Mechanistic Studies on Metaphosphate Generation from Fragmentation of 2,3-Oxaphosphabicyclo[2.2.2]octene Derivatives

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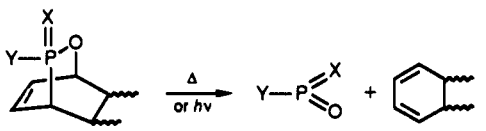
Abstract: The rates of fragmentation of 3-R-6-methyl-*N*-phenyl-2,3-oxaphosphabicyclo[2.2.2]oct-5-ene-8,9-dicarboximide 3-oxide, where R = Et_2N or EtO, and of the 3-sulfide, where R = EtO, were determined in various solvents and at various temperatures. All reactions were first-order, as they were also when alcohols were present as trapping agents for the released metaphosphoric acid derivatives. From the small solvent effects on rates and activation parameters, it was concluded that the thermal fragmentations occurred by a retrocycloaddition process. This was supported by the similarity in rates for the three substrates, which differ considerably in polarity at phosphorus. The metaphosphates showed selectivity in their reactivity to alcohol mixtures; rates were faster with more nucleophilic alcohols (ethanol vs 2,2,2-trifluoroethanol) and less crowded alcohols (ethanol vs *tert*-butyl alcohol). A secondary reaction of the released metaphosphate with two of the substrates was detected by kinetics measurements; first-order rate constants were larger when alcohol was not present to remove metaphosphate. Quantum yields in photochemical fragmentations of the substrates were unchanged when alcohols were present; metaphosphates generated in this fashion showed selectivity effects toward alcohols as seen in the thermal fragmentation. No evidence was found for radical intermediates in either process.

We have previously found that, when derivatives of the 2,3-oxaphosphabicyclo[2.2.2]octene ring system are heated at about 100–120 °C[1,2] or irradiated with UV light,[3] they decompose with the elimination of the P–O bridging unit and the formation of a cyclohexadiene moiety in the residual molecule. Such processes are of interest because the released species would appear to have phosphorus in the three-coordinate condition, as a derivative of metaphosphoric acid ($HO-PO_2$) or of a metaphosphonic acid anhydride (RPO_2). In much of our recent work, we have examined this possibility and attempted to develop the method as a useful, versatile route to these species.



Three-coordinate phosphoryl compounds have been the subject of many investigations over the years; there is strong evidence that such species can exist in the gas phase,[4-6] but they have proved to be exceedingly reactive in solution and quite elusive. For the most part, their existence in solution is inferred from kinetic effects and trapping reactions,[7] as well as by studies of the stereochemical consequences of reactions at the planar phosphorus.[8] Their appearance as intermediates in a number of chemical processes has received consideration, and several reports exist on the possible detection of metaphosphates by ^{31}P NMR spectroscopy in cases where the species is partially stabilized by coordinating substances such as amines[9,10] or possibly ethers.[11] Nevertheless, because of the experimental difficulties in directly observing these transient three-coordinate species, considerable controversy has surrounded them since their first appearance in the literature in 1955.[12] Even a very recent paper (1989) continues the discourse along the lines of doubt that the metaphosphate ion can be an intermediate in solvolysis reactions in aqueous solutions,[13] where indeed their participation was first proposed.[12] The 1989 paper by Herschlag and Jencks goes on to consider the question "When could metaphosphate be an intermediate?" and points out that since the ion is known to exist in the gas phase,[5,6] it should exist in nonnucleophilic or very weakly nucleophilic solvents and could be stabilized by substitution of sulfur or nitrogen for the phosphoryl oxygen. We can presume that these same comments would apply to neutral derivatives of metaphosphoric acid and related species, suggesting that the fragmentation of 2,3-oxaphosphabicyclo-[2.2.2]octene derivatives could well meet the requirements proposed by Herschlag and Jencks for the appearance of an intermediate; no reagents are required to effect elimination of the P–O bridge, avoiding the problem of preassociation phenomena, and at least in the thermolysis process solvents of wide-ranging nucleophilicity and polarity can be employed. We have therefore carried out some fundamental studies on these fragmentation reactions that were designed to elucidate their mechanisms and to reveal the nature of the intermediate at the time of its release. Most of our work has been concerned with the thermal process, where we have been able to apply kinetics measurements to great advantage. Quantum yield studies have been valuable in probing the photochemical fragmentation. As will be seen, the various experiments point to the release in both fragmentation processes of the bridging P–O unit as a free metaphosphate derivative. In another approach, we have sought to observe stabilized metaphosphoric acid derivatives at −75 °C by ^{31}P NMR with some success; the species Et_2N-PO_2 and $MesNH-PO_2$ in THF, which probably form solvates, have shifts of +12 and +8.5, respectively.[11]

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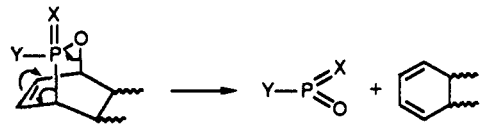
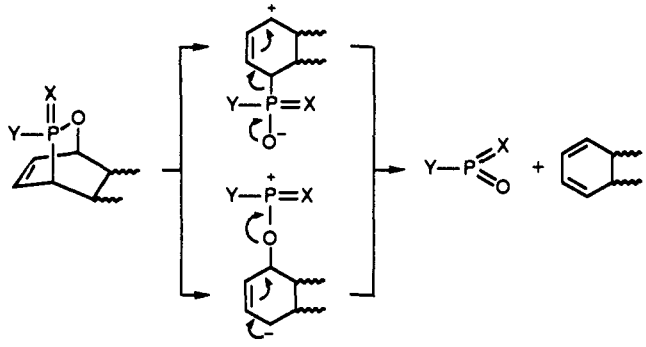
Thermal Fragmentation

The following unimolecular mechanisms may be considered.

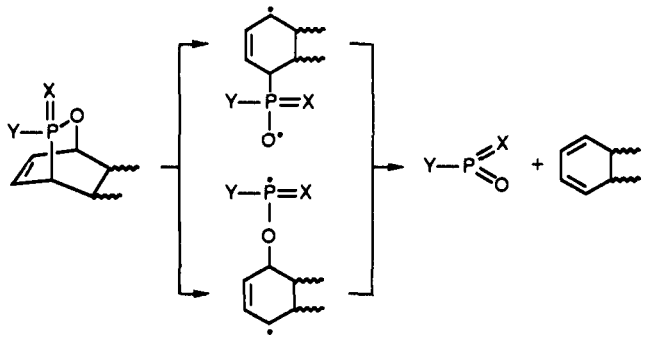
(1) retrocycloaddition:



(2) stepwise ionic:

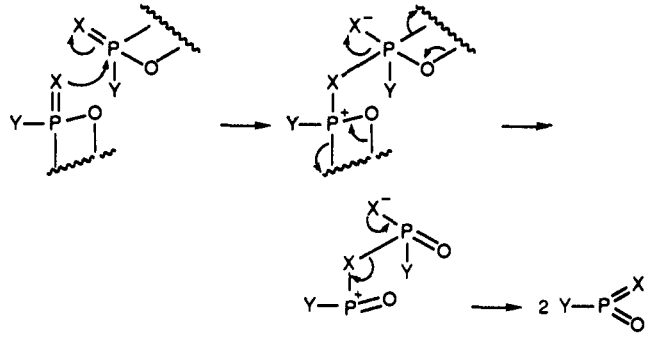


(3) radical:



In addition, it is necessary to consider a bimolecular process.

(4) bimolecular:



The bimolecular process can be identified from its second-order kinetics, if the first step is rate-controlling. Ionic intermediates would be detectable from solvent polarity effects. Both the retrocycloaddition (1) and the ionic mechanism (2) would follow first-order kinetics (the latter in the case of a fast step coupled with a slow step). The ionic mechanism, however, can be recognized by strong rate and entropy of activation effects accompanying solvent polarity changes. Furthermore, the entropy of activation should aid in differentiating between the two first-order processes, since retrocycloaddition reactions are associated with small, negative values.[14] Ionic processes frequently have positive entropy of activation values[15] that are sensitive to solvent polarity.

(14) See, for example: Kwart, H.; King, K. *Chem. Rev.* **1968**, *68*, 415. Snyder, J. P.; Harpp, D. N. *J. Am. Chem. Soc.* **1976**, *98*, 7821. Jenner, G.; Papadopoulos, M.; Rimmelin, J. *J. Org. Chem.* **1983**, *48*, 748.

(15) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, Germany, 1988; pp 136–170.

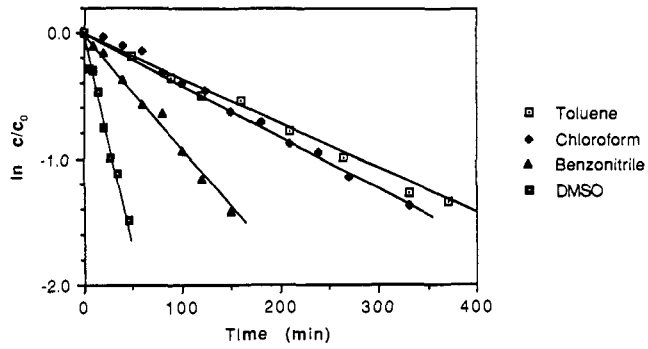
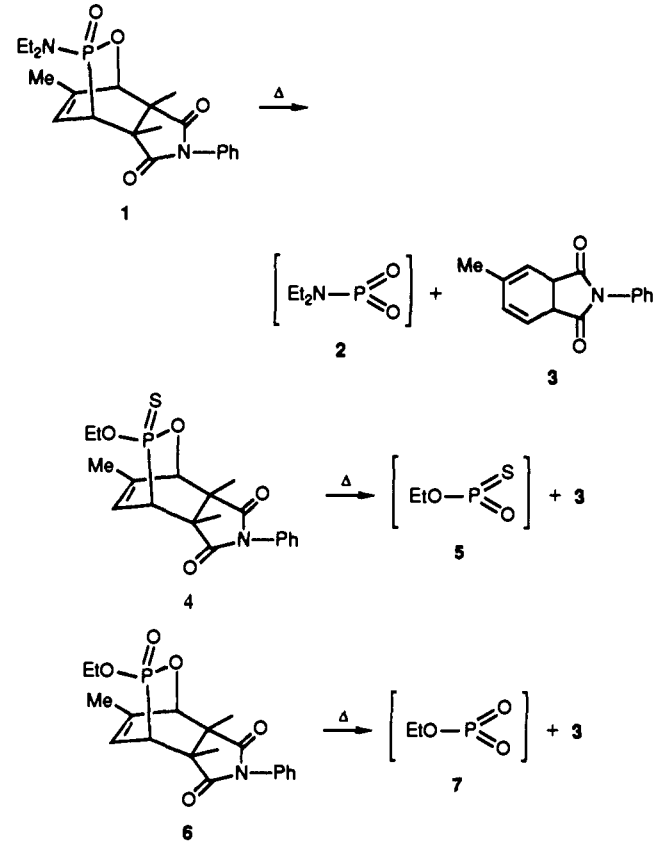


Figure 1. First-order plots for fragmentation of **1** in various solvents in the presence of ethanol at 100 °C.

Kinetics would also provide clarification for the role played by trapping agents included in the reaction medium; the agent would appear in the kinetic expression for the process as a participant having first-order involvement, if it were implicated in an association reaction with the substrate to form a P(V) intermediate before the fragmentation took place. This is an important question to answer before it can be confidently asserted that an intermediate is revealed by the formation of a trapping product.

Rate Constants for Thermal Fragmentations

The rate of fragmentation of precursors for three different types of metaphosphoric acid derivatives (**2**, a metaphosphoramide; **5**, a metathiophosphate; and **7**, an alkyl metaphosphate) were measured by following the rate of change of the intensity of the ^{31}P NMR signal for the substrate in various solvents and at various temperatures. Since the ejected fragment is unstable and undergoes rapid intermolecular condensations to P–O–P derivatives, it was not feasible to follow the rate of formation of products.



Decompositions of metaphosphate precursors **1**, **4**, and **6** were performed over the temperature range of 65–110 °C, employing toluene, chloroform, benzonitrile, and dimethyl sulfoxide (DMSO) as solvents. First-order kinetics were observed in all cases. Illustrative time–concentration plots for precursor **1** in various

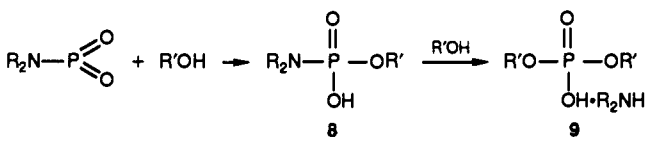
Table I. Concentration and Solvent Effects on the First-Order Rate Constant for Thermolysis of **1** and **6**

compd	solvent	t, °C[a]	concentration, mol/L substrate	ethanol	**3**	rate constant, 10^5k, s^{-1}
1	toluene	100	0.117	0.606		5.87 ± 0.23
			0.095	0.486	0.164	5.72 ± 0.18
			0.095	0.486	0.230	5.81 ± 0.43
	$CHCl_3$	100	0.100	0.523		8.43 ± 0.10
			0.096			9.50 ± 0.54
	DMSO	100	0.110	0.557		52.6 ± 2.7
			0.053	0.154		50.1 ± 1.2
6	$CHCl_3$	80	0.039	0.126		0.418 ± 0.012
			0.101	0.125		0.535 ± 0.040
			0.179	0.126		0.410 ± 0.017
			0.101	0.226		0.477 ± 0.015
			0.101	0.497		0.524 ± 0.032
	$CHCl_3$	100	0.104	0.129		3.24 ± 0.20
			0.100			7.13 ± 0.30
			0.192			6.84 ± 0.11
			0.113		0.198	8.50 ± 0.17
	DMSO	100	0.099	0.280		41.3 ± 1.1
			0.160	0.171		39.2 ± 0.47

[a] Actual temperatures were those of the vapor from the refluxing external liquid; the rate constants so obtained were then recalculated to 80 and 100 °C by use of the Arrhenius equation (Tables III and V).

solvents at 100 °C are shown as Figure 1 where the reaction was followed for 2–3 half-lives; some typical data for decompositions of **1** and **6** at different substrate concentrations are provided in Table I. The fragmentation process is therefore established to be unimolecular, and the bimolecular process shown as the first step in mechanism 4 is eliminated. The fragmentation rates were then found to be independent of the concentration of added ethanol. This convincingly rules out the possibility that an alcohol, when used as a trap in this process, has any significant reaction with the substrate before the fragmentation and validates the concept that the trapping agent is useful in this process for detecting a free metaphosphate. (It will be noted later that the presence of alcohol can in some cases influence the experimental first-order rate constant.) The fragmentation process is not reversible; there was no effect on the reaction rates when a sample of the dienic coproduct **3** was placed in the initial reaction mixture (Table I). Some specific observations made for each of the three precursors are recorded in the following subsections.

Formation of *N*,*N*-Diethylmetaphosphoramide (2). The product of trapping with ethanol from metaphosphoramide **2** is not simply that from the combination of the two reactants; as we have noted elsewhere,[16] phosphoramidates such as **8**, when generated in the hot medium in the presence of excess alcohol, react further with the displacement of the amino group to give dialkyl phosphate salts (**9**). The possibility has to be considered, however, that the



8 **9**

amine displacement by alcohol occurs on the bicyclic precursor (giving **6**), rather than on the trapping product. That the fragmentation is first-order with respect to **1** and zero-order in alcohol speaks against this possibility.

Also consistent with the conclusion that the trapping alcohol plays no role in the formation step of the metaphosphate is the fact that the rate of decomposition of bicyclic amide **1** was *independent of the structure of the alcohol.* Reaction media containing either the sterically hindered *tert*-butyl alcohol or the weakly nucleophilic 2,2,2-trifluoroethanol (TFE) as trapping agents gave virtually the same first-order rate constants as found for media containing ethanol (Table II).

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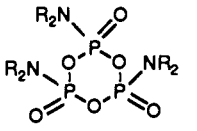
In the case of the fragmentation of **1** the first-order rate constants were the same in the presence or absence of trapping alcohol (Table III). This implies that metaphosphoramide **2**, when not trapped, simply reacts with itself to form condensates with P–O–P bonds and does not enter into any reaction with the remaining substrate **1**. The structure of the condensates is partially revealed by the ^{31}P NMR spectra taken on the reaction solutions. For condensates of alkyl metaphosphates, signals for internal phosphoryl units in chains or cycles appear at about δ −23 to −26, while terminal phosphoryl groups in chains appear at δ −10 to −12.[17] Condensates from the metaphosphoramide **2** had complex signals in both regions, although it might have been expected that more downfield signals would result from the replacement of OR by R_2N, as is common in phosphates (see, e.g., ref 18). Indeed, the cyclic trimer **10** (R = Me) is reported[19] to have ^{31}P δ −12. An authentic sample of the cyclic trimer (**10**, R = Et) was prepared by a different method[20] and found to have ^{31}P δ −12. However, we observed that heating the trimer in toluene caused its decomposition and gave the same type of complex ^{31}P NMR spectrum as observed from the condensation of **2**. The products have not been further examined.



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The effect on the first-order rate constants of changing the solvent polarity can be seen in the data of Table III to be quite small. Increasing the polarity from the low value of toluene to the very high value of DMSO increased the rate by a factor of only 8. This clearly speaks against the relevance of mechanisms 2 and 4, which involve ionic intermediates or highly polar transition states, and strongly supports the retrocycloaddition mechanism 1. Furthermore, the activation parameters calculated from the data of Table III and recorded therein support a concerted mechanism. Thus, the entropy of activation ($\Delta S^{\ddagger}$) is only about −2 eu at 373 K in chloroform, which is entirely consistent with values found for other retrocycloaddition processes.[14] Furthermore, $\Delta S^{\ddagger}$ was largely independent of solvent polarity; in DMSO, the value was −1.9 eu, and in chloroform it was −1.5. A pronounced effect on $\Delta S^{\ddagger}$ would accompany such solvent polarity changes if an ionic intermediate were involved.[15]

Formation of Ethyl Metathiophosphate (5) and Ethyl Metaphosphate (7). As for the amide derivative **1**, the fragmentation of the two esters **4** and **6** followed first-order kinetics in the presence or absence of ethanol (Tables IV and V). For **6**, again $\Delta S^{\ddagger}$ was relatively small and negative (Table V) and not greatly affected by pronounced solvent polarity changes. Both processes therefore can be assumed to employ the retrocycloaddition mechanism.

The condensation products from untrapped ethyl metaphosphate gave the complex ^{31}P NMR signals at δ −28 and −14 in the expected regions for internal and terminal phosphate units, respectively.[17] The products formed from untrapped ethyl metathiophosphate are being characterized in continuing studies.[21]

As noted, the fragmentation of the three bicyclic precursors **1**, **4**, and **6** follows first-order kinetics either in the presence or absence (see Figure 2) of added alcohol, but the rate constants for **4** and especially for **6** are noticeably larger when alcohol is absent from the medium (Tables III–V). In searching for an explanation for the rate-retarding effect of alcohol, we considered the possibility that, by removing the metaphosphate immediately

(17) Clapp, C. H.; Westheimer, F. H. *J. Am. Chem. Soc.* **1974**, *96*, 6710. Van Wazer, J. R.; Callis, C. F.; Shoolery, J. N.; Jones, R. C. *J. Am. Chem. Soc.* **1956**, *78*, 5715.
(18) Nielsen, M. L.; Pustinger, J. V., Jr. *J. Phys. Chem.* **1964**, *68*, 152.
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(21) Quin, L. D.; Jankowski, S. Work in progress.

Table II. Rate Constant ($10^5 \times k$, s^{-1}) for Thermolysis of **1** and **6** in the Presence of ROH at 100 °C

		R in ROH				
compd	solvent	Et[a]	*i*-Pr	*t*-Bu	CF_3CH_2	H
1	DMSO	48.7 ± 3.5	47.5 ± 1.4	47.8 ± 1.3	47.0 ± 1.8	
	$CHCl_3$	9.60 ± 0.73		7.48 ± 0.16		
6	DMSO	39.0 ± 1.4			42.1 ± 1.0	40.8 ± 1.0
	$CHCl_3$	3.11 ± 0.20	2.70 ± 0.15			

[a] Calculated from Arrhenius plots.

Table III. Kinetics of the Thermolysis of **1** in Various Solvents

	toluene[a]		$CHCl_3$[a]		$CHCl_3$[b]		benzonitrile[a]		DMSO[a]	
	t, °C	10^5k_1, s^{-1}	*t*, °C	10^5k_1, s^{-1}	*t*, °C	10^5k_1, s^{-1}	*t*, °C	10^5k_1, s^{-1}	*t*, °C	10^5k_1, s^{-1}
	100.0	5.87 ± 0.23	64.5	0.188 ± 0.012	64.1	0.1520 ± 0.0096	100	15.81 ± 0.81	64.5	1.19 ± 0.03
			79.7	1.01 ± 0.14	79.9	1.059 ± 0.078			79.7	4.98 ± 0.21
			95.7	5.84 ± 0.23	87.7	2.82 ± 0.16			100.3	54.2 ± 2.8
			100.7	9.06 ± 0.11	96.6	6.91 ± 0.35			109.2	114.8 ± 4.2
			109.7	30.2 ± 1.4	100.1	9.60 ± 0.55				
					110.2	32.9 ± 1.4				
ln A (s^{-1})				28.9 ± 1.4		30.71 ± 0.71				28.7 ± 1.3
E_a (kJ/mol)				118.4 ± 4.3		123.7 ± 2.1				112.7 ± 4.1
$10^5 \times k_{373K}$ (s^{-1})				9.60 ± 0.73		10.47 ± 0.38				48.7 ± 3.5
$\Delta H^{\ddagger}_{373K}$ (kJ/mol)				115						110
$\Delta S^{\ddagger}_{373K}$ (J/mol K)				−6.3						−8.1
$\Delta S^{\ddagger}_{373K}$ (eu)				−1.5						−1.9

[a] With 5 equiv of ethanol. [b] Without ethanol.

Table IV. Kinetics of the Thermolysis of **4** with and without Ethanol in Chloroform

	with ethanol[a]		without ethanol	
	t, °C	10^5k_1, s^{-1}	*t*, °C	10^5k, s^{-1}
	64.0	0.887 ± 0.083	64.0	3.11 ± 0.23
	79.7	5.76 ± 0.47	78.3	11.13 ± 0.36
	88.0	9.59 ± 0.57	87.6	27.9 ± 1.2
	100.6	35.7 ± 6.3	100.3	50.5 ± 4.1
	107.8	73.9 ± 6.1	109.4	99.9 ± 2.9
ln A (s^{-1})		27.9 ± 2.4		18.5 ± 1.5
E_a (kJ/mol)		110.0 ± 7.1		80.9 ± 4.5
$10^5 \times k_{373K}$ (s^{-1})		39.3 ± 5.1		54.7 ± 4.9
$\Delta H^{\ddagger}_{373K}$ (kJ/mol)		109		
$\Delta S^{\ddagger}_{373K}$ (J/mol K)		−14.8		
$\Delta S^{\ddagger}_{373K}$ (eu)		−3.5		

[a] 1 equiv.

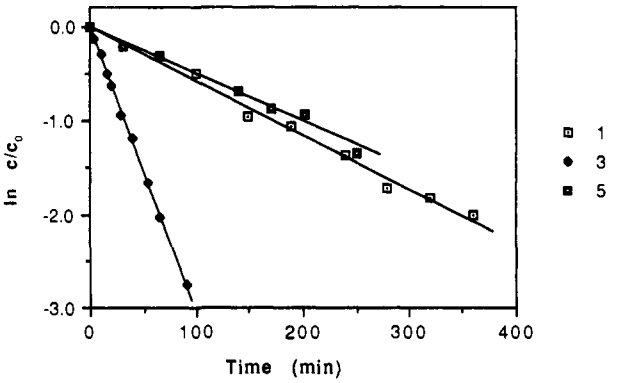
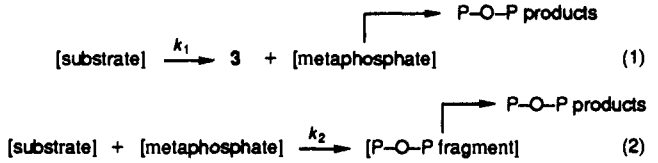


Figure 2. First-order plots for fragmentation of **1**, **3**, and **5** in chloroform in the absence of ethanol at 100 °C.

upon formation, a secondary P–O–P forming reaction between the metaphosphate and the bicyclic precursor was being prevented. This course of events is allowed by the observed first-order kinetics. Thus, if the primary process is expressed by eq 1 and the secondary process by eq 2, the steady-state approximation for metaphosphate



concentration gives the rate of substrate thermolysis shown by eq 3. In experiments in the presence of ethanol, metaphosphate

$$-\frac{d[\text{substrate}]}{dt} = [\text{substrate}]\{k_1 + k_2[\text{metaphosphate}]\} = 2k_1[\text{substrate}] \quad (3)$$

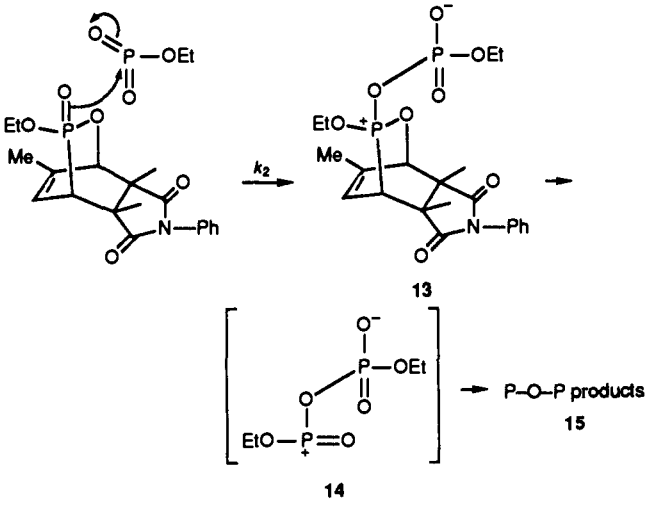
is removed and the precursor decomposes with rate constant k_1. However, in the absence of alcohol, the rate according to eq 3 should be twice that of eq 1. For decomposition of ester **6**, it is indeed seen that the rate at 110 °C is about 2 times as fast when alcohol is absent (Table V). It should be noted that the rate-

Table V. Kinetics of the Thermolysis of **6** in Various Solvents

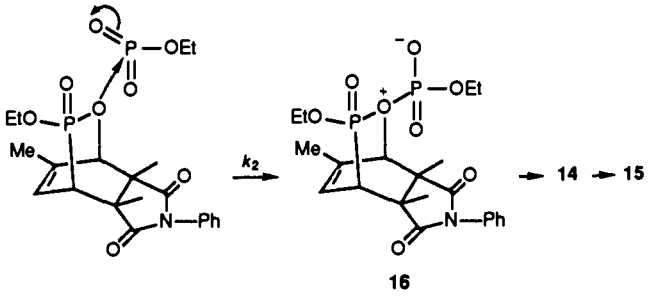
	$CHCl_3$[a]		$CHCl_3$[b]		benzonitrile[a]		DMSO[a]	
	t, °C	10^5k_1, s^{-1}	*t*, °C	10^5k, s^{-1}	*t*, °C	10^5k_1, s^{-1}	*t*, °C	10^5k_1, s^{-1}
	63.7	0.0736 ± 0.0035	63.9	0.187 ± 0.009	100	7.73 ± 0.56	63.5	10.040 ± 0.028
	79.9	0.418 ± 0.012	79.3	0.906 ± 0.031			80.0	6.44 ± 0.08
	86.7	1.015 ± 0.022	100.9	7.46 ± 0.12			87.6	12.48 ± 0.18
	99.6	3.12 ± 0.19	110.8	15.70 ± 0.75			100.0	34.90 ± 0.60
	109.5	7.11 ± 0.18					108.1	76.1 ± 2.0
ln A (s^{-1})		22.7 ± 1.3		23.88 ± 0.75				25.29 ± 0.88
E_a (kJ/mol)		102.7 ± 3.8		103.9 ± 2.3				102.8 ± 2.3
$10^5 \times k_{373K}$ (s^{-1})		3.11 ± 0.20		6.62 ± 0.27				39.0 ± 1.4
$\Delta H^{\ddagger}_{373K}$ (kJ/mol)		100						100
$\Delta S^{\ddagger}_{373K}$ (J/mol K)		−58						−36
$\Delta S^{\ddagger}_{373K}$ (eu)		−14						−9

[a] With 1 equiv of ethanol. [b] Without ethanol.

Scheme I



Scheme II

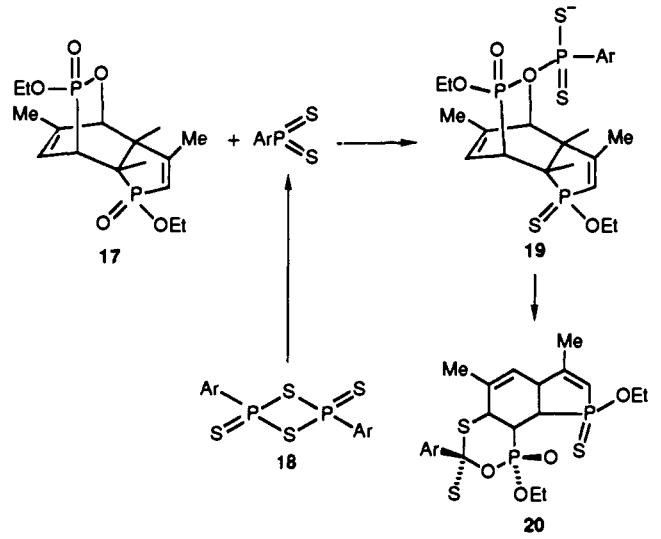


constant ratio is slightly affected by temperature; the reaction without ethanol is about 2.3 times faster at 80 °C and 2.5 times faster at 65 °C. Possibly at the lower temperatures the substrate is reacting not only with metaphosphate but also with some of the initially formed P–O–P fragment.

Two possible mechanisms can be considered for the attack of metaphosphate on its bicyclic precursor, and both depend on the very great electrophilic character of the species. In the first mechanism (Scheme I), the metaphosphate is proposed to attack the phosphoryl oxygen to form intermediate **13**, which collapses with ejection of a fragment (**14**) that goes on to give the observed ill-defined P–O–P material **15** with ^{31}P δ and −14 and −28. In the second mechanism (Scheme II), the metaphosphate attacks the bridging oxygen atom to form an intermediate or transition state represented by **16**; decomposition follows to give the same fragment (**14**) seen in Scheme I that then provides the P–O–P material **15**.

A precedent in fact exists for this second mode of attack; in earlier studies,[22] we isolated in good yield a product (**19**) from the attempted thionation of a related bicyclic species (**17**) with Lawesson's reagent (**18**) that clearly arose from an initial attack of the 3-coordinate species $ArPS_2$ (in equilibrium with the more stable dimer **18**) on the bridging oxygen atom. The intermediate formed (**19**) appears to undergo C–O cleavage and then a recyclization that results in incorporation of the unit $ArPS_2$ to give product **20** (Scheme III). We believe this reaction supports our proposal for an attack of a metaphosphate on an oxygen of the bicyclic precursors. Since it is also known that metaphosphates attack oxygen in carbonyl groups[23] as well as ethereal oxygen in small rings,[24] it is not surprising that complications are observed for a process where free metaphosphate is being generated in the presence of oxygen-containing substrates.

Scheme III[a]



[a] Ar = 4-MeO-C_6H_4.

Effect of Phosphorus Substituents on Fragmentation Rates

Consistent with the conclusion that the mechanism does not involve ionic intermediates is the observation of rather small effects on the first-order rate constants as the substituents on phosphorus are changed. These rate constants appear in Tables III–V. Thus under comparable conditions (100 °C in chloroform), a rate increase of only about 10 accompanied the replacement of sulfur on phosphorus by oxygen. This substituent exchange should greatly increase the electron-withdrawing power of phosphorus. That only a small rate effect occurs is consistent with a retrocycloaddition process, where relatively weak polarities would develop in the transition state. Similarly, replacing EtO in **6** by Et_2N caused a rate increase of only 3.1 in chloroform (1.3 in DMSO).

Competitive Reactions of Alcohols with Metaphosphates

We have already noted that there is no influence of the structure of the alcohol trapping agent on the first-order rate constants for fragmentation of the bicyclic compounds **1**, **4** and **6**. However, if the metaphosphate has a finite, if fleeting, existence, there should be a structural effect on the rate of its reaction with the alcohol, since such factors as steric crowding and electronic effects on nucleophilicity could be important. In fact, structural effects have been observed in other processes that are believed to involve free metaphosphate ion.[25] Such trapping reactions are too fast to be followed conveniently by kinetics, but the structural effects can be revealed by selectivity for a particular alcohol substrate in competition reactions where a mixture of alcohols is involved. We have performed competition experiments with ethyl thiometaphosphate (**5**) and indeed observed significant selectivity effects (Table VI). Thus, when **5** was generated in chloroform at 100 °C containing a 1:1 mixture of ethanol and the less nucleophilic 2,2,2-trifluoroethanol, the ratio of rate constants (k_{EtOH}:k_{TFE}) as determined by ^{31}P NMR analysis of the products and GC analysis of the unreacted alcohols, was 3.9. For a 2:1 EtOH/TFE mixture, the ratio was 3.8, and for a 1:2 mixture it was 4.0. We have also performed competition experiments involving ethanol and the secondary alcohol 1-methoxy-2-propanol (1:1), but here no significant effect was observed (ratio 1.1). This secondary alcohol, however, won the competition with TFE (ratio 4.1). A more meaningful test of the importance of steric crowding at the nucleophilic center used *tert*-butyl alcohol in competition with ethanol. For a 1:1 mixture of ethanol and *tert*-butyl alcohol, the rate constant ratio was 2.1, showing that a reaction of a metaphosphate can indeed be subject to steric effects.

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Table VI. The Ratios of the Rate Constants for Reaction of a Mixture of Alcohols with Metathiophosphate **5** (from **4**) and Metaphosphate **7** (from **6**)

			concentration, mol/L					
reactant	solvent	t, °C	substrate	ethanol	TFE	*tert*-butyl alcohol	1-methoxy-2-propanol	$k_{EtOH}:k_{ROH}$
4	$CHCl_3$	100	0.131	0.202	0.164			3.9
			0.111	0.120	0.226			4.0
			0.111	0.200	0.096			3.8
			0.114	0.130			0.098	1.1
			0.098		0.124		0.131	4.1[a]
			0.097	0.098		0.100		2.1
4	THF	30[b]	0.124	0.103	0.258			7.4
			0.105	0.293	0.106			7.6
			0.106	0.506		0.686		4.2
			0.101	0.537		1.015		4.7
6	$CHCl_3$	100	0.107	0.079	0.129			3.3

[a] $k_{1\text{-methoxy-2-propanol}}:k_{TFE}$. [b] Using photochemical generation of **5**.

Ethyl metaphosphate (**7**) was employed in one competition experiment and again a selectivity effect was observed. A 2:3 mixture of ethanol/TFE on reaction with **7** gave a ratio $k_{EtOH}:k_{TFE}$ of 3.3. It appears, therefore, that selectivity and hence relative reactivity does not differ greatly for ethyl metaphosphate and its thiono analogue (**5**). As noted earlier, it has been predicted by Herschlag and Jencks[13] that a thiono derivative might have greater thermodynamic stability than an oxo derivative, but this prediction, at least in the materials of the present study, does not seem to apply to kinetic properties.

The Radical Mechanism

Our kinetic results do not rule out the possibility that the thermal fragmentation occurs by a unimolecular process where one bond cleavage is homolytic rather than heterolytic, and where one bond cleavage is slow relative to the other. It is difficult to probe for a radical intermediate by examining the effect of radical trapping agents since such species would have little stability under the thermolysis conditions and probably would also be reactive to the released metaphosphate. Indeed, one attempt to use the radical trap TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) gave a complex mixture of products and no indications of any influence on the reaction rate. We therefore have made an attempt to search for a radical intermediate by means of electron-spin resonance spectroscopy. A reaction mixture prepared from heating bicyclic amide **1** in acetonitrile at 150 °C for 10 min in an ESR tube was plunged into a liquid nitrogen bath. The tube was rapidly inserted into the probe of an ESR spectrometer preset to this temperature. The mixture gave no ESR signals, however. We cannot rule out the possibility of a radical mechanism on the basis of this limited study, but we see no reason to invoke it.

Photochemical Fragmentation

The mechanistic question we have addressed in the photochemical process for metaphosphate generation is the timing of the reaction of added alcoholic trapping reagents that results in the formation of alkyl phosphates and the avoidance of any self reaction of the metaphosphate. If it could be shown that the alcohol does not preassociate with the substrate and does not quench the excited state, then its role as a true metaphosphate trapping agent in the photochemical process can be validated. We have approached this problem by studying quantum yields for fragmentation processes (Table VII). For this purpose we have employed a calibrated Rayonet photochemical reactor with low-pressure mercury lamps that provide radiation primarily at 254 nm. The quantum yield for fragmentation of **1** in THF at 30 °C was 0.28; a similar value (0.27) was found in the more polar solvent acetonitrile, suggesting that ionic or ion–radical intermediates are not involved. It was then established for both solvents that the addition of ethanol at about 1 mol/L had virtually no effect on the quantum yields (0.33 in THF, 0.32 in acetonitrile). The quantum yield (in THF) was nearly the same (0.29) when ethanol was replaced by *tert*-butyl alcohol as the trapping agent. Similar results were obtained on photolysis of **4** (Table VII). It is significant that the modification of the phosphorus functionality by replacing P=O with P=S had no appreciable effect on the quantum yield, implying that polarity at phosphorus plays no role in stabilizing the excited state. These results are consistent with the role of alcohol being played *after* the critical photochemical reactions are complete, that is, taking place with the released metaphosphate fragment. We therefore feel that here and in other photochemical metaphosphate generations it can be assumed that a free metaphosphate is being released when it can be shown that an alcohol successfully traps the fragment as a phosphate.

Table VII. Quantum Yield of the Photochemical Fragmentation of **1** and **4** at 30 °C and λ = 254 nm

		concentration, mol/L			
compd	solvent	substrate	ethanol	*tert*-butyl alcohol	quantum yield, $\Phi_{254\,nm}$
1	THF	0.101			0.28
		0.097	0.555		0.22
		0.097	1.030		0.33
		0.108		0.470	0.29
1	CH_3CN	0.096			0.27
		0.106	0.509		0.27
		0.095	0.631		0.22[a]
		0.095	0.903		0.32
4	THF	0.088			0.28
		0.105	0.399		0.33

[a] In the presence of oxygen.

Alcohol competition experiments have been performed to establish consistency with the generation of metaphosphates by the thermal process. We have generated ethyl metathiophosphate photochemically in THF at room temperature, with a mixture of ethanol/TFE (2:5) for trapping. The ratio $k_{EtOH}:k_{TFE}$ was 7.4. Similarly, for a 3:1 mixture, the ratio was 7.6. Taking into consideration that greater selectivity should occur at lower temperatures and allowing for the solvent difference, the average photochemical ratio of 7.5 (30 °C in THF) is not considered to be significantly different from the average thermal ratio of 4.0 (100 °C in chloroform). Selectivity was also observed in the reaction with a 1:1 ethanol/*tert*-butyl alcohol mixture in THF. The ratio $k_{EtOH}:k_{t\text{-}BuOH}$ was 4.2, and for a 1:2 mixture the ratio was 4.7. Again the ratio is larger than that in chloroform at 100 °C (2.1). These observations support the conclusion that in both processes the fragment being released from the bicyclic precursor is the free metaphosphate.

A test for radicals in the photochemical process was made by employing a radical scavenger during the reaction. This was accomplished by passing a stream of the scavenger oxygen through the cell during the period of photolysis of **1** in acetonitrile containing ethanol as trap. The only phosphorus-containing product was the expected ethyl *N,N*-diethylphosphoramidate. Furthermore, when the quantum yield was determined under these conditions, a value of 0.22 was found and thus was essentially unchanged from the value for an oxygen-free system (0.27).

Experimental Section

General. ^{31}P NMR spectra (FT, ^1H-decoupled) were recorded on an IBM-NR 80 spectrometer at 32.38 MHz; 85% H_3PO_4 was used as the standard with an external deuterium lock. Downfield shifts are positive.

^{1}H NMR spectra were obtained on the IBM-NR 80 spectrometer at 80 MHz with TMS as the internal standard. GC analyses were performed on a Perkin-Elmer 8410 instrument equipped with a column of 10% Carbowax 20M on Chromosorb WAW. ESR spectra were obtained on an IBM Instruments ESP-300 spectrometer at 9.602 GHz.

Synthesis of Substrates. *endo*-3-(*N*,*N*-Diethylamino)-6-methyl-*N*-phenyl-2,3-oxaphosphabicyclo[2.2.2]oct-5-ene-8,9-dicarboximide 3-oxide (**1**),[16] *endo*-3-ethoxy-6-methyl-*N*-phenyl-2,3-oxaphosphabicyclo[2.2.2]-oct-5-ene-8,9-dicarboximide 3-oxide (**6**),[1] and *endo*-3-ethoxy-6-methyl-*N*-phenyl-2,3-oxaphosphabicyclo[2.2.2]oct-5-ene-8,9-dicarboximide 3-sulfide (**4**)[2] were prepared as previously reported. The compounds were purified by column chromatography followed by several recrystallizations.

Synthesis of ***N*-Phenyl-4-methyl-1,2-dihydrophthalimide (3).** The bicyclic phosphonamide **1** (0.345 g, 0.92 mmol) and ethanol (0.35 mL, about 5 mmol) in 5 mL of dry $CHCl_3$ were heated in a closed ampule for 12 h at 100 °C. The product mixture was separated by column chromatography with CH_2Cl_2/hexane (2:1) as eluant. The eluate containing **3** was evaporated to dryness in vacuo to give a white solid whose ^{1}H NMR spectrum and mp (120.5-123 °C) were the same as were reported (lit.[26] mp 120-123 °C).

Solvents for Kinetics Experiments. DMSO was dried over molecular sieves and then fractionally distilled in vacuo. Chloroform, acetonitrile, and benzonitrile were fractionally distilled over P_2O_5. Toluene was dried by boiling over sodium and then fractionally distilled. Tetrahydrofuran was dried with $MgSO_4$ and then molecular sieves; it was further purified on an Al_2O_3 column and distilled over potassium.

Kinetics Measurements. The rate of disappearance of substrate was determined from the diminution of its ^{31}P NMR signal. Into a 10-mm NMR tube was placed a coaxial sealed 5-mm NMR tube containing D_2O or a $CDCl_3$ solution of a phosphorus standard ($(EtO)_2P(O)OH$ or $(EtO)_2P(O)Me$). A solution (2 mL) of the substrate (usually 0.2 mmol) was added and the external tube was sealed under argon. The assembly was placed in the vapor space of a 3-L flask containing a refluxing solvent (methanol, 65 °C; benzene, 80 °C; trichloroethylene, 87 °C; 2-propanol, 97 °C; dioxane, 101 °C; toluene, 110 °C). The temperature was constant within ±0.1 °C. At various time intervals (usually eight) the tube was removed, cooled, and the ^{31}P NMR spectrum recorded. The concentration of the remaining substrate was determined from peak area-concentration plots that were prepared for the $(EtO)_2P(O)OH$ or $(EtO)_2P(O)Me$ standards. In some experiments, an alcohol trapping agent was added to the solution of the substrate.

Calculations of the rate constants and the Arrhenius parameters were carried out by the least-squares method, and all data are given with standard deviations. The enthalpy and entropy of activation were calculated for 100 °C according to Eyring theory.

Photochemical Fragmentation. These experiments were carried out in a Rayonet photochemical reactor fitted with 16 low-pressure mercury lamps (253.7 nm). The light intensity was determined with a potassium ferrioxalate actinometer[27] and was found to be 13.2×10^{-7} einstein min^{-1} mL^{-1}. A quartz NMR tube containing 2 mL of a solution of **1** or **4** (occasionally with an alcohol as a trapping agent) was placed in a quartz thermostat with distilled water as the cooling medium (T = 28-30 °C). The thermostat was placed in the center of the UV reactor. The solution was flushed with dry argon during irradiation. To determine the change of concentration of the substrate, ^{31}P NMR peak areas were compared to a deuteriochloroform solution of $(EtO)_2P(O)OH$ as a standard in an internal sealed tube. The same procedure was used in competition experiments with metathiophosphate **5**. Data are recorded in Table VII.

Alcohol Competition Experiments. The ratios of the rate constants for reactions of mixtures of ethanol and another alcohol with metathiophosphate **5** and metaphosphate **7** were calculated according to eq 4.

$$k_{EtOH}/k_{ROH} = \frac{[(EtO)_2P(X)OH]}{[(EtO)(RO)P(X)OH]}\frac{[ROH]}{[EtOH]} \quad (4)$$

The sample of the solution of precursor **4** or **6** and the alcohol mixture was heated for about 2 half-lives (70% completion). The ratios of concentrations of phosphates were found from the ratios of the ^{31}P NMR integrations of these products. GC was used to determine the ratios of concentrations of the alcohols. Competition experiments were also performed with **4** when photochemically generated. Data are presented in Table VI.

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Conformational and Dynamic Changes of D- and L-Tryptophan Due to Stereoselective Interaction with Human Serum Albumin, As Revealed by Proton-Selective Relaxation Rate Measurements†

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Abstract: The proton selective relaxation rates of D- and L-tryptophan are affected to a different extent by the interaction with human serum albumin. These differences are correlated to a different degree of immobilization of the two enantiomers at the protein binding site. Conversely, no differences are detected in their intermolecular dipolar interaction with the protein protons.

Introduction

The growing interest in the relationship between stereochemistry and biological activity requires the development of methods for elucidating the interaction mechanism of chiral molecules with biological substrates. A number of methods have been proposed for the study of interactions between small ligands and macromolecules, such as substrate-enzyme or drug-protein interactions.[1,2] Nuclear magnetic resonance (NMR) methods based on

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