Reduced Nucleophilic Reactivity in Five-membered Cyclic Phosphites: Correlation with Transition State Structure

By C. BROWN, R. F. HUDSON, V. T. RICE, and A. R. THOMPSON
(*The Chemical Laboratory, University of Kent at Canterbury, Kent*)

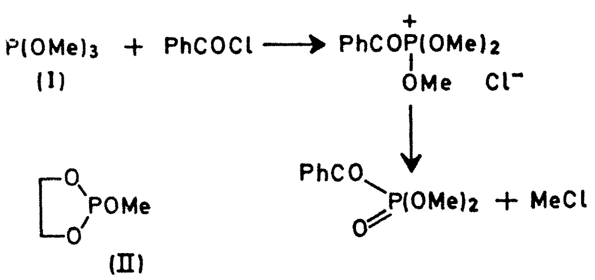
Summary The range in relative reactivities of cyclic and acyclic phosphites associated with ring strain effects towards a series of electrophiles can be related to the degree of bond making in the transition states for the reactions concerned.

THE enhanced reactivity of 5-membered cyclic phosphates, phosphonates,[1] phosphites,[2] and phosphonium salts[3] towards nucleophilic reagents is now well established. We report here large rate decreases for the reactions of cyclic phosphites with a wide range of electrophilic centres, and show how the relative reactivity of cyclic and acyclic esters changes in a regular way with transition state structure.

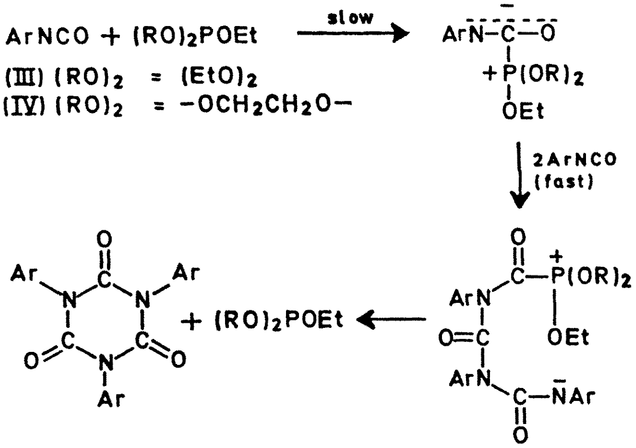
The rate constants for the Arbusov-type reactions of trimethyl phosphite (I) and 2-methoxy-1,3-dioxaphospholane (II) with benzoyl chloride[4] and for the polymerisation of 3-nitrophenyl isocyanate by the ethyl derivatives (III) and (IV) are given in Table 1. Both processes have been shown[5] to be bimolecular and to involve nucleophilic phosphorus (Schemes 1 and 2).

TABLE 1

Phosphite	Substrate	Temperature (°)	Rate constant ($l\ mol^{-1}\ s^{-1}$)
(I)	$PhCOCl$	25	$2{\cdot}13 \times 10^{-2}$
(II)	$PhCOCl$	25	$1{\cdot}07 \times 10^{-4}$
(III)	$ArNCO$	65	$1{\cdot}15 \times 10^{-4}$
(IV)	$ArNCO$	65	$3{\cdot}72 \times 10^{-6}$



SCHEME 1.



SCHEME 2.

In both reactions the acyclic phosphite is considerably more reactive than the cyclic analogue. This we ascribe to an increase in ring strain† accompanying quaternisation at phosphorus, as postulated previously.[6] In contrast, pyrrolidine and diethylamine have comparable reactivities towards acyl chlorides and other carbonyl compounds.[7]

As shown in Table 2, the acyclic:cyclic rate ratios, k_a/k_c, vary considerably with the nature of the substrate.

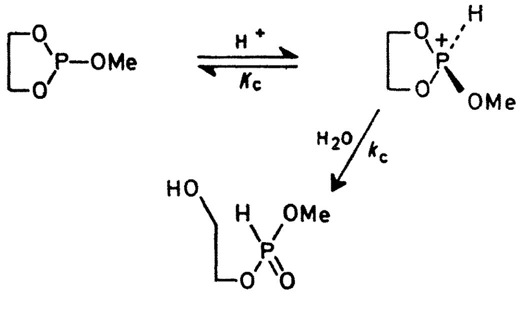
TABLE 2

Reaction	k_a/k_c	Brönsted α
MeI + $(RO)_2PNMe_2$	3·2[a]	0·22[f]
EtI + $(RO)_2POEt$	6·9[b]	
PhNCO + $(RO)_2PNHPr$ ..	20[c]	0·5[g]
PhNCO + $(RO)_2POEt$ ..	31[d]	
PhCOCl + $(RO)_2POMe$ ..	200[d]	0·78[f]
H^+ + $(RO)_2POMe$	*ca.* 10^6 [e]	1·0

[a] Ref. 6; [b] Ref. 8; [c] Ref. 9; [d] This work; [e] Estimated value, see text; [f] Ref. 10; [g] Calculated from data in ref. 7.

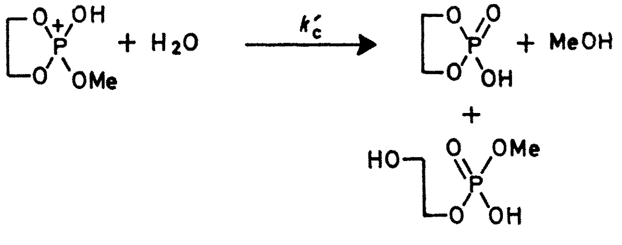
We attribute this variation to differences in transition state structure, in particular to differences in the extent of bond formation, as measured, for example, by the Brönsted coefficient for the reaction of nucleophiles with the substrate in question.

It is reasonable to suppose that the O–P–O bond angle increases with charge transfer as rehybridisation at phosphorus takes place, and hence the k_a/k_c ratio increases progressively with increase in the degree of bond formation in the transition state (Table 2). The k_a/k_c ratio for protonation of phosphites can be estimated from the work of Westheimer and Covitz,[2] who showed that (II) is hydrolysed *ca.* 3×10^3 times more rapidly‡ than (I) in alkaline solution, but *ca.* 6 times more slowly than (I) in acid solution. We interpret these results in terms of the mechanism for the acid hydrolysis shown in Scheme 3.

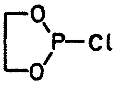


SCHEME 3.

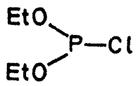
The second stage of this hydrolysis may be compared with the acid-catalysed hydrolysis of cyclic phosphates,[1] (Scheme 4) which proceeds *ca.* 10^6 times more rapidly than the acid hydrolysis of trimethyl phosphate. If we assume (i) $k_c'/k_a' \approx k_c/k_a$, (ii) a negligible concentration of intermediate P^+ ions, and (iii) similar equilibrium constants for protonation on the phosphoryl oxygen atom of cyclic and acyclic phosphates, it follows that K_a/K_c is *ca.* 6×10^6. This (predicted) large difference in basicity between cyclic and acyclic phosphites neatly accounts for the difference in reactivity of their derivatives towards acids. For example, 2-chloro-1,3-dioxaphospholane (V) may be prepared in the presence of hydrogen chloride,[11] unlike the phosphochloridite (VI). Finally, the mechanism previously suggested[9] for reaction of *N*-alkylphosphoramidites with phenyl isocyanate involving nucleophilic phosphorus gains considerable support from the similarities of the k_a/k_c ratios observed for such reactions to the k_a/k_c ratio reported here for the polymerisation of phenyl isocyanate by phosphites.



SCHEME 4.



(V)



(VI)

We believe that k_a/k_c values for the reactions of phosphites will provide a useful mechanistic criterion for the nucleophilic or electrophilic role of phosphorus in such reactions, and we are investigating the scope of this criterion.

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† The origin of this "strain" is still obscure, the relative contributions from enthalpy and entropy changes being unknown but this is currently under investigation in our laboratory.

‡ This factor compares well with those observed[6] for the reactions of phosphoramidites with benzaldehyde and phenyl isocyanate, both of which involve rate-limiting nucleophilic displacement at tervalent phosphorus.

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