one for molecules with uncharged nitrogen involving the entering and leaving groups at right angles to each other. The first mechanism is invoked for all acid catalyzed reactions and the decomposition of monoamidophosphoric acid, the second for all monoamion acids except monoamidophosphoric and possibly the N-arylphosphoramidic.

In the past years much work has been done on the solvolysis of phosphoramides but there is still, however, considerable uncertainty as to how the data may be explained. This paper presents a system which appears to satisfy all of the data. In order to do this it is necessary to postulate two mechanisms: one for compounds with uncharged nitrogen, and one for those where the nitrogen atom carries a positive charge.

From the work of Halmann, Lapidot and Samuel 1–5 the role played by the ability of the nitrogen to carry a positive charge has become clear. They showed that when the group attached to nitrogen is very electronegative, e.g. sulphonyl 4, phosphoryl 5 or carbonyl 1–3, there is little or no acid catalysis and the monoamions decompose faster than the uncharged acids. However, monoamidophosphate 5 (MAP: PO₃NH₂²⁻) is very readily acid catalyzed and its acid decomposes intrinsically faster than the monoanion. Chanley and Feageson 6, 7 have shown that arylamido-phosphates are also readily acid catalyzed but whether the acids behave like MAP or the acyl AP’s is one of the points of interpretation still contentious.

Jencks and Gilchrist 8 have studied various catalyzed reactions of MAP characterized by the formation of intermediates with positively charged nitrogen which then rapidly decompose in a manner similar to MAP acid, especially with respect to product distribution in mixed solvents.

From these works a clear division may be thus drawn:

a. Positively charged nitrogen: all acid catalyzed reactions; acid of MAP.

b. Uncharged nitrogen: acids and monoamions of N acyl, N phosphoryl and N sulphonylphosphoramidates, monoamions of arylamidophosphates.

At first glance it is not easy to see where MAP monoanion or the acid forms of Naryl compounds come. These can thus serve as a test of any hypotheses drawn from the rest of the data.

Positively charged nitrogen

Jencks and Gilchrist 8 have shown that there is no further catalysis by fluoride or pyridine of the decomposition of MAP catalyzed by formaldehyde or hypochlorite, unlike the monoamions which are so catalyzed 7. This would seem to indicate a decomposition independent of the attacking group, but the distribution of products in mixed solvents does not seem to bear out a unimolecular step going to an unstable intermediate which would react non-selectively with the solvent. For instance 7 in 50% methanol (29.2 mole-%) MAP gives only 8% methyl ester

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6 J. D. Chanley and E. Feageson, J. Amer. chem. Soc. 80, 2686 [1958].

7 J. D. Chanley and E. Feageson, J. Amer. chem. Soc. 85, 1181 [1963].

8 W. P. Jencks and M. Gilchrist, J. Amer. chem. Soc. 86, 1410 [1964].
from the acid catalyzed reaction, whilst \( N-p \)-chlorophenyl AP gives 27\%; and in 50\% ethanol (27.4 mole\-%) MAP gives under 10\% and the aryl compound 13\% ester. In 2 M sodium fluoride solution MAP gives a yield of 70\% fluorophosphate\(^5\).

Of interest too are the entropies of activation (see table), being quite large and negative, normally considered characteristic of a reaction leading to an increase in the number of particles going from the reagents to the transition state.

It has also been reported that in \( D_2O \) the rate increases 1–4 times for MAP\(^5\) and 1–2 times for the acid catalyzed reaction of \( N \)-Benzoyl AP\(^3\), whilst aqueous dioxan causes carboxyaryl APs to react rather slower than in water alone\(^9\). The acid catalyzed decomposition of \( (\text{MeO})_2\text{PONH}_2 \)\(^{10}\) is over four times slower in 50\% methanol than in water and yields only 12\% methylated products whilst the mono \( O \)-methyl ester is only 20\% slower in 50\% Methanol or dioxan\(^{10}\).

The reaction of the phosphoramidate by a rate-determining unimolecular step followed by a rapid reaction of the intermediate (the so-called “metaphosphate” intermediate) with its immediate solvation shell explains all these observations.

\[
\begin{align*}
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\text{OR'} & \quad \text{OR'} \quad \text{OR'} \\
\text{OR'} & \quad \text{OR'} \quad \text{OR'}
\end{align*}
\]

The negative entropy of activation is caused by an increased number of particles (the transition state being similar to the intermediate): the slower rate in less polar solvents by the destabilization of the more highly charged intermediate: the increased rate in \( D_2O \) is to be expected as a second order effect, \( \text{NH}_2\text{R} \) and \( \text{ND}_2\text{R} \) being different leaving groups, and hence as \( \text{ND}_2 \) is even more different from \( \text{NH}_2 \) it is MAP that has the largest isotope effect. Only the solvent distribution is questionable, but if the metaphosphate is as unstable as its elusiveness would suggest (it has often been postulated but never proved) then it would react not with the bulk solution but with its solvation shell (which will not be far different from that of the parent amidophosphate). Thus the smaller, more highly charged MAP would be expected to have a solvation shell containing an abnormally high proportion of the more electronegative solvent components: water in preference to alcohols, fluoride ion in preference to water etc. The larger arylamido compounds would have a more delocalized charge and hence give a much more equitable product distribution just as is found. This larger charge delocalization explains too why their rate is decreased in nonaqueous solvents more than MAP\(^9\),\(^7\), the change in polarity on going to the intermediate is greater for them.

**Uncharged Nitrogen**

Chanley and Feageson\(^7\) have reported the reactions of the monoanions of both \( N-p \)-chlorophenyl AP and MAP as being catalyzed by tertiary bases except alpha substituted ones which appear to be too sterically hindered. This would immediately suggest a bimolecular mechanism. The entropies of activation (see table) also bear this out, being of the order \(+5\) – \(+15\) e.u. corresponding to an increase in the ordering of the system.

It is most surprising however, that the monoanions decompose faster than the uncharged acids\(^1\)–\(^4\), although the dianions are quite stable, for one would imagine the negative charge to have a repellent effect on any nucleophilic reagent. The uptake of \(^1^8\)O from \( \text{H}_2\text{^18O} \) has been shown to be one in four\(^2\) so no reversible reaction can be taking place. In \( D_2O \) all the Naryl AP\(^1\)–\(^4\),\(^6\),\(^7\) monoanions decompose faster by 20\% or so, but MAP monoanion decomposes at the same rate\(^5\) or slower\(^7\). In dioxan the rates are slowed, except again for MAP which is slightly faster\(^7\). Product distributions in mixed solvents are quite asymmetric, \( N-p \)-chlorophenyl AP in 29 mole\-% \( \text{MeOH} \) giving nearly 70\% ester whilst in 22 mole\-% ethanol 39\% ester is formed, MAP giving under the same conditions just over 70\% and just under 40\% respectively. Thus the products seem to be determined by the nucleophilicity of the solvating molecule, again suggesting a bimolecular mechanism.

The most puzzling fact is the slowness of the acids to react compared with the monoanions. Because of this it seems that the attacking molecule ignores the charge on the ion. Hence it will approach where the charge is least i.e. at the uncharged edge of the tetrahedron between the protonated hydrogen.
oxygen and the amide group. This would lead to a scheme thus:

$$\text{H}_2 \text{O} \rightarrow \text{R}^+ \text{RNH} \rightarrow \text{X} \rightarrow \text{OH} \rightarrow \text{R}^+ \text{RNH}_2$$

A second reason for postulating such a bent transition state lies in the different characters of phosphorus and carbon. Phosphorus has d orbitals available for bonding, hence the path of minimum potential energy is not necessarily constrained, as for carbon, to a linear entering — leaving group relation, but can allow them to be at right angles. This may also be seen by considering the signs of the wave functions at each lobe of a p orbital: they are opposite, whilst for a d orbital the lobes of opposite sign are perpendicular.

How can this transition state explain the lack of reactivity of the acids? For the monoanions any attack by solvent molecules must be on the uncharged edge, but for acids attack from any direction, to an edge or a face, is possible. Thus the attacking group is not constrained to a favourable position and the reaction should proceed slower. This effect should be especially noticeable in the preexponential factor of the Arrhenius equation, and indeed the lower rates of the neutral species do seem to be due to this (phosphourethane $^2 \Delta S^+ 7.7, 14.4 \text{ e.u.}$, (PhO)$_2$PO-AP $^3 5.8, 13.2 \text{ e.u.}$ for acid and monoanion respectively). Furthermore most molecules not undergoing zwitterionic decomposition have very negative groups attached to nitrogen which will tend to hydrogen bond with the acidic protons and hinder the reaction yet more. This has been invoked to explain the abnormally low reactivity of (PhO)$_2$PO-NH-PO(OH)$_2$.$^9$

Such a transition state would show a preference for stronger nucleophiles, concomitant with the preference for methanol over water, and the catalysis by tertiary bases, whilst being open to steric hindrance: there being no catalysis by the z-substituted bases, or reaction with t-butanol.$^9$ In D$_2$O the reaction would be speeded up, a proton transfer being a contributor to the state, whilst in less polar solvents the rate would decrease, the transition state being more charged than the starting products.

**Conclusion**

The mechanisms proposed above fit all the data except for the two sets left out because they could not "a priori" be ascribed to reaction of a neutral or positively charged nitrogen, namely MAP monoanion and N-aryl acids.

Controversy over whether MAP exists as a zwitterion or not in solution as it does in the solid$^12$ has been going on some while. However the different behaviour in dioxan and D$_2$O from the other monoanions indicates something rather odd, for it is also opposite to the behaviour of the acids. Chanley and Feageson$^7$ have shown that the product distribution may be adequately explained in terms of a bimolecular reaction. The entropy of activation is very low, quite different from both mechanisms. The reaction may possibly fall between both mechanisms, giving a transition state with a much longer PN distance, stabilized by the more basic character of the NH$_2$ group. The proton transfer would then play a less important role in the transition state, so the isotope effect, here causing a decrease of rate in D$_2$O, could be due to quite different reasons, possibly to the solvation of the molecule and transition.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Acid Catalysis</th>
<th>Uncharged Acid</th>
<th>Monoanion</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>phosphourethane</td>
<td>—</td>
<td>7.7</td>
<td>14.4</td>
<td>$^1, 2$</td>
</tr>
<tr>
<td>N-benzyol AP</td>
<td>—</td>
<td>10</td>
<td>7.54</td>
<td>$^3$</td>
</tr>
<tr>
<td>(PhO)$_2$PO.NH.PO(OH)$_2$</td>
<td>—</td>
<td>5.8</td>
<td>13.2</td>
<td>$^3$</td>
</tr>
<tr>
<td>N-Benzenesulphonyl AP</td>
<td>—</td>
<td>—</td>
<td>0.56</td>
<td>$^4$</td>
</tr>
<tr>
<td>MAP</td>
<td>— 14.06</td>
<td>— 18.2</td>
<td>— 1.6</td>
<td>$^7$</td>
</tr>
<tr>
<td></td>
<td>— 21.1</td>
<td>— 20.7</td>
<td>— 0.4</td>
<td>$^{13}$</td>
</tr>
<tr>
<td></td>
<td>— 12.8</td>
<td>—</td>
<td>6.3</td>
<td>$^{6, 7}$</td>
</tr>
</tbody>
</table>

Table I. Entropies of activation (in e. u.) for the hydrolysis of various ionic forms of N-substituted amidophosphates.


state for D$_2$O solvates more strongly than H$_2$O, and this could hinder the reaction. The low entropy of activation is then explicable by there being little net loss or gain in ordering on forming the transition state. As there is less charge separation too, less polar solvents are not so inhibitory and the lesser solvation could then help the reaction. Thus it is seen that MAP monoanion may be fitted convincingly into the reaction scheme.

The N-aryl AP's present a more confused picture. The entropy of activation of N-p-chlorophenyl AP in 50% dioxan at pH 2.8 is given as $-12.6$ e.u. which suggests similarity to the acid catalyzed reaction. But the product distributions in mixed solvents do not change from the monoanion values until below pH 2 (see ref. 7 fig. 3). However interpretation is complicated by overlapping of the acid catalyzed and monoanion regions, so an accurate value of $pK_1$ is needed. Now for MAP this is quoted as 3.00 and 4.6, whilst a measurement taking into account all corrections needed gave 2.72. Thus even for this compound it is not well known; for the N-aryl ones it is even less. On changing to less polar solvents the rates are severely repressed which would suggest some sort of zwitterion depression. Until further evidence as to the zwitterionic contribution to the molecule in solution no firm conclusions can be drawn.

To conclude the reaction scheme given here seems to explain the data on the hydrolysis of phosphoramides, except that some more information on the state of the N-aryl derivatives is needed before a complete interpretation of their reaction can be given.

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