O-Ethyl Phosphoramidic Acids with Sterically Demanding N-Substituents: Useful Precursors of Ethyl Metaphosphate on Thermolysis[1]

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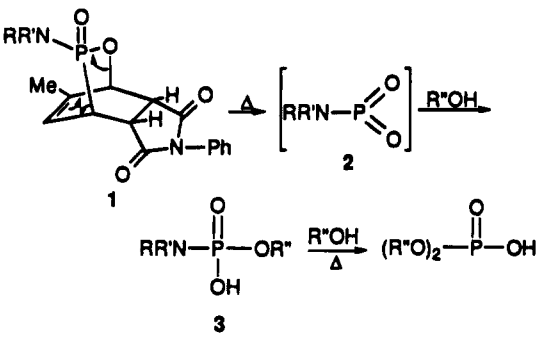
Kinetics of the thermal fragmentation of four *N*-substituted derivatives of *O*-ethyl phosphoramidic acids, (EtO–P(O)(NRR')(OH), were examined. When N contained either of the sterically demanding mesityl or 1-adamantyl groups, the reaction followed first-order kinetics, both in the absence and presence of an alcohol trapping reagent. In the former case, the product was a pyrophosphate (RR'N(EtO)(O)P–O–P(O)(OEt)OH). In the latter case, phosphorus was trapped as a dialkyl phosphate. Both reactions are therefore indicated to follow an elimination–addition mechanism, with ethyl metaphosphate as transient intermediate. The pyrophosphate is derived from reaction of the metaphosphate with unreacted phosphoramidic acid. With less bulky substituents (*N*-phenyl or *N,N*-diethyl), mixed first- and second-order kinetics were followed in the absence of a trapping agent; some bimolecular interaction of the substrate to form the pyrophosphate product is indicated by the second-order kinetics. Product analyses and quantitative measurements were made with ^{31}P NMR spectroscopy. From all phosphoramidic acids, the intermediate metaphosphate was effectively trapped by reaction with the OH group on the surface of solid silica gel. The presence of covalently bonded phosphate on the surface was shown by ^{31}P and ^{29}Si CP/MAS NMR spectroscopy.

In previous studies[2,3] on the trapping of thermally generated metaphosphoramides (**2**) with alcohols, we noted that the initially formed *O,N*-substituted phosphoramidic acids (**3**) reacted further with the alcohol to form dialkyl phosphate esters. It was also possible to



generate the metaphosphoramides at room temperature from precursor **1** by photochemical means, and under these milder conditions they were trapped successfully as the phosphoramidic acids **3**. Heating of the phosphoramidic acids with alcohols, the conditions of the thermal generation experiments, was then shown to give the phosphate esters.

We were especially attracted to the behavior of the compounds with sterically demanding groups as substituents on nitrogen, for we noted qualitatively that the replacement of these groups by alcohols proceeded faster than did replacement of simpler groups. *O*-Ethyl *N*-mesitylphosphoramidic acid especially seemed to give diethyl phosphate surprisingly rapidly on heating with ethanol. This behavior is not consistent with the common addition–elimination (AE) mechanism of displacement of groups from phosphoryl compounds that involves 5-coordinate intermediates or transition states; in these trigonal-bipyramidal structures, the group to be displaced occupies an apical position, but this is not the position preferred by sterically demanding groups because of interaction with the substituents in the equatorial plane (bond angle 90°).[4] An alternative mechanism[5] for displacements at phosphoryl groups involves an elimination of a group from phosphorus to form a 3-coordinate intermediate that then adds the attacking nucleophilic agent (elimination–addition, EA mechanism). The 3-coordinate intermediate is a derivative of metaphosphoric acid, a species that is of such high reactivity that no form has even been observed directly as a product or an intermediate in any reaction conducted in solution.[6,7] Nevertheless, this mechanism is known to operate for substitutions at certain types of phosphoric acid derivatives.[5]

During the 1950s and 1960s, certain *O,N*-substituted phosphoramidic acids attracted considerable attention because they were found in the laboratories of Todd[8] and of Khorana[9] to be peculiarly useful as agents for the creation of pyrophosphate groups from phosphates, with special and, at the time, extremely important application in the nucleotide field. Additionally, it was noticed that

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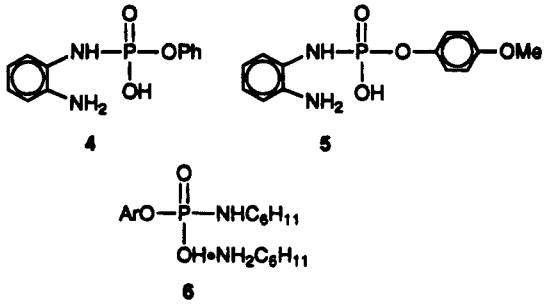
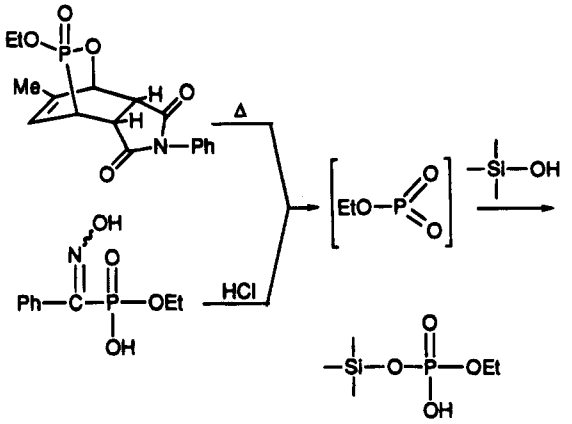
the reaction of a phosphate with this form of phosphoramidic acid occurred more readily than did reaction with an alcohol to form a simple dialkyl phosphate, thus giving the process important specificity properties. Consideration was given to the possibility that the phosphorylation might occur by the EA mechanism with an alkyl metaphosphate intermediate,[10] but this could not be confirmed by mechanistic studies. Thus, *O*-benzyl phosphoramidic acid on reaction with water in dioxane gave second-order kinetics (at 70 °C, k = 14.6 L mol^{-1} h^{-1}) speaking against the EA mechanism which would require first-order kinetics.[11] *O*-Methyl *N*-cyclohexylphosphoramidic acid similarly followed second-order kinetics in the formation of the pyrophosphate at 70 °C in anhydrous dioxane (k = 12.6 L mol^{-1} h^{-1}) or in acetonitrile (k = 33.0 L mol^{-1} h^{-1}),[12] as did *O*-benzyl *N*-cyclohexylphosphoramidic acid in dioxane (k = 14.6 L mol^{-1} h^{-1}).[12] There has been little interest in this type of phosphoramidic acid since that time; a review of the annual reports on phosphorus chemistry[13] for the period June 1969 to June 1991 revealed only three publications concerned with their properties, none of which provided fresh mechanistic insight. Koizumi et al.[14] refluxed phosphoramidic acid **4** in methanol and obtained a 95% yield of methyl phenyl phosphate; it was noted that this could arise from either the EA or AE mechanism. A similar compound **5** was found by Takaku et al.[15] to give the alkyl aryl phosphate on reaction with an alcohol (with catalysis by cupric chloride) or the pyrophosphate on reaction with an aryl phosphate. The cyclohexylamine salt of *O*-aryl phosphates **6** at 200 °C (neat) gave the dicyclohexylamine salt of the diaryl pyrophosphate.[16]



The observations we have made on the behavior in anhydrous media of *O*,*N*-substituted phosphoramidic acids bearing sterically demanding groups on nitrogen are just the opposite of those reported in the early literature for simpler derivatives; in dilute solutions, displacement of the amino group by alcohols occurs quite readily, and in preference to pyrophosphate formation. The EA mechanism would, as noted, explain these results, but the literature does not justify the assumption that it is in operation. It therefore appeared from our observations that the steric size of the *N*-substituent must be playing a crucial role in determining the mechanistic pathway, a point not hitherto considered in the phosphoramidic acid literature. Furthermore, it was suggested that properly designed phosphoramidic acids could serve as useful new sources of alkyl metaphosphates. We have therefore proceeded to explore the mechanism of the displacement of the amino group by determining the kinetics of fragmentation of some phosphoramidic acid derivatives of types not previously examined in the early studies. Our work was greatly facilitated by the powerful technique of ^{31}P NMR spectroscopy, which was not available to the early investigators. It was employed not only to identify reaction products but also for quantitative analysis in rate determinations. We have furthermore performed trapping reactions with the novel agent silica gel to probe for the transient existence of a metaphosphate intermediate in the thermal decomposition of the acids. The surface hydroxy groups of this solid are readily phosphorylated by metaphosphates; we have previously employed this technique to detect the intermediacy of metaphosphates when generated by two entirely different techniques,[17] as shown in Scheme 1. That surface phosphorylation has taken place in these experiments is indicated by CP/MAS ^{31}P and ^{29}Si NMR spectral measurements. This process is of interest in another sense; phosphorylated silica gel has shown some valuable chromatographic properties,[18] and availability from simple phosphoramidic acids would be a preparative advantage over the use of the precursors of Scheme 1.

Scheme 1



Synthesis of Phosphoramidic Acids. Simple *O*,*N*-substituted phosphoramidic acids are not well known compounds since they are frequently unstable. However, their synthesis is straightforward and can be performed with conventional reactions as outlined in Scheme 2. The starting material, ethyl phosphorodichloridate, is commercially available. The overall yields were generally around 60%. The intermediate monochlorides **7a–d** were identified by ^{31}P NMR, but not isolated except for **7c**, which proved to be stable enough for elemental analysis. The NMR spectra showed no other phosphorus species to be present in detectable amounts. The phosphoramidic acids **8a–d** were generally made immediately before use by the hydrolysis of the chlorides **7a–d**. Their instability made attempts to prepare pure solids for elemental analysis only partly successful, but the struc-

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(16) Ruveda, M. A.; Zerba, E. N.; Podesta, R.; de Licastro, S. A. *Tetrahedron* **1975**, *31*, 885.
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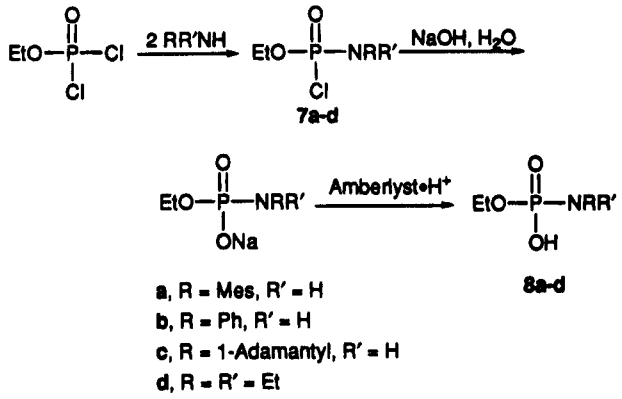
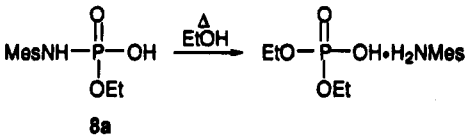
(18) Quin, G. S.; Wu, X.-P.; Quin, L. D.; Stewart, C.; Uden, P. C. 33rd International Union of Pure and Applied Chemistry Congress, Budapest, Hungary, August 1991; Abst. 1031.

Scheme 2



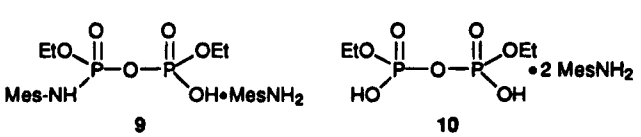
ture and purity of the acids was confirmed by ^{31}P NMR spectroscopy. The salts were characterized by negative ion mass spectrometry.

Fragmentation of *N*-Aryl *O*-Ethyl Phosphoramidic Acids. The *N*-Mesityl Derivative (8a). Phosphoramidic acid **8a** (^{31}P NMR δ 7.0 in $CDCl_3$) was heated at 80 °C in anhydrous ethanol. ^{31}P NMR spectroscopy showed that all starting material had reacted after 1 h and formed a single product with δ −0.68, attributed as in earlier work[2] to diethyl phosphate (probably as the amine salt). This upfield shift is expected from the replacement of the amino group by alkoxy. When the



8a

phosphoramidic acid was heated in toluene without a trapping agent, the only product gave a ^{31}P NMR spectrum which consisted of a doublet of doublets at δ −5.9 and δ −12.5 with J = 19 Hz. These signals are indicative of a pyrophosphate bond as in **9** (Scheme 3). The upfield doublet is in the region characteristic of a phosphate ester moiety (e.g., diethyl pyrophosphate salt **10** has δ −11.7). A phosphoramidate moiety as part of the pyrophosphate would account for the downfield signal, since the usual effect of *P*-amino giving more downfield signals than *P*-alkoxy would be expected. This is, in fact, the same type of structure proposed by the earlier workers for the product of thermolysis of other phosphoramidic acids but not supported by ^{31}P NMR spectroscopy. When the acid was heated in toluene that contained 2 equiv of ethanol, signals for both diethyl phosphate and the pyrophosphate **9** were present. On occasion, a singlet has also appeared at δ −11.7 that appears to arise from **10**, which would form if a trace of water were present in the medium that would compete with **8a** in the reaction with ethyl metaphosphate.



9 **10**

Consideration of the mechanism of these processes must begin with the observation that phosphoramidic acids can exist in an equilibrium between the neutral form **8a** and the dipolar forms **8a'** (Scheme 3). Either form could presumably be the reactant giving the pyrophosphate, or the dialkyl phosphate when alcohol is

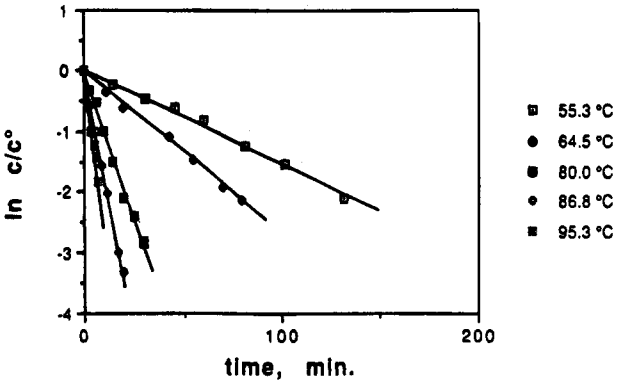


Figure 1. Kinetics of the thermolysis of **8a** in toluene.

Table 1. Kinetics of the Thermolysis of 8a in Toluene at Various Temperatures

temp, °C	rate constant: k × 10^3, s^{-1}
55.3	0.261 ± 0.007
64.5	0.441 ± 0.011
80.0	1.612 ± 0.047
86.8	2.809 ± 0.064
95.4	4.218 ± 0.160

present. The literature provides ample precedents for the importance of the dipolar form. Thus, an X-ray analysis of the parent phosphoramidic acid confirmed the dipolar structure,[19] and infrared studies on *N*-benzylphosphoramidic acid[11] showed the existence of this structure in solution, furthermore detecting considerable influence of the solvent on the position of equilibrium. In work to be reported elsewhere,[20] we have established that the species in the equilibrium that undergoes cleavage of the N—P bond is the dipolar form **8a'**. This was accomplished by the use of the kinetic isotope effect based on the changes in the $^{14}N/^{15}N$ ratio in the phosphoramidic acid as the reaction proceeds, as well as by the effect of deuterated ethanol on the reaction rate.

The kinetics followed by the processes that led to the pyrophosphate or (in the presence of alcohol) to the dialkyl phosphate allow a clear-cut discrimination between the EA and AE mechanisms; in both cases, the reactions followed first-order kinetics for three half-lives, convincingly pointing to the EA mechanism with the slow formation of a metaphosphate intermediate followed by a fast reaction to form the products. The AE mechanism is bimolecular and would require second-order kinetics. Thus, the rate of disappearance of the phosphoramidic acid in toluene at various temperatures was determined by recording the intensity of the ^{31}P NMR signal relative to that of a standard (triphenylphosphine oxide, δ 28.0 in $CDCl_3$). The plots of concentration against time were linear, as seen in Figure 1 and Table 1. This was true for the solvents acetonitrile and dimethyl sulfoxide as well (Table 2), in which rather similar first-order rate constants were observed. This attests to the lack of an appreciable solvent effect on the rate-controlling step. The origin of the pyrophosphate **9** that is formed in the absence of an alcohol requires further consideration, since two processes can be visualized. The most obvious explanation, also considered in the early literature, is that the metaphosphate intermediate attacks some unreacted starting phosphoramidic acid (Scheme 3). An

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(20) Jankowski, S.; Paneth, P. Submitted for publication.

Scheme 3

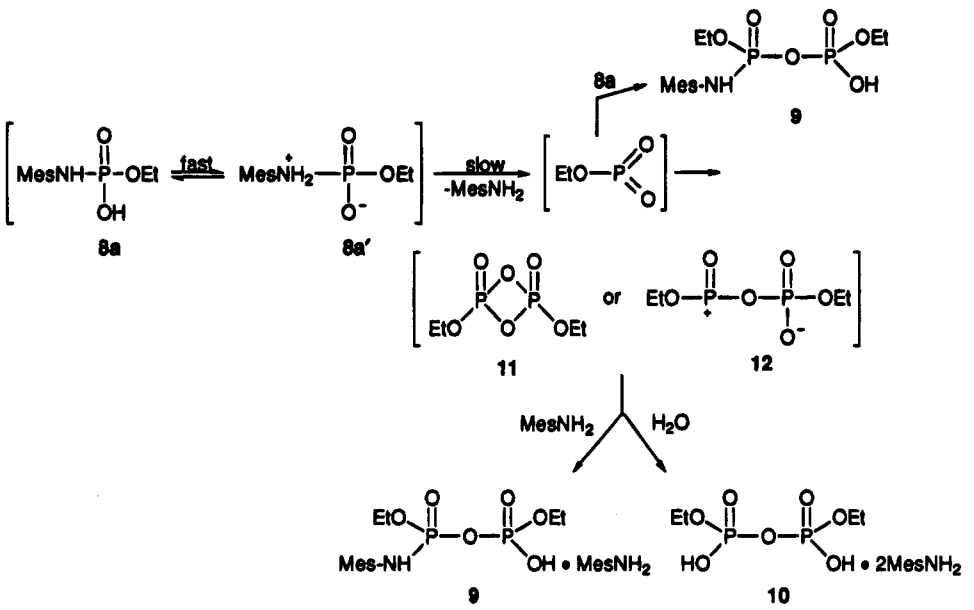


Table 2. Kinetics of the Thermolysis of 8a in Various Solvents at 80 °C

solvent	concentration, mol/L	rate constant: k × 10^3, s^{-1}
toluene	0.04	1.95 ± 0.06
toluene	0.19	1.61 ± 0.05
acetonitrile	0.17	0.99 ± 0.02
DMSO	0.27	2.29 ± 0.06

Table 3. Kinetics of the Thermolysis of 8a with Ethanol Present

medium	temp, °C	rate constant: k × 10^3, s^{-1}
100% EtOH	86.0	7.38 ± 0.29
100% EtOH	80.0	4.98 ± 0.09
100% EtOH	75.4	3.34 ± 0.16
100% EtOH	64.0	1.57 ± 0.05
100% EtOH	40.5	0.243 ± 0.014
toluene/2 equiv EtOH	80.0	1.77 ± 0.09
toluene/5 equiv EtOH	70.6	1.31 ± 0.02
toluene/5 equiv EtOH	60.6	0.718 ± 0.037

alternative is that the pyrophosphate bond is first formed by condensation of two molecules of the metaphosphate, giving either a cyclic (**11**) or dipolar (**12**) intermediate that then rapidly is attacked by the mesitylamine in the medium (Scheme 3). However, monitoring the reaction by ^{31}P NMR showed that the pyrophosphate begins to form almost immediately, and there were no transient signals that could be associated with forms **11** or **12**.

First-order kinetics were also observed when the fragmentation of **8a** was performed in pure ethanol, or in toluene containing 2 equiv of ethanol (Table 3). While the first-order kinetics eliminate bimolecular mechanisms for the formation of the pyrophosphate in the absence of alcohol, and the formation of dialkyl phosphate in the presence of ethanol, it needs to be considered further why the more complicated case of pyrophosphate formation should follow first-order kinetics, since the starting materials is involved both in forming the metaphosphate and then in a secondary reaction with it. We have, in fact, encountered such behavior before in kinetics studies on **1**;[21] the kinetic *order* remains the same, but the rate of decomposition of substrate increases. We can explain the competition between pyrophosphate and dialkyl phosphate formation in the following way by analysis of the kinetics. Consider first the dipolar species, in equilibrium with the neutral form, as the source of the metaphosphate (k_3). The metaphosphate can react either with starting material (k_4) or with alcohol when present (k_5).

$$\mathrm{RNHP(O)(OEt)OH} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{RN^+H_2P(O)(OEt)O^-}$$

$$\mathrm{RN^+H_2P(O)(OEt)O^-} \xrightarrow{k_3} \mathrm{EtOPO_2 + RNH_2}$$

$$\mathrm{EtOPO_2 + RNHP(O)(OEt)OH} \xrightarrow[\mathrm{RNH_2}]{k_4} \mathrm{RNHP(O)(OEt)OP(O)(OH)(OEt)\cdot RNH_2}$$

$$\mathrm{EtOPO_2 + EtOH} \xrightarrow[\mathrm{RNH_2}]{k_5} \mathrm{(EtO)_2POOH\cdot RNH_2}$$

If the equilibrium constant (K) for k_1/k_2 is much less than 1, the concentration of the dipolar form is given by

$$[\mathrm{RN^+H_2P(O)(OEt)O^-}] = K[\mathrm{substrate}]$$

The rate of metaphosphate formation is

$$\mathrm{d[EtOPO_2]}/dt = k_3[\mathrm{RN^+H_2P(O)(OEt)O^-}] - k_5[\mathrm{EtOPO_2}][\mathrm{EtOH}] - k_4[\mathrm{EtOPO_2}][\mathrm{RNHP(O)(OEt)OH}]$$

and the rate of decomposition of substrate is

$$-\mathrm{d[substrate]}/dt = k_3[\mathrm{RN^+H_2P(O)(OEt)O^-}] + k_4[\mathrm{EtOPO_2}][\mathrm{RNHP(O)(OEt)OH}]$$

The steady-state approximation for metaphosphate concentration $\mathrm{d[EtOPO_2]}/dt = 0$ gives the equation for the rate of decomposition of substrate:

(21) Jankowski, S.; Quin, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 7011.

$$-\text{d[substrate]}/dt = Kk_3\left(1 + \frac{k_4[\text{substrate}]}{k_4[\text{substrate}] + k_5[\text{ethanol}]}\right)[\text{substrate}]$$

When ethanol is not present in the solution (k_5[ethanol] = 0) the equation reduces to first-order kinetics:

$$-\text{d[substrate]}/dt = 2Kk_3[\text{substrate}] = k_{exp}[\text{substrate}]$$

In pure ethanol k_4[substrate] $\ll$ k_5[ethanol] (pyrophosphate is not observed) and

$$-\text{d[substrate]}/dt = Kk_3[\text{substrate}] = k_{exp}[\text{substrate}]$$

When concentrations of substrate and ethanol are comparable, the ratio

$$\{k_4[\text{substrate}]/(k_4[\text{substrate}] + k_5[\text{ethanol}])\} < 1$$

and

$$Kk_3\left(1 + \frac{k_4[\text{substrate}]}{k_4[\text{substrate}] + k_5[\text{ethanol}]}\right) \approx Kk_3 = k_{exp}$$

The decomposition of **8a** is somewhat faster in toluene in the presence of ethanol (Table 3) than in pure toluene (Table 1), but the effect is not strong. This can be explained by a higher concentration of the dipolar species in the presence of ethanol.

By performing the decomposition in ethanol and toluene at various temperatures, it was possible to obtain values for the common activation parameters. As seen in Table 4, and consistent with the similarity in rate constants, there was no significant difference in the parameters, confirming the lack of a strong solvent effect in the first-order process.

The *N*-Phenyl Derivative 8b. The importance of the steric effect in suppressing the AE mechanism and guiding the fragmentation into the EA mechanism was clearly seen from the results when the bulky *N*-mesityl group was replaced by *N*-phenyl. Acid **8b** (δ 2.77) was found to follow second-order kinetics (Table 5 and Figure 2) when it was fragmented in toluene at 80 °C. The ^{31}P NMR spectrum of the major product showed the usual doublet of doublets for the pyrophosphate type of product (δ −5.6 and −10.3, J = 12.5 Hz). However, the observed second-order rate constant was found to *increase* with decreasing concentration of the acid. This can be explained by the fragmentation following two different pathways simultaneously, the first-order (k_1) EA mechanism and the second-order (k_2) AE mechanism, according to the rate equation:

$$\text{d(substrate)}/dt = k_1(\text{substrate}) + k_2(\text{substrate})^2 = k_{exp}(\text{substrate})^2$$

When the fragmentation was performed in ethanol, all phosphorus was trapped as diethyl phosphate. The reaction was first-order (probably pseudo-first-order); this allowed a direct comparison of the rate constants (Table 5) at various temperatures with those for fragmentation of the *N*-mesityl derivative in ethanol, also first order. For example, for *N*-phenyl at 80 °C in ethanol, the value was 0.406 × 10^{-3}, while for the *N*-mesityl at the same concentration (0.10 M), it was 4.98 × 10^{-3} s^{-1}, which reveals clearly the higher reactivity of this more crowded compound. The differences between the two compounds were further revealed by comparison of the activation parameters (Table 4). The enthalpy of activation was higher for the *N*-phenyl compound (79.8 kcal/mol) than for the *N*-mesityl (67.0 kcal/mol), in keeping with the operation of the steric effect. The entropy of activation was more positive, but by only 3.6 eu, for the *N*-phenyl compound.

Table 4. Activation Parameters at 80 °C for 8a and 8b in Ethanol and 8a in Toluene

compound	solvent	E_a, kJ/mol	ln A, s^{-1}	$\Delta H^{\ddagger}_{80}$, kJ/mol	$\Delta S^{\ddagger}$ J/mol K	$\Delta S^{\ddagger}$ eu
8a	ethanol	69.9 ± 1.1	18.49 ± 0.38	67.0	−100.9	−24.1
8a	toluene	73.3 ± 3.5	18.5 ± 1.2	70.4	−100.9	−24.1
8b	ethanol	82.7 ± 4.7	20.3 ± 1.6	79.8	−85.9	−20.5

Table 5. Kinetics of the Thermolysis of 8b and 8d

concentration, mol/L	temp, °C	observed rate constant: k × 10^3
8b, 0.04[a]	80	142.9 ± 5.0
8b, 0.09[a]	80	89.0 ± 3.4
8b, 0.21[a]	80	6.75 ± 0.21
8b, 0.10[b]	109.4	3.47 ± 0.30
8b, 0.10[b]	93.9	0.903 ± 0.070
8b, 0.10[b]	80.0	0.406 ± 0.028
8b, 0.10[b]	75.3	0.294 ± 0.012
8b, 0.10[b]	64.1	0.090 ± 0.002
8d, 0.03[a]	100	42.6 ± 2.5
8d, 0.05[a]	100	13.20 ± 0.58
8d, 0.09[a]	100	8.23 ± 0.46
8d, 0.16[a]	100	7.77 ± 0.18
8d, 0.36[a]	100	3.40 ± 0.10

[a] In toluene; second order, with k in L mol^{-1} s^{-1}. [b] In ethanol; first order, with k in s^{-1}.

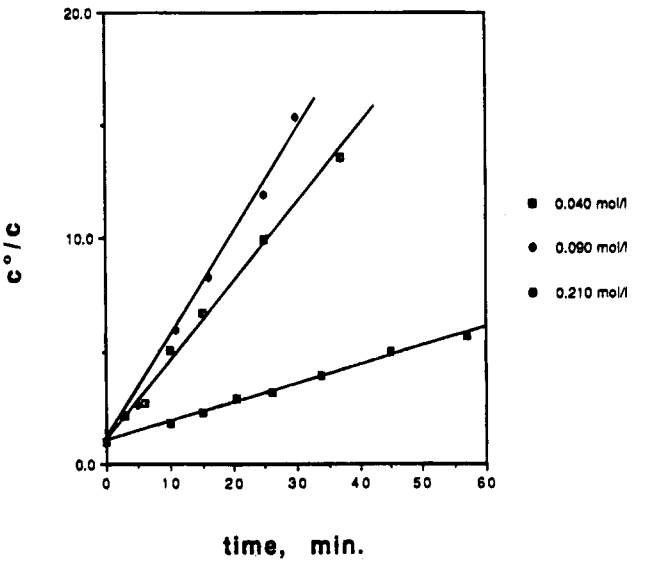


Figure 2. Kinetics of the thermolysis of **8b** in toluene at 80 °C.

Fragmentation of *N*-Alkyl *O*-Ethyl Phosphoramidic Acids. The *N*-1-Adamantyl Derivative 8c. Acid **8c** was found to follow clean first-order kinetics, with k = 2.0 × 10^{-4} s^{-1}, when it was heated in toluene at 79.6 °C. This rate constant is smaller than that of the *N*-mesityl derivative at this temperature (k = 1.6 × 10^{-3} s^{-1}). The ^{31}P NMR spectrum showed that the sole product from **8c** was the pyrophosphate **13**. The P atom substituted by the adamantylamino group had a more

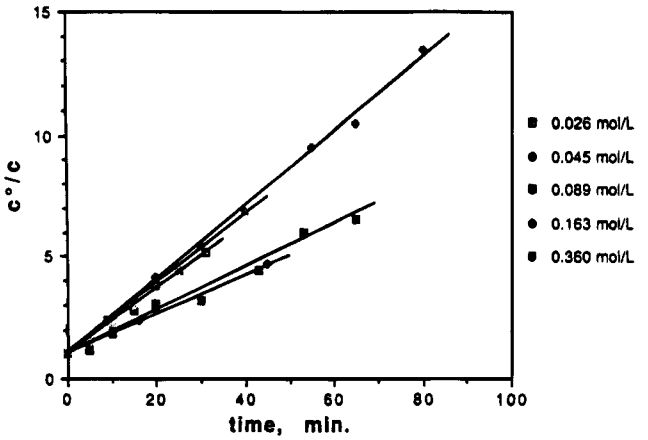
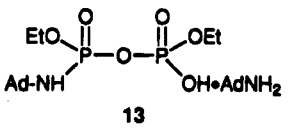


Figure 3. Kinetics of the thermolysis of **8d** in toluene at 100 °C.

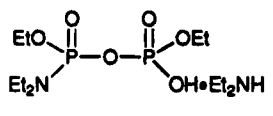
downfield signal of δ −1 (*N*-alkyl is shifted downfield relative to *N*-aryl; cf. δ 9.4 for $(EtO)_2P(O)NHEt$ to δ 3.0, $(EtO)_2P(O)NHPh$,[22] and other examples in ref 22) and was significant in assigning structure **13**, while the phosphate ester signal was at δ −10.2. The spectrum was a well-resolved doublet of doublets, with J = 13.8 Hz. Again the kinetic evidence is convincing that the



13

bulky 1-adamantyl substituent has directed the fragmentation along the EA mechanistic pathway.

The *N,N*-Diethylamino Derivative 8d. Replacement of the bulky adamantyl group by the diethylamino group had the same effect on the mechanism as replacing the bulky mesityl by phenyl; compound **8d** followed second-order kinetics in its fragmentation in toluene with an experimental rate constant that increased with decreasing concentration (Table 5, Figure 3). The main product was the usual N-substituted pyrophosphate **14** (δ −1.14 and −12.06, J = 18.5 Hz), but in addition there was present a compound having the NMR characteristics of a triphosphate (δ −12.8 (d) and −22.3 (t), J = 16.4 Hz, ratio 2:1), possibly for structure **15** (or a salt).



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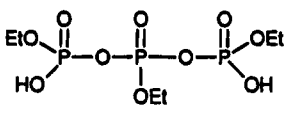
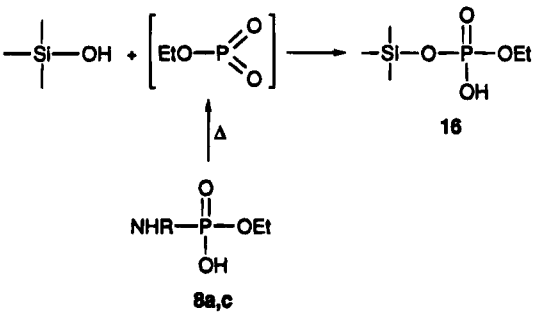


15

Trapping of the Intermediate Metaphosphate with Silica Gel. We have been successful in trapping metaphosphate intermediates suspected to occur in some other processes by their phosphorylating action on surface OH groups of solids.[17] This technique was therefore applied to the case of fragmentation of the *O,N*-substituted phosphoramidic acids. The *N*-mesityl derivative **8a** was decomposed (20 min) at 100 °C in toluene in the presence of suspended anhydrous silica gel. The ratio of ethyl metaphosphate intermediate to silica gel was about 1.3:1 relative to the OH content known[17] for the silica gel. Examination by ^{31}P NMR of the mother liquor after removal of the solid revealed practically no phosphorus to be present. The solid after thorough washing that included the polar 2-propanol was found to have a relatively strong ^{31}P NMR signal at δ −10, using the CP/MAS technique. This is exactly the same shift (and with the same signal appearance[23]) as found for silica gel after phosphorylation by ethyl metaphosphate generated by two entirely different precursors[17] to form **16**. Examination of the solid by ^{29}Si NMR was also helpful in showing that the surface OH was essentially eliminated in the process; the signal associated with Si−OH, which is strong at δ −104 in the silica (as originally reported by Maciel and Sindorf[24]) was absent after the phosphorylation. As noted in other studies,[25,26] no new signal appeared; silica gel also has a strong signal at δ −114 for Si with no OH and it is possible, but not confirmed, that it overlaps the new signal from the surface phosphate group. Similar results were obtained when silica gel was phosphorylated with derivative **8c**. It was further



noted that both the *N*-phenyl (**8b**) and *N,N*-diethyl (**8d**) derivatives, both of which were indicated by kinetics to undergo competing EA and AE mechanistic pathways, gave the same result; essentially all of the phosphorus was incorporated on the surface, and only minor signals for the pyrophosphate from the interfering bimolecular AE process, commonly seen in reactions when small amounts of alcohol were used as traps, were present in the mother liquor. This specificity for metaphosphate attack on the surface makes it possible to consider the entire group of phosphoramidic acid derivatives used in the present study as valuable materials for use in surface phosphorylation reactions.

By using the phosphorylated silica obtained from *N*-mesityl derivative **8a** as the metaphosphate precursor, the question of retention of the displaced amine on the surface through salt formation was addressed. In fact, elemental nitrogen analysis showed the N content of the solid after 2-propanol washing to be less than 0.1%. It is presumed that the washing has removed the amine; this is consistent with observations made on use of the phosphorylated silica as a HPLC packing,[18] where it was observed that aromatic amines were effectively eluted from the column with solutions containing 2-propanol. The absence of nitrogen in the silica product also eliminates another possibility. Hydroxy groups on some

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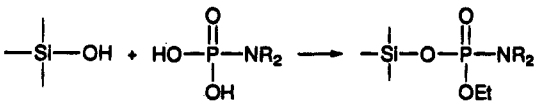
(23) Quin, L. D. In *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis*; Quin, L. D., Verkade, J. G., Eds.; VCH Publishers: Deerfield Beach, FL, in press.

(24) Maciel, G. E.; Sindorf, D. W. *J. Am. Chem. Soc.* **1980**, *102*, 7606. See also: Leonardelli, S.; Facchini, L.; Fretigny, C.; Tougne, P.; Legrand, A. P. *J. Am. Chem. Soc.* **1992**, *114*, 6412.

(25) Quin, L. D.; Wu, X.-P.; Quin, G. S.; Jankowski, S. *Phosphorus Sulfur Silicon* **1993**, *76*, 91.

(26) Lukes, I.; Quin, L. D. *J. Am. Chem. Soc.* **1994**, *116*, 1737.

phosphorus acids have been found by us[26] to react directly with silica OH to place phosphorus ester groups on the surface. If this reaction occurred with the phosphoramidic acid derivatives, nitrogen would remain bonded to phosphorus as in the product **17**. The ^{31}P NMR shift is not that expected for such a group, which usually is found some 5–10 ppm downfield from a corresponding P–OR compound, and the absence of N in the product completely eliminates this structural possibility.



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Conclusions

O-Ethyl *N*-substituted phosphoramidic acids, as indicated in the earlier literature, are thermally unstable. However, this instability can be used to advantage if the *N*-substituent is sterically large. In this case, as is clearly shown by kinetics measurements, the fragmentation is first order and proceeds to release ethyl metaphosphate as a discrete intermediate. This substance is then available to act as a powerful phosphorylating agent toward substrates present in the medium. Since the phosphoramidic acids can be synthesized in two simple steps from the available ethyl dichlorophosphate, this method for metaphosphate generation and its use as a phosphorylating agent may stand as the most practical of the methods in the literature.[7] However, the phosphoramidic acid itself can be phosphorylated by the metaphosphate; this can compete with the reaction with the substrate, although the nature and concentration of the latter can control the result. It has already been shown that the technique can be used to phosphorylate the OH groups on the surface of silica gel, and other applications are being studied.[1]

The phosphoramidic acids have variable stability at room temperature, and are difficult to obtain in high purity. However, this has not yet proved to be a difficulty in the subsequent fragmentation to form metaphosphates.

Preliminary results indicate that the general method can be extended to the generation of other types of metaphosphates. By synthesizing the appropriate alkyl dichlorophosphate and subjecting it to the same reaction sequence, we have obtained evidence for the satisfactory generation of isopropyl metaphosphate and of (+)-menthyl metaphosphate.[1] Other extensions of the process are under study.[27]

Experimental Section[28]

Synthesis of *O*-Ethyl *N*-Substituted Phosphorochloridates (7a–d). 7c. A solution of 1-adamantylamine (3.90 g, 25 mmol) and 2.52 g (25 mmol) of Et_2NH as HCl acceptor in 30 mL of ether was added to a solution of 4.08 g (25 mmol) of ethyl phosphorodichloridate in 30 mL of ether. After 20 h, the precipitated $Et_2NH{\cdot}HCl$ was removed by filtration and the filtrate evaporated to leave a solid residue of crude **7c**. This was recrystallized from chloroform–hexane, mp 125.4–126.8 °C, 67% yield; ^{31}P NMR ($CDCl_3$) δ 10.5.

Anal. Calcd for $C_{12}H_{21}ClNO_2P$: C, 51.89; H, 7.62; P, 11.15. Found: C, 51.73; H, 7.67; P, 10.74.

7b. Prepared in the same way from aniline, except that the reaction was complete in 30 min. The residue of **7b** failed to crystallize and was used directly in the next step; ^{31}P NMR ($CDCl_3$) δ 8.9.

7a. Prepared as above from 4.9 g (30 mmol) of $EtOPOCl_2$ in 40 mL of CCl_4 and 9.74 g (72 mmol) of mesitylamine in 40 mL of CCl_4, 21 h. The oily residue of **7a** had ^{31}P NMR δ 10.2 (CCl_4).

7d. Diethylamine was used as reactant and HCl acceptor; in benzene solution, the reaction required 30 min, after which solvent was removed and the residue taken up in ether. The $Et_2NH{\cdot}HCl$ was filtered off and the filtrate evaporated to leave a noncrystallizing residue of **7d**; ^{31}P NMR ($CDCl_3$) δ 15.1.

Synthesis of *O*-Ethyl *N*-Substituted Phosphoramidic Acids (8a–d). 8c. Phosphorochloridate **7c** (6.95 g, 25 mmol) was dissolved in 60 mL of acetone–water (1:1) containing 2 g (50 mmol) of NaOH. After 5 min, the solvent was evaporated and the residue dried over P_2O_5 *in vacuo*. The Na salt of **8c** was extracted from the residue with absolute EtOH; filtration removed the insoluble NaCl. Evaporation of the solution left the Na salt of **8c** as a white solid (85%); FAB-MS calcd for $[M - Na]^-$ *m/z* 258.13, found 258.1. ^{31}P NMR δ 5.04 (H_2O–acetone): The salt (0.513 g) was dissolved in 10 mL of methanol and passed through a column of 7 g of Amberlyst·H^+. Elution of **8c** was completed with 50 mL of methanol. The eluate was evaporated to dryness, and the residue of **8c** was dissolved in 200 mL of chloroform. Some solids were filtered off, and the filtrate was evaporated to about 30 mL, whereupon **8c** crystallized (needles) mp 126.4–127.0 °C, 95% yield; ^{31}P NMR δ 9.29 ($CDCl_3$).

Anal. Calcd for $C_{12}H_{22}NO_3P$: N, 5.40. Found: N, 5.04.

8b. The same procedure was applied to 0.24 g of phosphorochloridate **7b**. The Na salt of **8b** (74%) had ^{31}P NMR ($CDCl_3$) δ 0.98; FAB-MS calcd for $[M = Na]^-$ *m/z* 200.05, found 200.0. After ion exchange, **8b** was obtained (90%) as a crude solid, ^{31}P NMR ($CDCl_3$) δ 2.77. The dicyclohexylamine salt had mp 179–180 °C. Anal. Calcd for $C_{20}H_{35}N_2O_3P$: N, 7.33. Found: N, 7.16.

8a. Reaction of **7a** with NaOH as above gave the Na salt of **8a** (60%); FAB-MS calcd for $[M - Na]^-$ *m/z* 242.09, found 242.1. ^{31}P NMR δ 4.9 ($CDCl_3$). Anal. Calcd for $C_{11}H_{17}NNaO_3P$: C, 49.81; H, 6.46; N, 5.28. Found: C, 49.42; H, 5.94; N, 5.12. Passage through Amberlyst·H^+ gave **8a**, ^{31}P NMR δ 7.0 ($CDCl_3$). The compound was not sufficiently stable for elemental analysis.

8d. Reaction of **7d** with NaOH gave the Na salt of **8d** (previously reported[29]), ^{31}P NMR δ 10.3 (D_2O); it was converted to **8d** with Amberlyst, ^{31}P NMR δ 11.7 (toluene).

Thermolysis of Neat *O*-Ethyl *N,N*-Diethylphosphorochloridate (7d). A 1.0-g sample of **7d** was distilled in a Kugelrohr apparatus at 120 °C (8 mmHg). The residue remaining in the flask was the cyclic trimer $(Et_2NPO_2)_3$,[30] [confirmed by ^{31}P NMR (δ –12.0); cf. to $(Me_2NPO_2)_3$, δ –12.0[31]]. The trimer was not affected by exposure to EtOH in $CDCl_3$ for 1 h at 60 °C, and then 30 min at 100 °C.

Thermal Fragmentation of Phosphoramidic Acids 8a–d in Solution. Reactions were generally performed in NMR tubes placed in a constant temperature bath (generally 60–100 °C). Toluene was most frequently used as solvent; others included absolute ethanol, acetonitrile, and dimethyl sulfoxide. Solutions were examined by ^{31}P NMR immediately after the reaction period (generally 0.5–2 h). In ethanol, the only observed phosphorus product was the amine salt of diethyl phosphate, e.g., ^{31}P NMR δ –0.68 from **8a** (converted to methyl diethyl phosphate with CH_2N_2, identical by GC to a known sample[27]).

Typical ^{31}P NMR results from fragmentations in inert solvents: **8a** (CH_3CN, 80 °C) d of d, δ –6.0 and –13.2, $^2J_{PP}$ =

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(28) Instrumentation and general techniques are described in ref 21. FAB-MS spectra were obtained with an MI 1201E instrument on thioglycerol matrices.

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(30) Michaelis, A. *Liebig's Ann.* **1903**, *326*, 191.

(31) Schwarzmann, E.; Van Wazer, J. R. *J. Am. Chem. Soc.* **1960**, *82*, 6009.

19.1 Hz, sometimes with s, −12.4; (DMSO, 80 °C) d of d, δ −6.0 and −11.1, $^2J_{PP}$ = 20.1, with s, −10.5; (toluene, 80 °C) d of d, δ −5.9 and δ −12.5, $^2J_{PP}$ = 19 Hz. The singlet is attributed to $(MesNH_2)_2EtO(OH)(O)P-O-P(O)(OH)OEt$, which on one occasion crystallized from toluene.

Anal. Calcd for $C_{22}H_{38}N_2O_7P_2$: C, 52.37; H, 7.59; N, 5.55. Found: C, 51.88; H, 7.23; N, 5.24.

8b. (Toluene, 80 °C) d of d, ^{31}P δ −5.6 and −10.3, $^2J_{PP}$ = 12.5 Hz, with s, δ −8.3.

8c. (Toluene, 80 °C) d of d, ^{31}P δ −1 and δ −10.2, $^2J_{PP}$ = 13.8 Hz.

8d. (Toluene, 100 °C) ^{31}P, dd, δ −1.1 and δ −12.1, $^2J_{PP}$ = 18.5 Hz, and dt, δ −12.8 and −22.3, $^2J_{PP}$ = 16.4 Hz.

Kinetics Measurements. Samples were placed in NMR tubes in thermostats as described elsewhere.[28] Analysis was performed by ^{31}P NMR also as described.[28] Kinetic data are described for **8a** in Tables 1−3; data for **8b** and **8d** are given in Table 5. Activation parameters for **8a** and **8b** are given in Table 4. For **8c**, fewer measurements were made: in toluene at 79.6 °C, first-order $k = 2.0 \times 10^{-4}$ s^{-1}.

Phosphorylation of Silica Gel. A 1.0-g sample of Aldrich silica gel[17] (0.69 ± 0.14 mequiv OH) was suspended in a solution of 1.0 mmol of the phosphoramidic acids **8a−d** in 10 mL of toluene. The mixture was stirred and heated: **8a**, 20 min, 100 °C; **8b**, 15 min, 110 °C; **8c**, 70 min, 110 °C; **8d**, 80 min, 100 °C. The mixture was filtered, and the residue was washed with toluene and then twice with 2-propanol. Tests of the filtrates for P by ^{31}P NMR were generally negative. The silica was dried *in vacuo* over P_2O_5. The silica from use of any of **8a−d** had CP/MAS ^{31}P NMR δ −10 ($CaHPO_4$ = 0) and CP/MAS ^{29}Si δ −114 (Me_4Si = 0).

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