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Chemistry of the 2,3-Oxaphosphabicyclo[2.2.2]octene Ring System: Extrusion of Metaphosphates

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ABSTRACT

The 2,3-oxaphosphabicyclo[2.2.2]octene 3-oxide (or sulfide) ring system is of considerable value because it easily fragments on being heated or irradiated (254 nm) to provide three-coordinate phosphoryl species. The system is synthesized by O-insertion with peracids into a C–P bond of 7-phosphanorbornene derivatives with a variety of P-substituents. With rare exception, the insertion has been found to proceed with retention of the configuration at phosphorus, as established by X-ray and NMR techniques. The thermal fragmentation that produces the metaphosphate derivatives EtO–PO_2, EtO–P(S)O, and Et_2N–PO_2 follows first-order kinetics, and is independent of the concentration of a trapping agent for these species. Solvent effects and activation parameters join in defining a retrocycloaddition mechanism that ejects the free metaphosphate. The species Ph–PO_2 can also be easily generated either thermally or photochemically. Metaphosphates have been found to attack ethereal oxygen in epoxides and oxetanes, and may undergo anchimeric participation with a properly placed methoxy group on the substituent used in the 2,3-oxaphosphabicyclo[2.2.2]octene precursor.

The 2,3-oxaphosphabicyclo[2.2.2]octene 3-oxide (or sulfide) ring system has proved to be of great value as a general framework that fragments to give 3-coordinate, highly reactive phosphoryl derivatives. We first utilized this property in 1985 for the generation of ethyl metaphosphate (EtO–PO_2), as well as the metaphosphonic anhydrides $MePO_2$ and $PhPO_2$ (Equation 1) [1].

These fragmentations were accomplished thermally (110° in toluene). We later found that the fragmentations could be conducted at room temperature by subjecting the precursors to ultraviolet light (254 nm) [2], and we generated both alkyl metaphosphates and *N,N*-dimethylmetaphosphoramidate (Me_2N–PO_2) by this method. Other studies have led to the generation of alkyl metathiophosphates [3]; applications of the 3-coordinate species for special phosphorylations have also been described [4]. We have continued to develop the chemistry of the 2,3-oxaphosphabicyclo[2.2.2]octene ring system, and we report in this paper some new observations on the synthesis and stereochemistry of the system, as well as on some kinetic studies of the thermal fragmentation that provide compelling proof that a free metaphosphate is indeed released. Additional proof for a free metaphosphate has come from the use of chiral P-alkoxy derivatives of the bridged ring system, which are useful in proving the planarity of the species, but also reveal that an oxy function properly placed may undergo anchimeric participation with the metaphosphate function.

In Scheme 1 is outlined the general synthetic method used for the construction of the requisite ring system. Phosphole oxide intermediates are first generated and instantly trapped by Diels–Alder reaction with a maleimide derivative to give a product with the 7-phosphanorbornene framework. No other dienophile has yet been found to be superior

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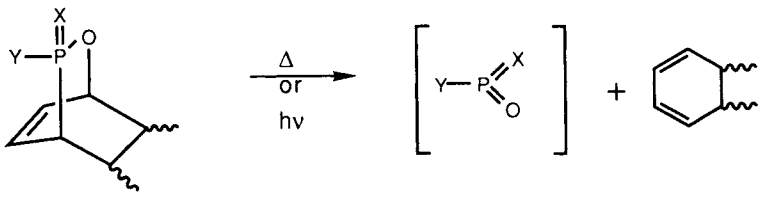
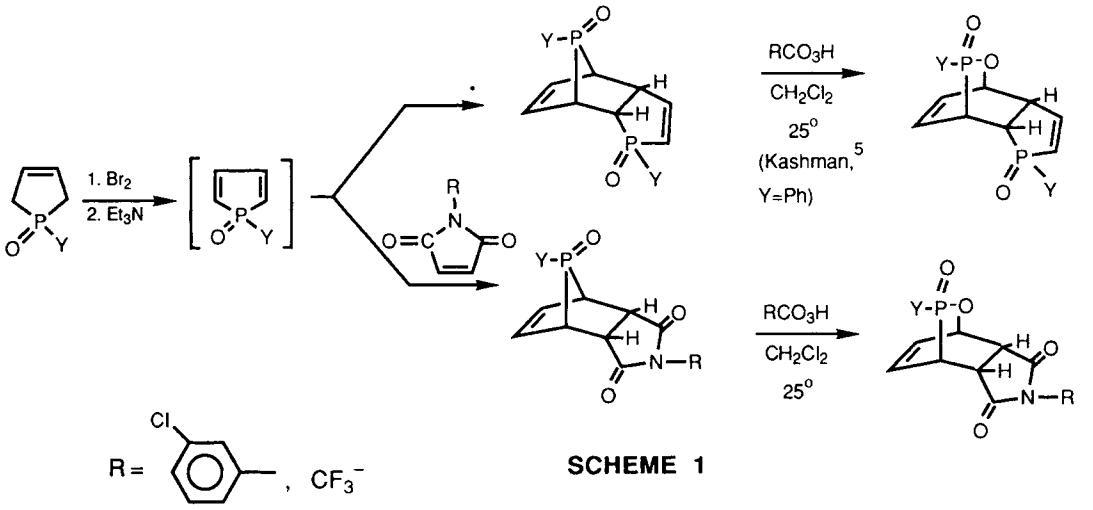
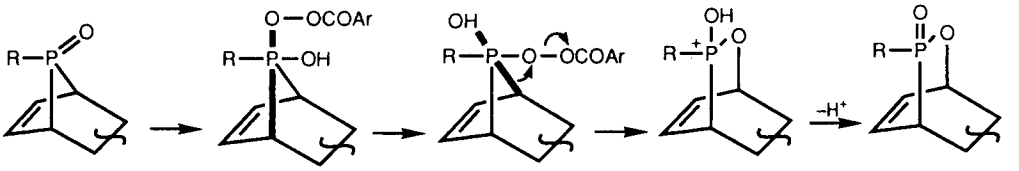


(1)



SCHEME 1

SCHEME 1



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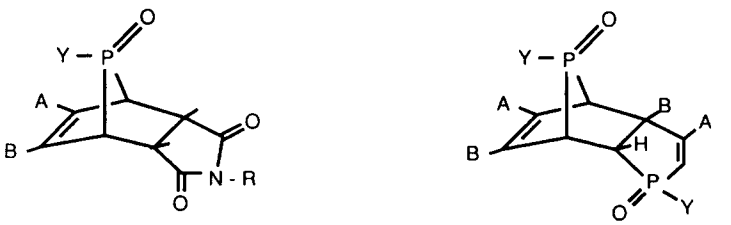


1. A = B = H
2. A = B = Me
3. A = Me, B = H

(R = Ph or Me)

A = B = H

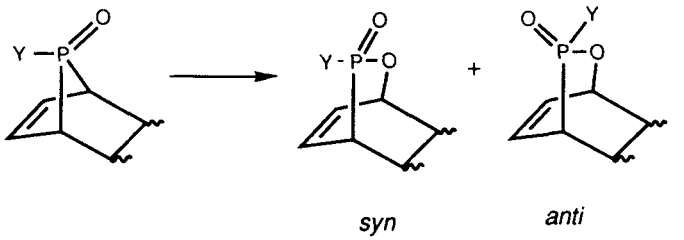
A = B = Me

A = Me, B = H

For both, Y may be alkyl, aryl, RO, ArO, OH, R_2N, RNH.

SCHEME 3

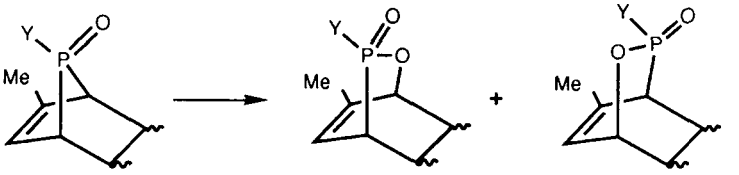
a. Stereoisomers



syn *anti*

(2)

b. Regioisomers



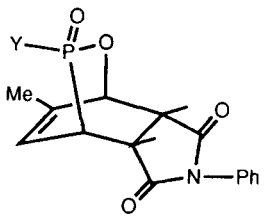
6-methyl 5-methyl

(plus stereoisomer of each)

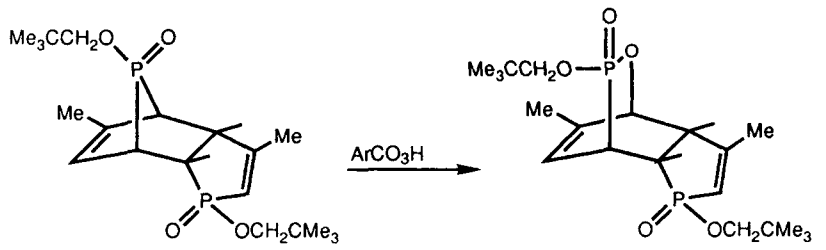
(3)

to the maleimide type, except for the phosphole oxide itself, which gives dimeric products. Both types of 7-phosphanorbornene derivatives have proved to be remarkably sensitive to a reaction with peroxy acids, which smoothly accomplishes at room temperature the selective insertion of oxygen into a carbon–phosphorus bond. This type of reaction, first observed by Kashman [5], only occurs with cyclic phosphorus compounds where considerable contraction of the internal C–P–C bond (to 80–85°) is present [6]. A plausible mechanism for the process is given in Scheme 2; support for the stereochemical result of retention at phosphorus will be presented later in this paper.

The O-insertion has been performed on compounds with a great variety of phosphorus functions at the 7-norbornene position, as well as with various C-methyl derivatives of the ring systems (Scheme 3). Most of our work has been conducted, however, with the framework from the use of *N*-phenylmaleimide, with one methyl group present. With this particular framework, two regioisomers are possible from the O-insertion, and each of these is capable of existing in syn, anti configurations at phosphorus (Equations 2 and 3). However, up to the present, we have observed only one instance (vide infra) of the formation of an anti isomer. The two regioisomers frequently do form in the reaction, however; with only one or two exceptions, one isomer greatly predominates over the other, and the minor isomer is usually lost in the product workup. The single product obtained from many such reactions always has been found to have the 6-methyl structure:

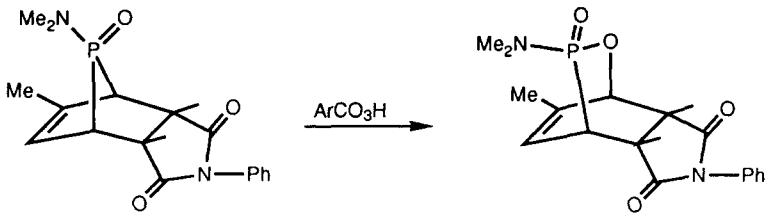


To place our structural assignments on a firm basis, we have now performed (with Professor R. O. Day) single crystal X-ray diffraction studies on a 7-phosphanorbornene precursor (**1**) and on the single isolated (major) O-insertion product (**2**) (Equation 4). Both the regio- and stereochemistry (retention) of the insertion process are revealed by these new studies. The internal O–P–C bond angle in the insertion product **2** is rather small (98°; but compare to 83° for C–P–C in the precursor **1**) for a phosphinate, indicating that some strain may still be present in the reaction product. This may be relevant to the ease with which the fragmentation occurs. We have previously reported [7] that the different type of 7-phosphanorbornene shown as **3** also gives a product with exactly the same regio- and stereochemistry (and O–P–C bond angle, 98°) (Equation 5), and we conclude that the reaction in general proceeds with retention and gives the 6-methyl regioisomer. However, we have recently encountered cases where the two initially formed isomers can either be isolated or obtained in enriched forms, and this has added greatly to our knowledge of the reaction. The assignment of the syn and 6-methyl features to one isomer is easily made by ^{1}H and ^{13}C NMR spectroscopy, making use of the pa-



(4)

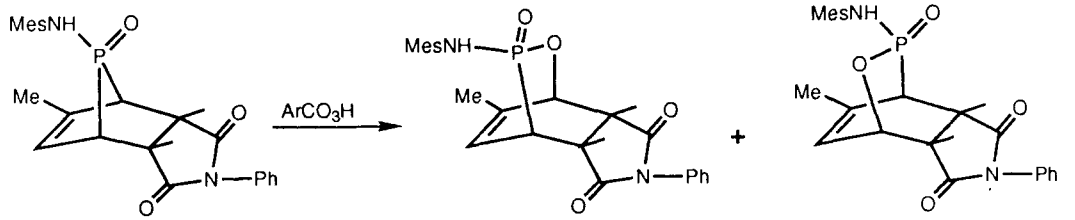
1, δ ^{31}P 81.0, 69.1 (J = 48.8 Hz) 2, δ ^{31}P 28.4, 68.4 (63.1)



(5)

δ ^{31}P 82.7 3, δ ^{31}P 25.0

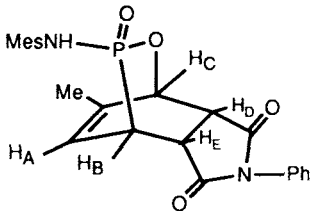
rameters for the compounds **2** and **3** unequivocally established by the X-ray analyses to have these features. In most of the cases studied so far, the other isomer has proved to be the regioisomer, with the 5-methyl feature. As yet, we have no direct evidence that this isomer has the syn configuration, and an X-ray analysis, once a suitable crystal has been obtained, is needed. A case in point is provided by the O-insertion into the mesitylamino derivative **4**, which has given two isomeric products (roughly 1:1) that are particularly stable and easily isolated by column chromatography. Some of their properties are summarized in Scheme 4. One isomer (**5a**) is assigned with confidence to have the same regio- and



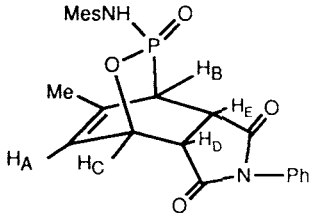
4 5a 5b (ratio 1:1)

		a	b
	mp	164-165.5°	207-220° (dec.)
	sol.	good	poor ($CHCl_3$, PhH, etc.)
	31p	23.20	22.05
^{13}C	O-C	74.37 (10.3)	70.68 (8.3)
	P-C	33.84 (112.2)	38.81 (112.8)
	=C-$\underline{C}H_3$	18.7 (^4J ~ 0)	19.6 (^3J = 4.4)
	O=C	170.96 (~0),	171.2 (~0),
		173.35 (18.9)	173.20 (19)

SCHEME 4



5a



5b

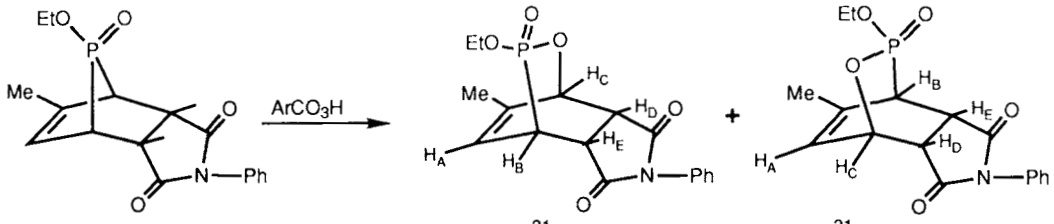
$C{=}CH_A$	δ 5.58 (J_{AB} = 8.4, $J_{A\text{-}Me}$ = 1.4, J_{PH} =8.4)	δ 6.17 (J_{AC} = 4.0, $J_{A\text{-}Me}$ = 1.5, $^4J_{PH}$ ~ 0)
$O\text{-}CH_C$	δ 5.11 (J_{CD} = 4.1, $J_{C\text{-}?}$ = 2.0, J_{PH} = 22.7)	δ 5.34 (J_{CA} = 4.0, J_{CD} = 5.3, J_{PH} = 23.4)
$=C\text{-}CH_3$	δ 1.71 ($J_{Me\text{-}A}$ = 1.4, $^5J_{PH}$ = 4.89)	δ 1.92 ($J_{Me\text{-}A}$ = 1.5, $^4J_{PH}$ = 1.5)

SCHEME 5

stereochemistry as determined for the dimethylamino analog (**3**) by X-ray analysis, since great similarities exist in the ^{13}C NMR spectra. The other isomer is assigned structure **5b**; this is based on the quite easily detected influence of the methyl group on the two bridgehead carbons, since it causes a several ppm downfield shift at that carbon to which it is β-oriented. The regioisomerism is fully confirmed by the ^1H NMR spectra, which must be taken at high field and with the aid of the 2-D technique to sort out the couplings. The data for some of the more informative protons are summarized in Scheme 5. There are quite distinct differences in the coupling parameters that form a firm basis for the assignments. For example, the olefinic proton is clearly coupled to the proton H–CP in the known structure and to H–CO in the other. Another situation where the isomers can be examined is presented by the O-insertion products of the O-ethyl derivative **6**. Here the regioisomers cannot be separated by chromatography, since the minor isomer is lost in the process. Careful fractional crystallization does allow the separation into enriched forms, however, and both ^1H and ^{13}C NMR spectra (Scheme 6) fully confirm that the two products are the regioisomers **7a** and **7b**.

A quite different result has been obtained for the O-insertion into the sterically crowded neopentyl ester. The two isomers can be separated in reasonable purity by column chromatography. The ^{13}C spectra are easily interpreted as proving the bridged structure, but the significant shift effects caused by methyl are missing. The olefinic proton is coupled to H–CP in both isomers, and it must be concluded that we have here the first example of stereoisomers formed in the O-insertion process (Scheme 7). Just how the bulky substituent affects the stereochemistry is not yet clear, but it presumably influences the P(V) intermediate structure. The O-insertion process is clearly sensitive to steric effects, for we have found that the O-insertion fails completely with the very bulky 2,4,6-tri-*t*-butylphenyl ester and is very slow with the adamantyl ester (three weeks reaction time) and the mesityl ester.

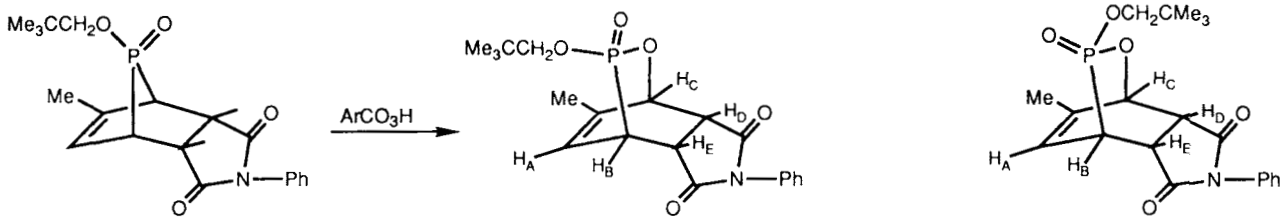
2,3-Oxaphosphabicyclo[2.2.2]octene derivatives with a P-phenyl substituent were included in our first studies [1] on the use of this ring system for the generation of 3-coordinate phosphoryl species, and it was established that the fragmentation could indeed be used to release the species $PhPO_2$. The early work made use of the phosphole oxide dimer framework as the O-insertion substrate, but we have now devised a superior route to a $PhPO_2$ precursor that will facilitate study of this species (Scheme 8). The phosphole **8** is easily prepared by the Mathey method [8] in over 80% yield; we have found that it can be oxidized with *t*-butyl hydroperoxide or *m*-chloroperbenzoic acid to the phosphole oxide **9**, which can be trapped by *N*-phenylmaleimide present in the mixture to give the desired 7-phosphanorbornene derivative **10**. This can be used successfully in the O-insertion reaction to form **11** (stereospecifically). However, a faster route to **11** has also been developed. When an excess (2–3 mo-



6 → 7a, ^{31}P = 25.09 + 7b, ^{31}P = 24.48

		^1H (2-D)		^{13}C		
		7a	7b		7a	7b
C=CH_A	δ	6.10	6.11	O-C	77.7 (8.1)	74.0 (7.7)
	$^3J_{PH}$	8.7	~0	P-C	33.6 (124.9)	38.5 (122.4)
	$^3J_{HH}$	8 (H_B)	4.5 (H_C)	=C-CH_3	20.0 (0)	21.9 (4.0)
O-CH_C	δ	5.17	5.32	O=C	173.1 (0),	173.3 (0),
	J_{PH}	23.5	24.0		175.4 (21.0)	175.2 (21.0)
	$^3J_{HH}$	4.0 (H_D)	4.5 (H_A)			

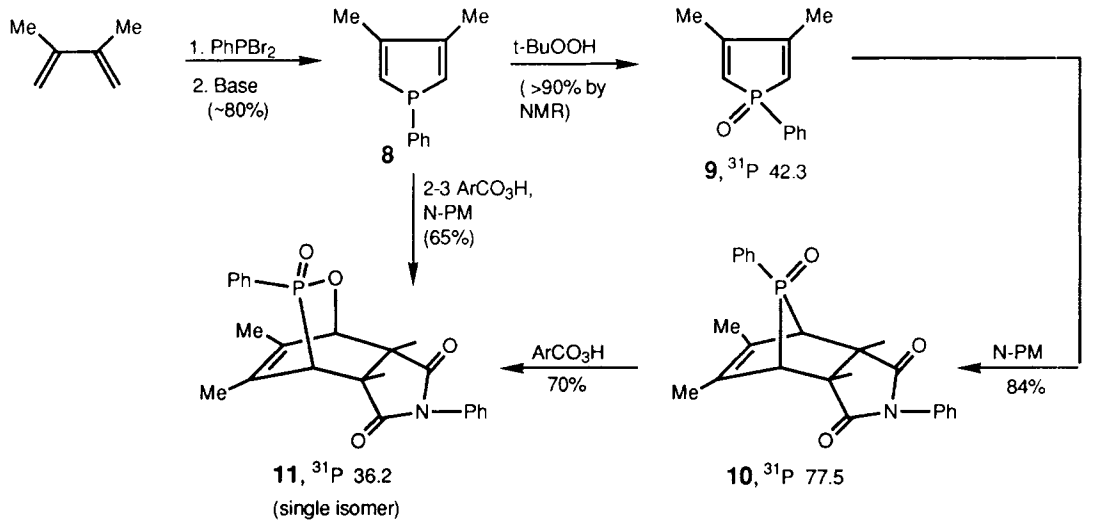
SCHEME 6



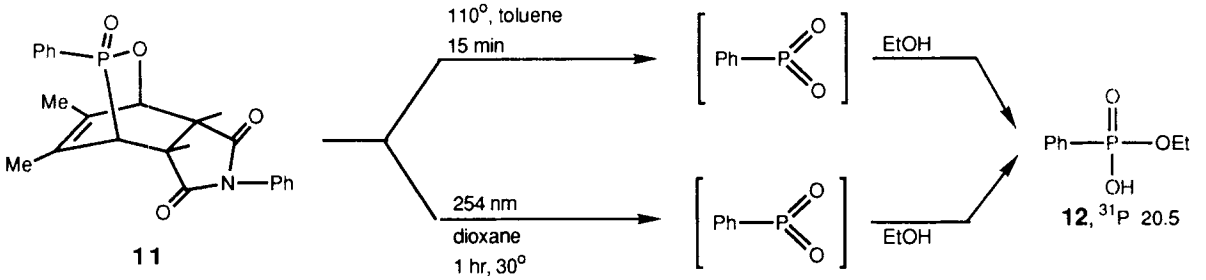
A, ^{31}P = 25.60 (major) B, ^{31}P = 22.58 (minor)

		^1H (2-D)		^{13}C		
		A	B		A	B
C=CH_A	δ	6.05	6.18	O-C	77.29 (4.6)	77.2 (6)
	J_{AB}	present	present	P-C	33.08 (125.8)	32.67 (126.3)
O-CH_C	δ	5.13	5.17	C=O	175.07 (20.7),	174.96 (17.3),
	J_{CD}	present	present		172.85 (~0)	172.71 (~0)

SCHEME 7



SCHEME 8

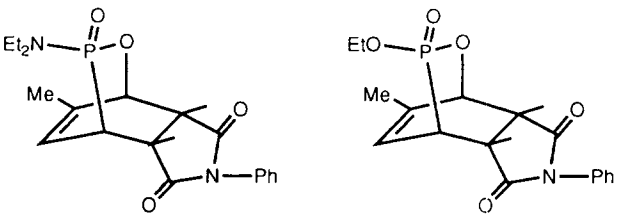


SCHEME 9

lar) of *m*-chloroperbenzoic acid is used to oxidize phosphole **8** in the presence of the maleimide, the 7-phosphanorbornene that is formed proceeds to undergo the O-insertion reaction. It is therefore possible to effect a one-step transformation of the phosphole **8** to the O-insertion product **11** in 65% yield (Scheme 8).

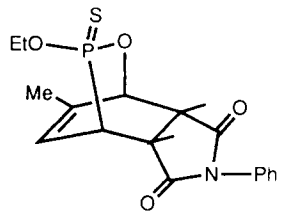
The new compound **11** has been found to decompose smoothly when heated in toluene at 110° for only 15 minutes. When ethanol is present, all phosphorus is trapped in the form of ethyl phenylphosphonate (**12**). Of more significance is the observation that the O-insertion product is also fragmented easily by ultraviolet light (254 nm) at room temperature (Scheme 9). This makes the species $PhPO_2$ readily accessible, and will expedite further research on its characteristics.

The mechanism by which the 2,3-oxaphosphabicyclo[2.2.2]octene system fragments thermally is of considerable interest. Establishment of a unimolecular, retrocycloaddition mechanism would provide compelling proof that a free metaphosphate, of but fleeting existence, is being released. Employing ^{31}P NMR as our analytical technique, we have performed a number of determinations of the kinetics of thermal fragmentations. Runs were made in solvents of widely different polarities (toluene, chloroform, benzonitrile, and dimethylsulfoxide), using as starting materials the compounds **13**, **14**, and **15**. The rate of disappearance of the starting materials in various solvents was measured and it was found that strictly first-order kinetics were followed in every case. The reaction

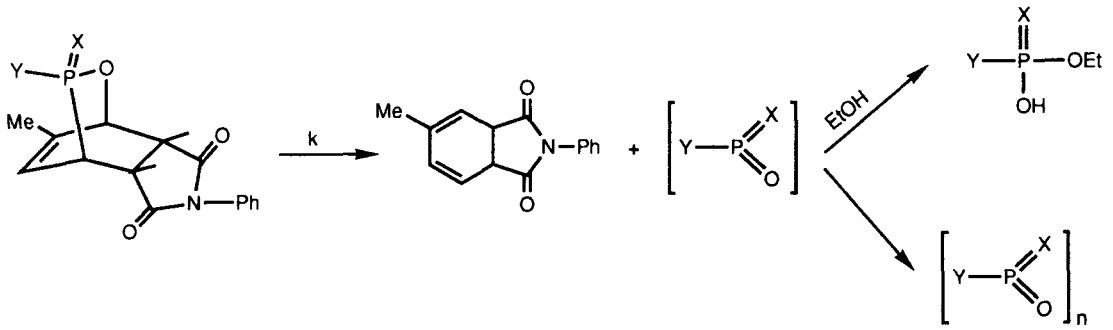


13

14



15



SCHEME 10

rates did not differ greatly, implying that the polarity of the groups on phosphorus had little effect on the reaction (Scheme 10).

The kinetics were also determined when ethanol was present as a trapping agent for the released metaphosphate, and the important observation was made that the rate of fragmentation was still first-order in the starting material. (Some small, variable effects on the first-order rate constants were observed). Some illustrative data are shown in Figure 1. This implies that the trapping agent plays no preliminary role in the fragmentation, and only acts after the highly reactive metaphosphate is released. Consistent with this conclusion was the observation that the rate of fragmentation was independent of the identity of the alcohol; half-lives for the reaction in DMSO with different alcohols are given in Table 1.

The effect of solvent can be seen in the data in Table 2, especially for compound **13**. The reaction is faster in the more polar solvents, but the increase is relatively small compared to the great change being made in polarity. The solvent effect supports a unimolecular, retrocycloaddition process in which weak polarity develops in the transition state, but speaks against the formation of an ionic intermediate and hence of a two-step process. Activation parameters determined from the effect of temperature on the first-order rate constants are given in Table 3. The values for the entropy of activation are especially important; they are small and negative, and are in the range expected for retro-Diels–Alder reactions. A fragmentation that occurred in steps with a charge-separated intermediate would likely have an entropy of activation that is positive, and influenced by solvent polarity.

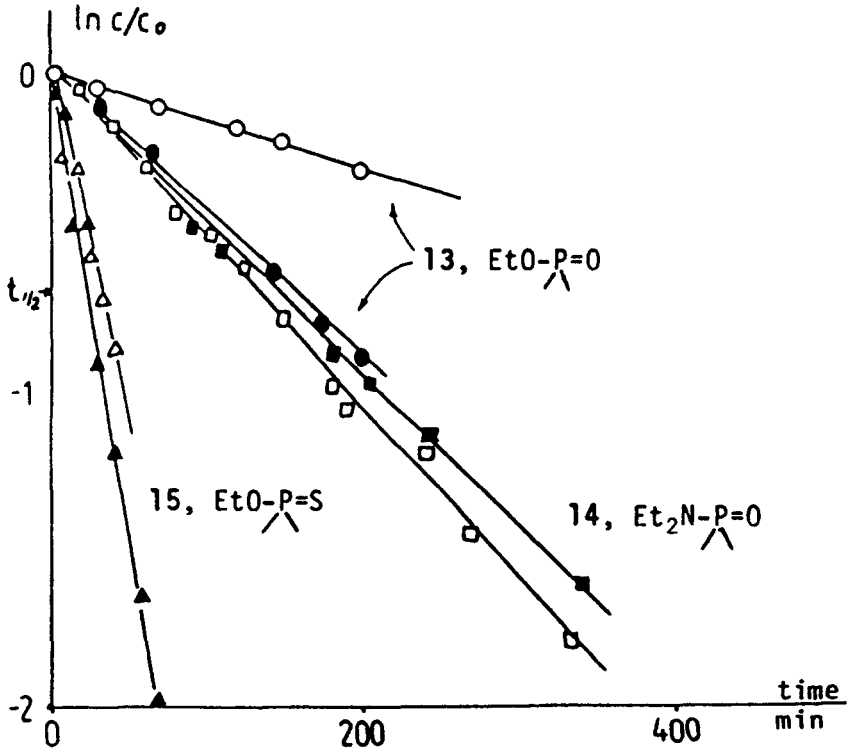


FIGURE 1 Kinetics of Fragmentation of **13**, **14**, and **15**. Unfilled marks are for reaction in the presence of ethanol; filled marks in the absence of ethanol.

TABLE 1 Half-Lives ($t_{1/2}$, min) for Thermolysis of **13** and **14** in DMSO

	EtOH	*i-PrOH*	CF_3CH_2OH	*H—OH*
13	23.7 ± 1.7	24.32 ± 0.72	24.57 ± 0.93	
14	29.61 ± 1.1		27.43 ± 0.65	28.31 ± 0.69

TABLE 2 Half-Lives ($t_{1/2}$, min) for Thermolysis of **13**, **14**, and **15** at 373 K

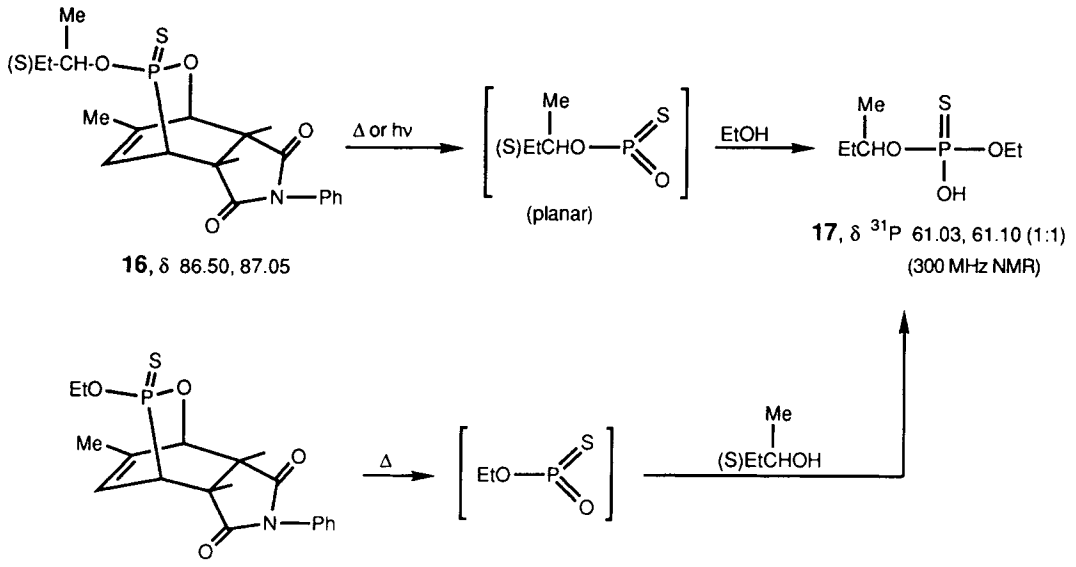
Compound	*Solvent*	*Without ROH*	*With EtOH*
13	DMSO	—	23.7 ± 1.7
	Benzonitrile	—	73.06 ± 0.83
	$CHCl_3$	127 ± 15	119 ± 12
	Toluene	—	196.8 ± 7.7
14	DMSO	—	29.6 ± 1.1
	Benzonitrile	—	152 ± 11
	$CHCl_3$	174.5 ± 7.1	371 ± 24
15	$CHCl_3$	21.1 ± 1.9	34.6 ± 4.3

TABLE 3 Activation Parameters

Compound	*Solvent*	*lnA* s^{-1}	E_a *kJ/mol*	$\Delta H^{\ddagger}_{373K}$ *kJ/mol*	$\Delta S^{\ddagger}_{373K}$ *J/mol·K*	*(e.u.)*
13	DMSO	28.7 ± 1.3	112.7 ± 4.1	110	−17	(−3.9)
	$CHCl_3$	28.6 ± 1.6	117.6 ± 4.8	115	−17	(−3.9)
14	DMSO	25.29 ± 0.88	102.8 ± 2.3	100	−45	(−11)
	$CHCl_3$	22.7 ± 1.3	102.7 ± 3.8	100	−66	(−16)
15	$CHCl_3$	25.6 ± 2.1	104.1 ± 6.2	102	−43	(−10)

Finally, we have performed competition experiments in which the metaphosphate has the opportunity to react with two hydroxy species of quite different nucleophilicities [9]. As an example, ethyl metaphosphate was generated in the presence of an equimolar mixture of ethanol and the less nucleophilic trifluoroethanol; the reaction with ethanol was 3.3 times faster than that with the less nucleophilic fluoro derivative. A selectivity effect is consistent with the fleeting existence of the metaphosphate in free form. Drawing upon all the points mentioned above, we feel that our kinetics studies provide compelling reasons to believe that the thermal fragmentation of the 2,3-oxaphosphabicyclo[2.2.2]octene system proceeds by a retrocycloaddition process that releases a free metaphosphate.

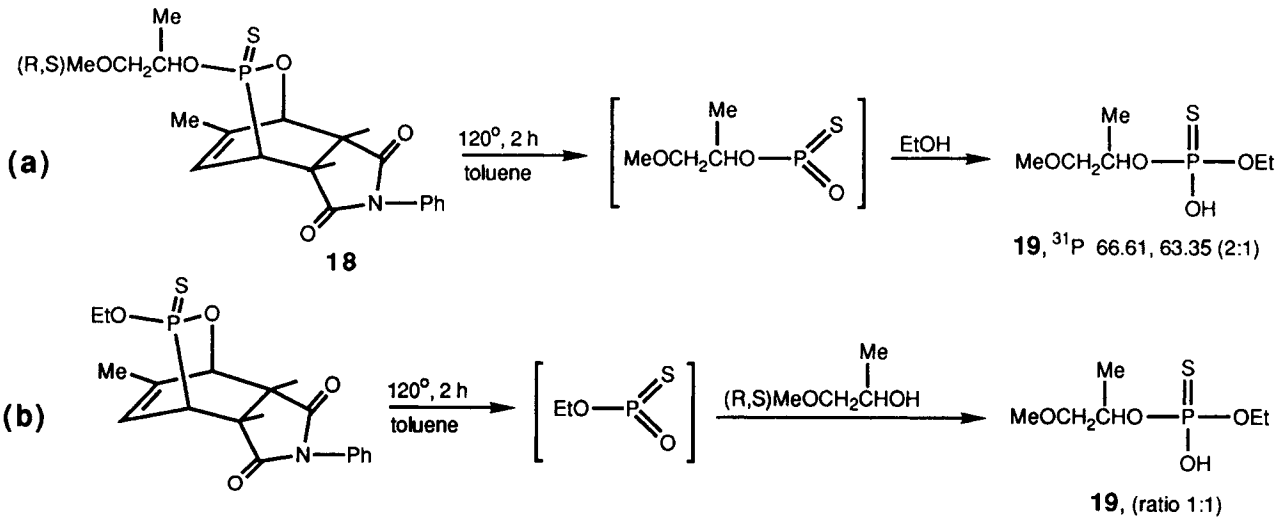
Consistent also with the results of the kinetics studies are observations on the stereochemistry of the species being released in the fragmentation. A free metaphosphate is a planar species [10] and presents equal opportunity to an attacking nucleophile to approach from either face. If the metaphosphate has three different groups present on P, a chiral phosphorus function will be created. An alkyl substituent in the metaphosphate that is also chiral (either as a single enantiomer or as a racemate) should lead to a 1:1 mixture of diastereoisomers. This is a concept that is readily tested experimentally using 2,3-oxaphosphabicyclo[2.2.2]-octenes as the source of metaphosphates, since it is easy to construct an appropriate chiral precursor. In our first experiments [3], we synthesized compound **16** for this purpose, and as noted in Scheme 11 its decomposition (both thermally and photochemically) in the presence of ethanol did indeed give the predicted result of a 1:1 mixture of diastereoisomers of **17**. A similar result should be obtained when a chiral alcohol reacts with an appropriate metaphosphate, and indeed the (S) isomer of *sec*-butyl alcohol reacted with ethyl metathiophosphate to give the same 1:1 mixture of diastereoisomers **17** as when the reverse combination was used (Scheme 11). We have proceeded to test another concept in metaphosphate chemistry, that of anchimeric participation from a properly positioned nucleophilic substituent. Metaphosphates when generated in solution are extraordinarily electrophilic, and, as will be discussed shortly, are capable of attacking ethereal oxygen. A methoxy group positioned on a chain so as to give a 5-membered ring



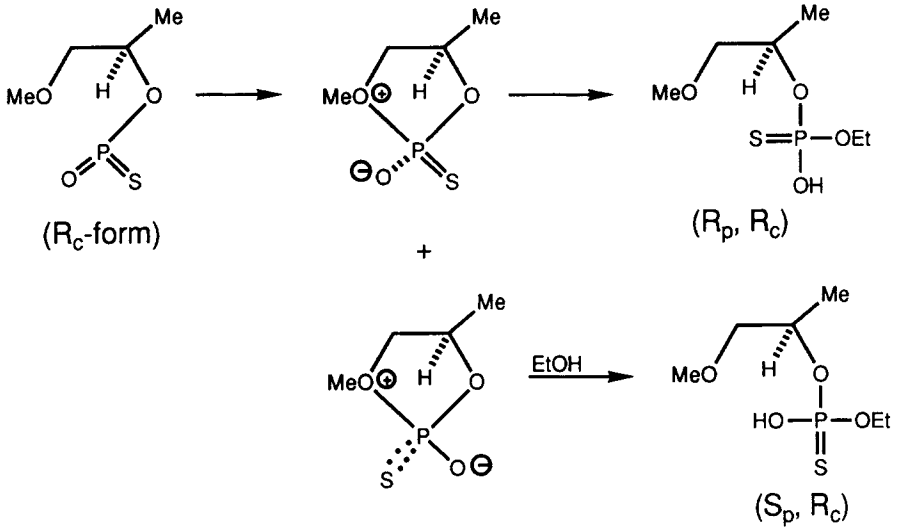
SCHEME 11

through internal interaction with the metaphosphate could modify the steric characteristics of this function and bias the direction of attack of an approaching nucleophile. We have synthesized compound **18** as a model to test this concept of anchimeric participation, since the methoxy group is positioned to give a 5-membered ring through interaction with the phosphorus function (Scheme 12). Indeed, when the metaphosphate was generated thermally from **18** in the presence of ethanol, the mixture of diastereoisomers was in the ratio 2:1. However, when the same ester product **19** was generated from the reverse combination (with ethyl metathiophosphate and the chiral alcohol), the ratio was the expected 1:1. In Scheme 13, the cyclic oxonium ions from the methoxy group participation are shown, and it can be seen that an attacking nucleophile will find a different steric environment on the two faces of the ring. We propose that this accounts for the stereochemical result of Scheme 12a, but further study of this effect is needed.

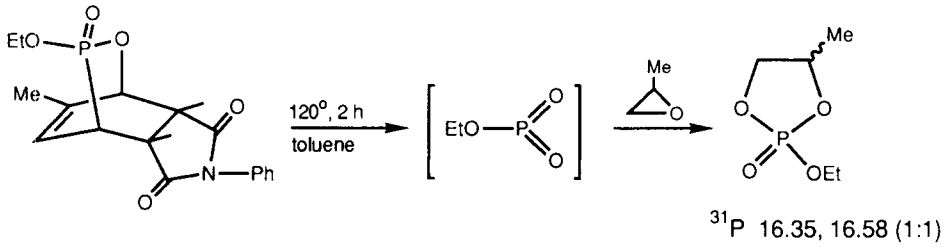
What is the evidence that a metaphosphate can form an oxonium ion with an ether? The best indication of this comes from a new reaction we have observed when ethyl metaphosphate is generated thermally from a 2,3-oxaphosphabicyclo[2.2.2]-octene in the presence of an epoxide (Scheme 14). The epoxide is a very efficient trapping agent for the metaphosphate, and gives a product conclusively identified (by NMR, GC-MS, and synthesis) as a 1,3,2-dioxaphospholane oxide. The reaction has also been performed with great success with other types of metaphosphates (Scheme 15) and with various epoxides. The reaction must commence with



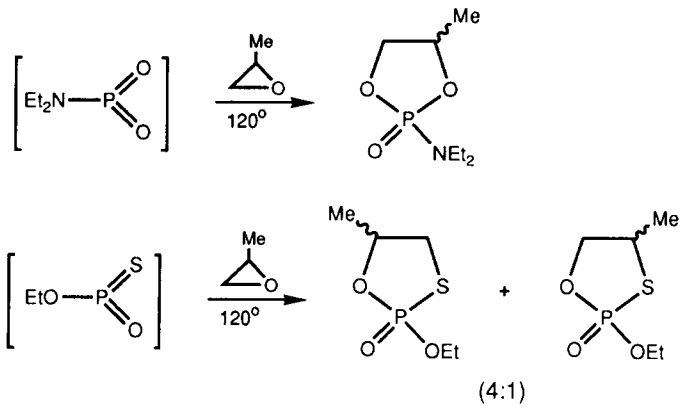
SCHEME 12



SCHEME 13



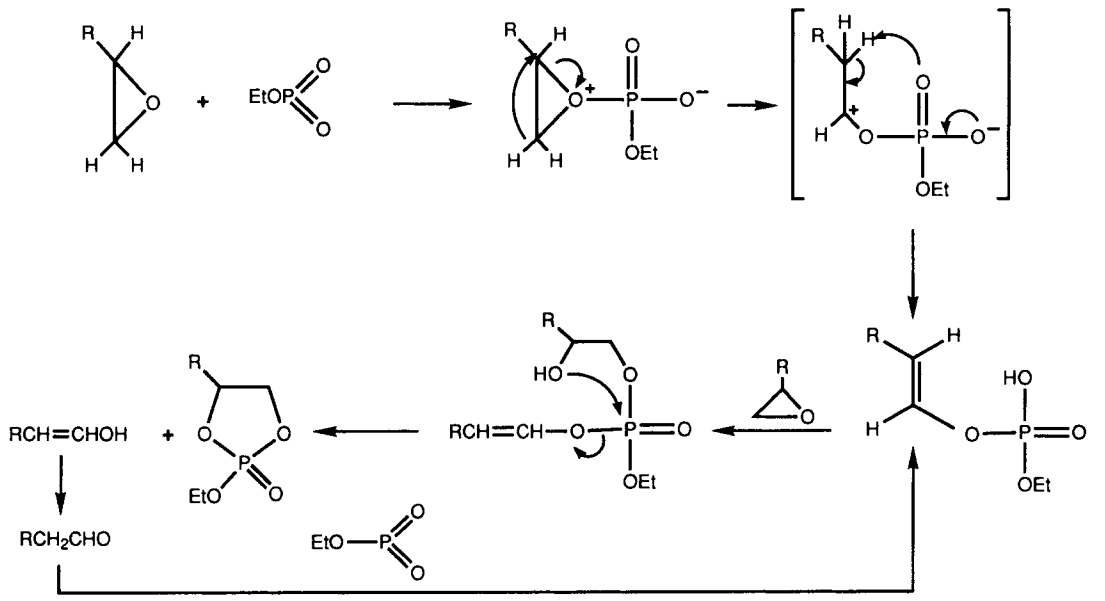
SCHEME 14



SCHEME 15

the formation of an oxonium ion (Scheme 16), which then is proposed to rearrange by a hydride shift as is common for Lewis salts of epoxides. Various pathways are then possible to explain the formation of the cyclic product [11]; a prominent route is shown in Scheme 16. It has also been observed that a methyloxetane undergoes ring cleavage when present in the medium for thermal generation of a metaphosphate. From the complex ^{31}P NMR signals at δ 0 to −2, the major product is indicated to be polymeric with non-cyclic phosphate groups and has not been characterized. The significant point is that the oxetane oxygen has been attacked by the metaphosphate.

We conclude with the observation that the 2,3-oxaphosphabicyclo[2.2.2]octene ring system has already served admirably as a precursor of 3-coordinate phosphoryl compounds; much new knowl-



SCHEME 16

edge of these transient species has already been gained, and more can be expected from future research. There no longer seems to be a basis for questioning the existence of the freedom of the 3-coordinate species being generated by this approach, although the lifetime of the species under the conditions being used is exceedingly short and will always present a formidable challenge in laboratory experiments.

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