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ACCELERATION OF P-O CLEAVAGE REACTIONS OF PHOSPHATE MONOESTER DIANIONS IN DIPOLAR APROTIC SOLVENTS

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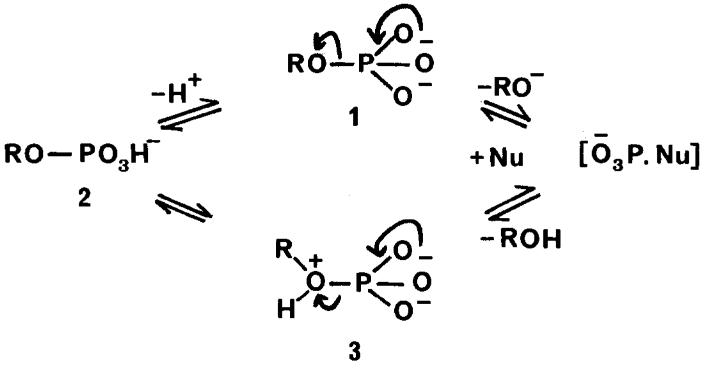
Abstract: The 10^6 - 10^7-fold acceleration of the hydrolysis of p-nitrophenyl phosphate in >95% aqueous DMSO or HMPA is shown to be specific for the dianion, and attributed primarily to decreased H-bonding from solvent water.

Phosphate monoester dianions are more reactive towards P-O cleavage than related diesters because of the enhanced π-donor capability of their negatively charged oxygens.[1] This drives the expulsion of good leaving groups RO^- from dianions (1), and of ROH from the zwitterionic form (3) of monoanions (2).



Much evidence suggests that the new bond to the nucleophile which accepts the electrophilic metaphosphate (PO_3^-) is not far developed in the transition state,[2] though results with chiral phosphates show that it has developed far enough to effect inversion at P in all enzymic[3] and non-enzymic[4] systems so far investigated. So the very large rate accelerations observed in enzyme-catalysed phosphate transfer reactions must depend particularly heavily on the microenvironment of the active site.

Oxyanions (1) and (2) are powerfully stabilised by hydrogen-bonding to solvent water, and there is mounting evidence that rates of P-O cleavage -

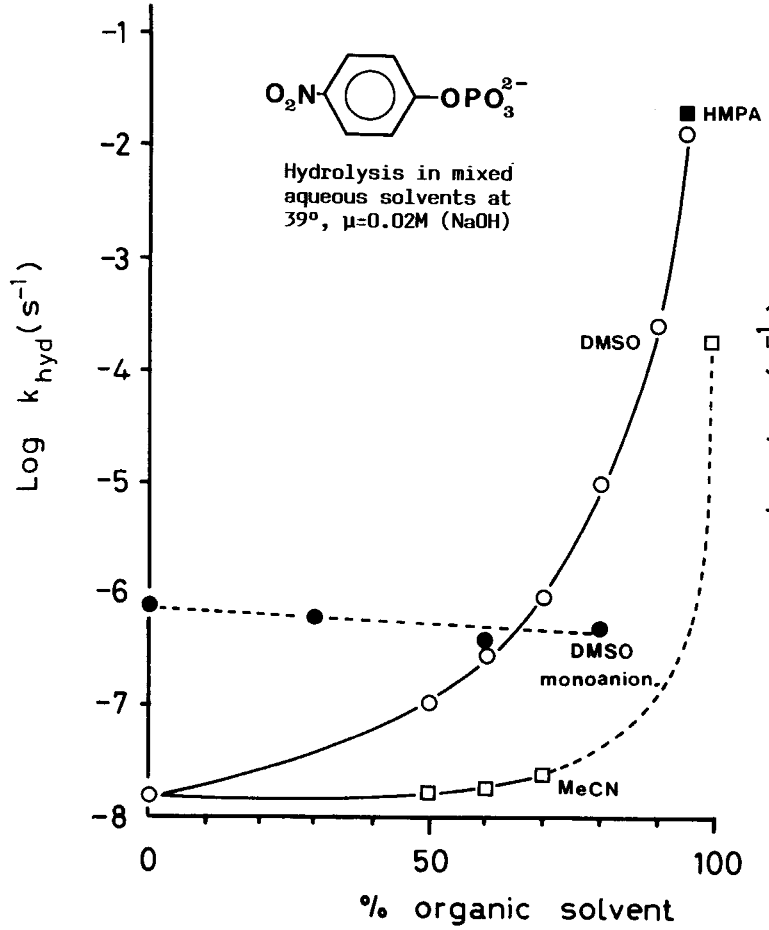
like related decarboxylations[5] - are accelerated in less protic media, where H-bonding must eventually be reduced. For example, Beltran et al. showed recently that the hydrolysis of p-nitrophenyl phosphate dianion is over 10^6 times faster in acetonitrile containing 0.02 M water than in water alone.[6] As part of a wider investigation of the effects of decreasing water concentrations on $S_N2(P)$ reactions we have measured rates of hydrolysis of several phosphate esters. We find large rate enhancements in dipolar aprotic solvents, and show that these are specific for the dianions.

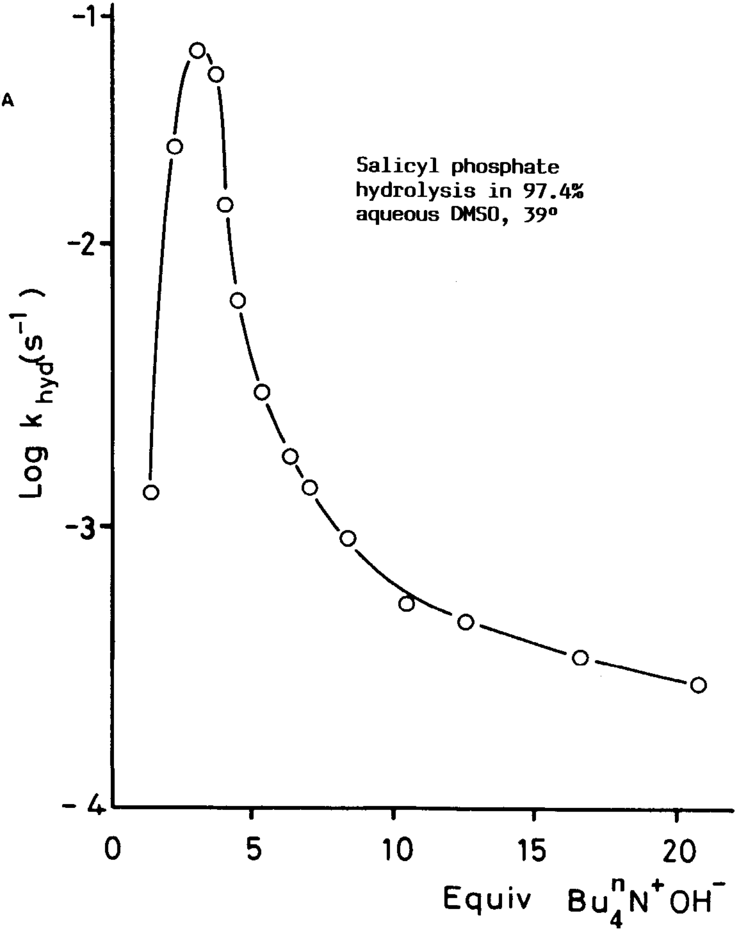
Results are shown in the Figures. Our early data in 30-70% mixed aqueous solvents[1] showed dimethyl sulphoxide (DMSO) to have the largest effect of eight solvents tested on the rate of hydrolysis of p-nitrophenyl phosphate dianion. In 95% DMSO, 0.02 M in NaOH, hydrolysis is 8 x 10^5 times faster than in water, and reaction is 3 times faster still when the cation is $\underline{n}$-Bu_4N^+. Similar accelerations are observed in hexamethyl phosphoramide (HMPA), but in 70% acetonitrile the rate has not even doubled. Rates are independent of hydroxide concentration: in 90% DMSO the rate constant ($1.16 \times 10^{-3} s^{-1}$) is unchanged when the concentration of hydroxide is varied over the range 0.01-0.05M at constant ionic strength ($\underline{n}$-Bu_4N^+ OH^-/Br^-). The much slower hydrolysis in water is catalysed by hydroxide, but involves C-O cleavage.[1,2] Evidently the dipolar aprotic solvents used in this work accelerate P-O cleavage selectively.

Various problems hampered measurements at <5% H_2O, but the indications are that the rate increase reaches a limit between 10^6 - 10^7. The hydrolysis of m-nitrophenyl phosphate dianion, for example, is only 4.6 times faster in 98.5% than in 95.1% DMSO (where the acceleration, compared with pure water, is 2.8 x 10^5. These figures are similar to the accelerations found by Parker[7] for reactions of other small anions in dipolar aprotic, compared with protic solvents, and attributed primarily to ground state desolvation, plus significant transition state stabilisation in aqueous-dipolar aprotic solvent mixtures.

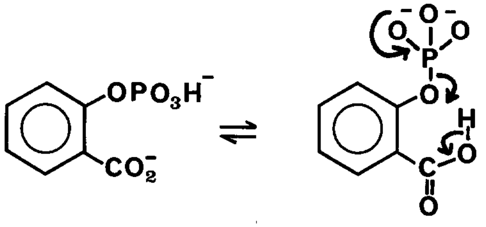
The behaviour of monoanions is quite different. The hydrolysis of p-nitrophenyl phosphate is actually slower in 80% DMSO - 20% aqueous formate buffer, pH 3.72, than in water (broken line in Fig. 1). Presumably any acceleration of the breakdown of the zwitterion (3) is outweighed by a less favourable equilibrium constant for its formation in the less protic solvents.

An intermediate case is salicyl phosphate. The $[HO^-]$-rate profile (Fig. 2) in 97.4% DMSO is dominated by the reaction of the dianion (4), as it is in water.[8] No significant reaction of the trianion is observed (as expected if the acceleration in 97.4% DMSO is less than 10^9-fold). The rate of hydrolysis of the dianion is about 330 times greater than in water, qualitatively consistent with the suggested mechanism (5),[8] which involves


$O_2N-C_6H_4-OPO_3^{2-}$
Hydrolysis in mixed aqueous solvents at 39°, μ=0.02M (NaOH)
HMPA
DMSO
DMSO monoanion
MeCN
Log $k_{hyd}(s^{-1})$
-1
-2
-3
-4
-5
-6
-7
-8
0
50
100
% organic solvent


Salicyl phosphate hydrolysis in 97.4% aqueous DMSO, 39°
Log $k_{hyd}(s^{-1})$
-1
-2
-3
-4
0
5
10
15
20
Equiv $Bu^n_4N^+OH^-$

both well-advanced P-O cleavage and partial proton transfer from the neighbouring COOH group in the transition state, and thus combines characteristics of both mono and di-anion reactions.



4 **5**

In an enzyme active site proton transfer to the leaving group can take place in a quite different microenvironment to that around the PO_3^{2-} group. Our results suggest that attenuation of hydrogen bonding when this group binds, relative to the situation in solution, or in the transition state, is a likely source of large rate accelerations in phosphate transfer reactions.

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