Hydrolysis of α-Keto-phosphate Triesters

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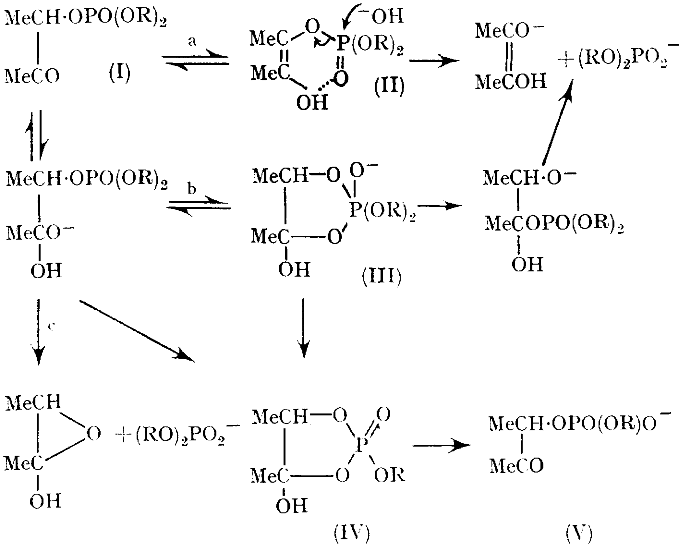
RAMIREZ, HANSEN, and DESAI[1] first noted the rapid base-catalysed hydrolysis of dimethyl phosphoacetoin (I; R = Me) to dimethyl phosphate and acetoin. We record some observations which favour one mechanism and exclude certain other possible ones. The processes considered are:



The bimolecular rate constants (in l. mol.$^{-1}$ sec.$^{-1}$ at 25° in 0·07M-$KClO_4$) for the hydroxide ion-catalysed hydrolysis of some α-keto-phosphate esters are shown in the Table.

It is to be noted, first, that the formation of dialkyl phosphate is in competition with that of the alternative product (V) formed by loss of RO^-, the latter becoming exclusive in the case of the phenyl ester (4). Others[2] had already noted this with other diphenyl and di-*p*-nitrophenyl α-keto-phosphates.

Hydrolysis in $H_2{}^{18}O$ shows incorporation of 90—100 atom % oxygen from the solvent into the dimethyl phosphate (see also Cox and Ramsay[3]). Conceivably this could occur in a fast step prior to the hydrolysis. However, partial hydrolysis in

R'OPO(OR)$_2$	Formation of (RO)$_2$PO$_2^-$	% P–O Cleavage[a]	Formation of R'OPO(OR)·O$^-$
(1) MeCO·CHMe·OPO(OMe)$_2$	387[b]	97	9[c]
(2) MeCO·CHMe·OPO(OEt)$_2$	64[d]		
(3) MeCO·CHMe·OPO(OPr^i)$_2$	2·2		
(4) MeCO·CHMe·OPO(OPh)$_2$			820
(5) MeCO·CMe$_2$·OPO(OMe)$_2$	60	77[e]	14
(6) PhCO·CHPh·OPO(OMe)$_2$	130	85	14

[a] By mass spectrometry on trimethyl phosphate prepared by diazomethane treatment of the dimethyl phosphate ormed on hydrolysis in H$_2{}^{18}$O.

[b] Ramirez *et al.*[1] give k_2 = 360 l. mol.$^{-1}$ sec.$^{-1}$.

[c] Calculated from data of Frank and Usher, ref. 7.

[d] Witzel, *et al.*[6] give k_2 = 81·6 l. mol.$^{-1}$ sec.$^{-1}$.

[e] Considered to be a lower limit but might indicate the incursion of another process; the acyloin formed showed *ca.* 5% ^{18}O incorporation.

H$_2{}^{18}$O of (6) and hydrogenolysis of recovered triester afforded dimethyl phosphate with < 1·0 atom % oxygen incorporation from the solvent. Incorporation and hydrolysis therefore occur in the same step. This excludes c as a major pathway,[4] confirmed by the finding that the acyloin formed from (5) shows *ca.* 5% ^{18}O-enrichment; the conditions of the experiment ensured equilibration of the carbonyl oxygen with enriched water prior to, and with normal water after, hydrolysis. However, the fast methoxide-catalysed cleavage of (1) and (5), yielding dimethyl phosphate, also gave products expected for a reaction involving a methoxyoxiran intermediate, *i.e.* MeC(OMe)$_2$·CHMe·OH and Me$_3$C·CO$_2$Me respectively.[5] This confirms the view of Witzel *et al.*[6] that the major pathway in MeO$^-$–MeOH is the epoxide route c. Had this route been important in water a considerable rate increase of the reaction of (5) over that of (1) might have been expected,[4] in contrast to the small rate decrease observed. Since, too, it seems clear that both (1) and (5) react by the same mechanism, the rapid hydrolysis of (5) excludes mechanisms such as a, involving an enol or enolate (II) (see also ref. 6).

We now consider process b in which a pentaco-ordinate intermediate (III)[1,7] leads to dialkyl phosphate or, through (IV), to (V). Product (V) is only evident with the methyl and aryl esters in agreement with the order ArO$^-$ $\gg$ MeO$^-$ > EtO$^-$ > Pr^{i}O$^-$ of leaving ability in other phosphate ester hydrolyses.[8] This mechanism provides an explanation of the ^{18}O-incorporation (through pre-equilibration of the carbonyl oxygen). It is consonant with the rate differences in the order (1) > (2) > (3) ascribable, as in related systems, to steric effects.[9] The major argument in favour of a cyclic intermediate (III) derives from the fact that the hydrolysis rates are in the range 10^5—10^6 times that for trimethyl phosphate. The sole circumstance at present known in which this situation pertains in phosphate esters is in the hydrolysis of 5-membered ring cyclic phosphates, *e.g.* methyl ethylene phosphate, in which bond fission both internal and external to the ring is largely accelerated over that of open-chain analogues (for review see Westheimer).[10] The rate order (1) > (5) is to be expected on this basis. Frank and Usher[7] have shown that hydrolysis of the phosphonate, MeCO·CHMe·OPO(OMe)Me proceeds almost entirely by loss of methanol and explain this in terms of pseudorotational restrictions in a 5-membered ring intermediate. Our own experiments provide complementary evidence.

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