Between pH 10 and 12, steps D and E start to come in. Due to E, the $TMPD^{+}\cdot$ yield decreases. At pH ≥12 steps B, F, and H, by which $Cy^{-}\cdot$ is produced, become dominant, and the $TMPD^{+}\cdot$ yield increases again. The conclusion that, at pH ≥12, $Cy^{-}\cdot$ and not $Cy(OH)O_2\cdot$ is responsible for the oxidation of TMPD is supported by the observation that the rate constant for oxidation of TMPD (2×10^9 M^{-1} s^{-1}) is the same as that in the absence of O_2.

It may be interesting to note that, in contrast to the cytosine system, in the uracil system under the same conditions the dehydration reaction was not able to compete with the reaction with oxygen.[14] This again shows that Cy-5-OH dehydrates more easily than the analogous OH adduct of uracil, probably as a result of the higher electron density of cytosine as compared to uracil.

3. Conclusions

The reaction of the OH radical with cytosine and its derivatives has been shown to proceed by addition to the C(5)/C(6) double bond, with a ≈9:1 preference for addition at C(5). No evidence for addition at C(4)/N(3) was found. The radical formed by addition to C(5) has reducing properties, and that produced by attachment to C(6) is a weak oxidant. The radicals of the Cy-5-OH type undergo a base-catalyzed dehydration reaction to yield cytosine radicals that have oxidizing properties. Substituting H at N(1) by alkyl groups (as with the cytosine nucleosides and nucleotides) prevents the dehydration reaction.

From a comparison of the yields of oxidizing and reducing radicals from (a) cytosine and (b) cytosine nucleosides and nucleotides, it is estimated that >80% of the OH radicals react with the heterocyclic ring and not by H abstraction from the sugar part of the molecule.

In the presence of oxygen the OH adducts yield peroxyl type radicals which are able to oxidize TMPD. In basic solution these peroxyl radicals decompose, presumably by unimolecular elimination of $O_2^{-}\cdot$.

Registry No. OH, 3352-57-6; cytosine, 71-30-7; 3-methylcytosine, 19380-02-0; 5-methylcytosine, 554-01-8; 5-carboxylcytosine, 3650-93-9; 6-methylisocytosine, 3977-29-5; 1-methylcytosine, 1122-47-0; cytidine, 65-46-3; 2-deoxycytidine, 951-77-9; cytidylic acid, 63-37-6; 2-deoxycytidylic acid, 1032-65-1; 5-methylcytidine, 2140-61-6; 6-hydroxycytosine, 85761-81-5; 6-hydroxy-3-methylcytosine, 85761-88-2; 6-hydroxy-5-methylcytosine, 85761-84-8; 6-hydroxy-5-carboxylcytosine, 85761-82-6; 6-methyl-6-hydroxyisocytosine, 85761-87-1; 6-hydroxy-1-methylcytosine, 85761-89-3; 6-hydroxycytidine, 85761-91-7; 6-hydroxy-5′-deoxycytidine, 85761-90-6; 6-hydroxycytidylic acid, 85761-93-9; 6-hydroxy-2′-deoxycytidylic acid, 85761-92-8; 6-hydroxy-5-methylcytidine, 85761-80-4; 5-hydroxycytosine, 85761-80-4; 3-methyl-5-hydroxycytosine, 85761-95-1; 5-hydroxy-5-methylcytosine, 85761-85-9; 5-hydroxy-5-carboxylcytosine, 85761-83-7; 5-hydroxy-6-methylisocytosine, 85761-86-0; 5-hydroxy-1-methylcytosine, 85762-01-2; 5-hydroxycytidine, 85761-96-2; 5-hydroxy-2′-deoxycytidine, 85761-98-4; 5-hydroxycytidylic acid, 85761-99-5; 5-hydroxy-2′-deoxycytidylic acid, 85762-00-1; 5-hydroxy-5-methylcytidine, 85761-97-3.

Imidazole-Promoted Hydrolysis of Oxaphospholene Esters.[1] Nucleophilic vs. General Base Catalysis

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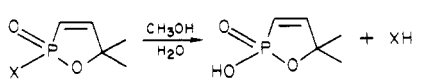
Contribution from the Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221. *Received December 10, 1982*

Abstract: A 2.4-fold excess of imidazole (Im) accelerated the hydrolysis of 5,5-dimethyl-2-methoxy-1,2-oxaphosphol-3-ene 2-oxide (**2a**) in 50% aqueous methanol by a rate factor of >50 compared to the uncatalyzed hydrolysis of **2a**. The reaction was first order in Im and **2a** and led to the imidazolium salt (**3**-Im) of 5,5-dimethyl-2-hydroxy-1,2-oxaphosphol-3-ene 2-oxide and methanol via two independent routes. One route involved direct nucleophilic attack at the methoxy carbon; the other route was a multistep process with nucleophilic attack at phosphorus to give a ring-opened intermediate which was observed by ^1H NMR. Im reacted slowly with **2a** in deuteriochloroform to give **3** and *N*-methylimidazole (**6**) via direct nucleophilic attack at the methoxy carbon. The stability of **6** and its conjugate acid in aqueous methanol precluded their intermediacy in the hydrolysis. Possible intermediate 5,5-dimethyl-2-imidazoyl-1,2-oxaphosphol-3-ene 2-oxide (**7**) was prepared and demonstrated to be highly reactive toward solvolysis in methanol and aqueous methanol. The Im-promoted hydrolysis was interpreted as involving general base catalysis.

We recently described the hydrolytic behavior of several esters and an amide of 5,5-dimethyl-2-hydroxy-1,2-oxaphosphol-3-ene 2-oxide (**1**). In 50% aqueous methanol the methyl (**2a**),[1,2] neopentyl (**2b**)[2] and phenyl (**2c**)[2] esters underwent hydrolysis to **1** without detectable intermediates, though in each case the instantaneous pseudo-first-order rate constant increased monotonically with time owing to acid catalysis provided by **1** (pK_a = 1.70 in water)[2]. The related *N*,*N*-diethylamide **2d** was nearly inert under these conditions, requiring added strong acid to bring about hydrolysis.[2]



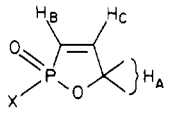
2a, X = OCH_3 **1**
b, X = OCH_2-*t*-Bu
c, X = OPh
d, X = Et_2N

When methyl ester **2a** was treated with a slight excess of potassium hydroxide in aqueous methanol it was immediately converted to **3**, the conjugate base of **1**, again without detectable

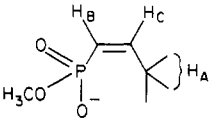
(1) Paper 3 in the series Reactions of Oxaphospholenes. For paper 1, see: Macomber, R. S.; Krudy, G. A. *J. Org. Chem.* **1981**, *46*, 4038.
(2) Macomber, R. S.; Krudy, G. A.; Amer, M. Z. *J. Org. Chem.* **1983**, *48*, 1420.

0002-7863/83/1505-4386$01.50/0

Table I. ^{1}H NMR Spectral Parameters for **2a**, A, and **3**[a]



2a, 3



A (**4a**-O$^-$)

compd	H_A	H_B	H_C	OCH_3
2a (X = OCH_3)	1.53, 1.54	6.16 (33.6, 8.4)	7.37 (49.0, 8.4)	3.72 (12.6)
A (**4a**-O$^-$)	1.40	5.62 (11.1, 14.7)	6.46 (46.5, 14.4)	3.61 (10.8)
3-Im (X = O$^-$)[b,c]	1.43	6.10 (31.7, 8.5)	6.81 (44.4, 8.5)	
CH_3OD				3.40

[a] ppm downfield from DSS in 50% CD_3OD/D_2O[6] at 300 MHz; J_{PH} and J_{HH}, respectively, in parentheses. See Figure 1. [b] This hydrolysis product was identical with material prepared directly from **1** with a 2.4-fold excess of Im. [c] The proton on C_2 of Im underwent H/D exchange at ca. the same rate as **2a** disappeared (64.5 °C).

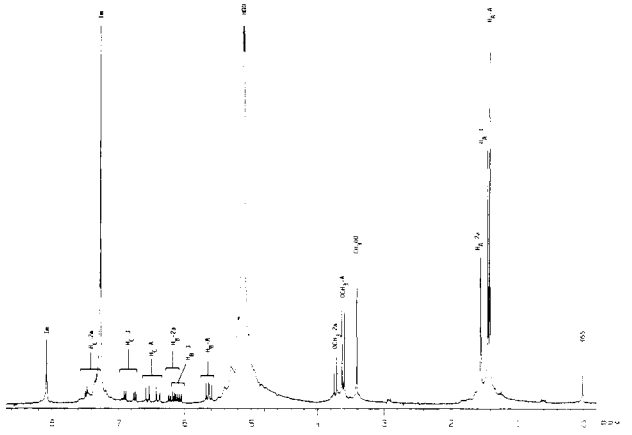
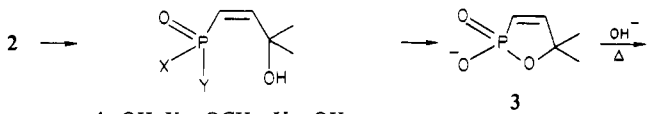
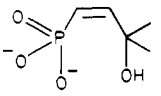


Figure 1. ^{1}H NMR (300 MHz) spectrum of the reaction mixture initially 0.39 M in **2a** and 0.97 M in Im in 50% aqueous methanol (deuterated) after 4.1 h at 64.5 °C.

intermediates.[1] Only when salt **3** was heated (80.5 °C, 72 h) with excess potassium hydroxide did it undergo endocyclic hydrolysis to ring-opened phosphonate **5**. This contrasted with a report[3] that the hydrolysis of methyl ester **2a** in water containing sodium acetate led to **1** (sic) with the intervention of an intermediate, "probably" methyl 3-hydroxy-3-methyl-1-(*Z*)-butenylphosphonate (**4a**-OH). We subsequently found[2] that a slight excess of po-



4a-OH, X = OCH_3; Y = OH
4a-O$^-$, X = OCH_3; Y = O$^-$
4b-O$^-$, X = OCH_2-*t*-Bu; Y = O$^-$
4c-O$^-$, X = OPh; Y = O$^-$
4d-O$^-$, X = NEt_2; Y = O$^-$



5

tassium hydroxide converted neopentyl ester **2b** instantaneously (25 °C) to ring-opened salt **4b**-O$^-$, which then slowly recyclized to **3**. Although similar behavior was noted for phenyl ester **2c**[2] and diethylamide **2d**,[2] we were not able to observe the ring-opened *methyl* phosphonate **4a**-OH (under acidic conditions) or **4a**-O$^-$ (under basic conditions). We attributed this[1,2] to rapid *alkyl-oxygen* cleavage in methyl ester **2a** (a path unavailable to **2b**, **2c**, and **2d**), which took place faster than endocyclic hydrolysis to **4a**-O$^-$.

(3) van Aken, D.; Castelijns, A. M. C. F.; Buck, H. M., *Recl. Trav. Chim. Pays-Bas*, **1980**, *99*, 322.

Table II. Rate Constants for the Reactions in This Study

substrate	process[b]	temp, °C	k
2a	k_{obsd}	23.5	4.04×10^{-4} M^{-1} min^{-1}
2a	k_1	23.5	2.0×10^{-4} M^{-1} min^{-1}
2a	k_2	23.5	2.0×10^{-4} M^{-1} min^{-1}
A	k_A	23.5	8.7×10^{-5} min^{-1}
2a	k_{obsd}	64.5	5.68×10^{-3} M^{-1} min^{-1}
2a	k_1	64.5	2.6×10^{-3} M^{-1} min^{-1}
2a	k_2	64.5	3.1×10^{-3} M^{-1} min^{-1}
A	k_A	64.5	3.5×10^{-3} min^{-1}
2a	k_{Im}	64.5	1.7×10^{-4} min^{-1} M
7	k_h[c]	37[d]	10×10^{-1} min^{-1}
7	k_{MeOH}[c]	37[d]	5×10^{-1} min^{-1} M^{-1}
CH_3I	k_{CH_3I}[e]	37[d]	1.1×10^{-2} min^{-1} M^{-1}

[a] Errors are ±1 in the last significant figure. See Experimental Section. [b] k_1 and k_2, the sum of which is k_{obsd}, were found by multiplying k_{obsd} times the average mole fraction of the appropriate product;[8] k_A was estimated from the decay of A after **2a** was exhausted; k_{Im}, k_h, k_{MeOH}, and k_{CH_3I} are defined in the text. [c] Because the rates of these reactions are relatively fast, only a few integrations were possible before the reaction was complete, accounting for the lower precision of the rate constants. [d] Probe temperature of the NMR spectrometer. [e] See ref 12 and 13; k_{CH_3I} is the rate constant for disappearance of the limiting reagent, CH_3I.

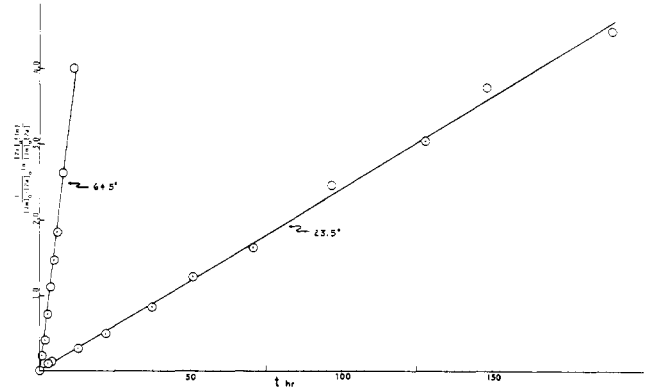


Figure 2. Second-order rate plots for the disappearance of **2a** in the presence of Im.

It seemed reasonable that if one could maintain the pH at neutral or slightly basic and avoid hard nucleophiles, one might gain conclusive evidence regarding the intermediacy of ring-opened intermediates from methyl ester **2a**. Although imidazole (Im) has long been of interest as a nucleophilic catalyst in the hydrolysis of carboxylate esters,[4] there have been relatively few studies on its catalytic activity toward phosphorus esters.[5] We describe here the pronounced effect of Im on the hydrolysis of **2a**.

(4) Bruice, T. C.; Benkovic, S. "Bioorganic Mechanisms"; W. A. Benjamin, Inc.: New York, 1966; p 47–60.
(5) As a leading reference, see: Bunton, C. A.; Hong, Y. S.; Romsted, L. S.; Quan, C. *J. Am. Chem. Soc.* **1981**, *103*, 5784.

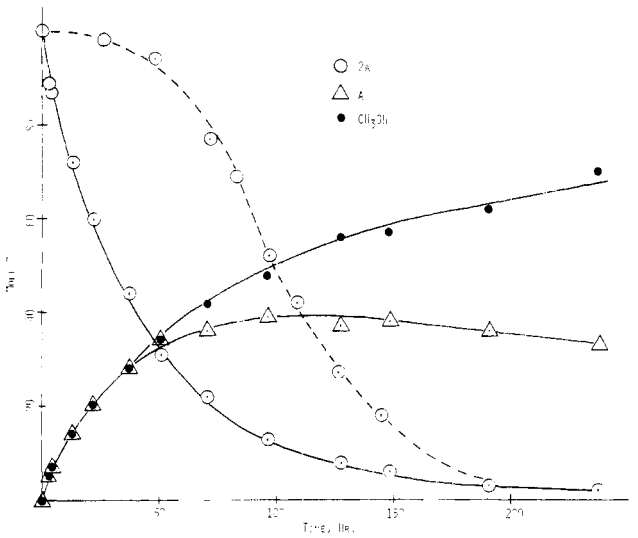
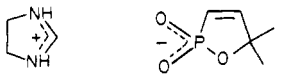


Figure 3. Components of the reaction mixture initially 0.48 M in 2a and 1.14 in M Im in 50% aqueous methanol (deuteriated), as a function of time (23.5 °C).

Results

The hydrolysis of methyl ester **2a** in 50% aqueous methanol[6] with a 2.4-fold excess of Im could be readily followed by ^{1}H NMR (see Figure 1 and Table I). The disappearance of **2a** (k_{obsd}, Table II) was strictly governed to >97% completion by a rate law that was first order in **2a** and first order in Im, with 1:1 stoichiometry (Im being consumed by protonation from **1** to form the imidazolium salt **3**-Im); see Figure 2 and Table II. During the reaction

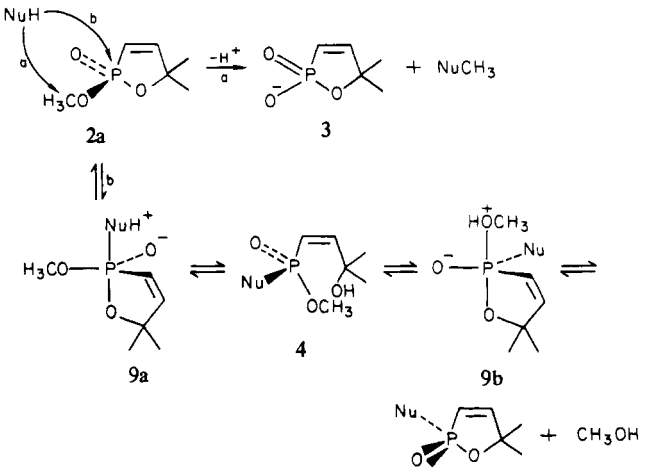


3-Im

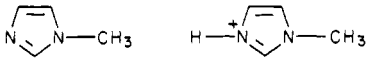
only three products appeared: methanol, **3**-Im, and a third product (A) whose ^{1}H NMR spectrum (Table I) was highly similar to those of ring-opened phosphonates **4b**-O$^-$, **4c**-O$^-$, and **5**.[1,2,7] The relative amounts of these three products were constant and nearly equal through >50% consumption of the starting ester.[8] Subsequently A itself recyclized cleanly to **3**-Im and methanol in a pseudo-first-order process (k_A, Table II). The composition of the reaction mixture at 23.5 °C is shown graphically in Figure 3. The s-shaped dashed line in Figure 3 shows the "unbuffered" autocatalytic hydrolysis of **2a**,[1,2] which was less than $^1/_{50}$ as fast as the Im-promoted reaction until the pH of the former process dropped below 2.0.[1,2] It is significant that in the Im-promoted hydrolysis neither the rate constants (Figure 2) nor the initial product ratios (Figure 3)[8] varied during the reaction although the pH dropped from an initial value of 9.7 (unbuffered Im) to a final value of 6.8 (excess Im buffered by **1**).[9] This observation excludes the stoichiometric involvement of hydroxide ion in the hydrolysis.

In order to assess their possible involvement in the Im-promoted hydrolysis of **2a**, two possible intermediates were prepared and their behavior examined. Evidence that methylimidazole (**6**) or its conjugate acid (**6**-H$^+$), conceivably formed via direct S_N2 attack by Im at the methoxy carbon of **2a**,[1,2] were *not* involved came from the observation that authentic **6**-H$^+$ (as its iodide salt[10]) was

Scheme I

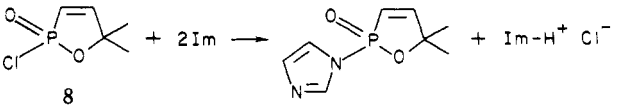


unchanged in 50% aqueous methanol[6] after 4.3 h at 64.5 °C (ester **2a** was 77% consumed under these conditions).



6 6-H$^+$

The other candidate, imidazole phosphonamide **7**, was prepared by the *instantaneous* (23 °C) reaction of chloride **8**[1] with a twofold excess of Im in methylene chloride.[11] Evidence for its highly



reactive nature (in contrast to that of diethylamide **2d**) came from several observations: (1) attempts to purity **7** via distillation or exposure to moist air led instead to salt **3**-Im, (2) upon dissolving in 50% aqueous methanol[6] **7** was converted within 3 min (k_h, Table II) to a 59:41 mixture of ester **2a** (deuterated methoxy) and **3**-Im, and (3) treatment of **7** in deuteriochloroform with a 32% excess of methanol led within 5 min to quantitative formation of ester **2a** (k_{MeOH}, Table II).

Finally, the direct reaction between methyl ester **2a** and Im in an inert solvent was examined by treating the ester with a 1.7-fold excess of Im in deuteriochloroform. A slow second-order reaction took place at 64.5 °C (k_{Im}, Table II), with less than 3% conversion after 2.0 h (**2a** was 52% consumed in aqueous methanol during the same period). The products of this direct reaction were salt **3**-Im and methylimidazole (**6**) (19% **6**-H$^+$);[12,13] no methanol was detected. For comparison, methyl iodide reacted with a 2.6-fold excess of Im fairly rapidly at 37 °C (k_{CH_3I}, Table II) to give **6** (82%, δ 3.77)[12] and **6**-H$^+$ (iodide salt, 18%, δ 4.02).[12,13]

Discussion

The exocyclic hydrolysis of methyl ester **2a** to **1** (or **3**) might occur either by S_N2 cleavage of the methyl–oxygen bond or nucleophilic attack at phosphorus followed by phosphoryl–oxygen

(6) Solvent composition reflects volume percentage before mixing; deuteriated solvents were used.

(7) The ^{1}H NMR spectrum of, e.g., **2** or **3** changes dramatically upon ring opening:[1,2] the *gem*-dimethyl protons shift upfield by 0.03–0.14 ppm, H_B shifts upfield by ca. 0.5 ppm (with a large decrease in J_{PH} and an increase in J_{HH}), H_c shifts upfield by ca. 1.0 ppm (increase in J_{HH}), and the methoxy resonance shifts upfield by ca. 0.1 ppm (decrease in J_{PH}).

(8) The ratio of A/MeOH was 1.0 through 69% reaction at 23.5 °C; the ratio was 1.2 through 56% reaction at 64.5 °C.

(9) Measured independently on a 1.33 M solution of Im in 50% aqueous methanol (pH 9.71), to which was then added enough **1** to give [**1**] = 0.62 F (pH 6.83).

(10) Prepared from Im and a 1.38-fold excess of methyl iodide in dry THF (19 h, 23.5 °C); methyl resonance at 4.00 (50% aqueous deuterated methanol).

(11) See Experimental Section.

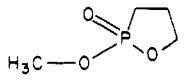
(12) Because of the equilibrium

$$\mathbf{6}\text{-H}^+ + \text{Im} \rightleftharpoons \text{Im-H}^+ + \mathbf{6}$$

the stoichiometry of the Im + **2a**($CDCl_3$) reaction is not exactly 1:1, as some of the reactant Im is consumed by protonation. Nonetheless, good second-order kinetics were observed (r = 0.998) with use of 1:1 stoichiometry in the rate law. In contrast, the reaction of methyl iodide with excess Im was better fit by a *second*-order rate law with 2:1 stoichiometry (r = 0.998) than 1:1 (r = 0.996).

(13) The chemical shifts of both **6** and **6**-H$^+$ are dependent on pH (and hence extent of reaction); both move downfield and their difference in chemical shift diminishes as the reaction proceeds.

cleavage. Although there is precedent for S_N2 cleavage when the alkyl group is unhindered,[1,14] the usual course of phosphorus ester hydrolysis is believed to involve attack at phosphorus to generate a trigonal-bipyramidal (TBP) intermediate.[15] The hydrolyses of compounds where the phosphorus atom is confined to a five-membered ring are especially interesting[1,2,15a,16] because the TBP must satisfy several constraints:[15a] the ring carbon and oxygen must occupy equatorial and apical positions, respectively, and the incoming or outgoing nucleophile must occupy an apical position as in TBP intermediates **9a** and **9b** (Scheme I).[15c] These intermediates are well set up for *endocyclic* cleavage to **4** and such is, in fact, observed in the case of methyl phostonate (**10**),[16] which

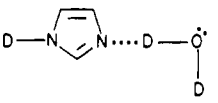


10

undergoes exclusive (and very rapid, owing to relief of ring strain) endocyclic cleavage, with no loss of the methoxy. However, for leaving group OCH_3 to be lost from **9a** some process must occur to place the group in an apical position. Attempts to do this through pseudorotation about any equatorial pivot[15a] would either place the ring carbon apical or require the ring to span two equatorial positions, both alternatives being unfavorable.[15a] Thus, nucleophilic displacement at oxaphospholene phosphorus is most likely to occur via opening of **9a** to **4**, then reclosure to **9b**.[15c] Notice that such a sequence involves two consecutive backside nucleophilic displacements at phosphorus (**2a** → **4** and **4** → product), with net *inversion* for the overall reaction (**2a** → product). This stereochemical prediction is being tested in our laboratory.

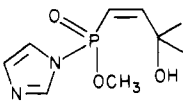
There are sporadic precedents for Im serving both as a nucleophilic catalyst[17] and as a general base catalyst[18] in phosphate ester hydrolyses. Its rapid reaction with chloride **8** to give amide **7** in methylene chloride demonstrates that Im *can* be an effective nucleophile toward oxaphospholene phosphorus, and that conversion of TPB intermediates **9a** to **9b** (Nu = Im, OCH_3 = Cl) is facile.[15c] The reaction of Im with methyl ester **2a** in deuteriochloroform to give methylimidazole and salt **3**-Im, slower than the reaction Im with methyl iodide by a factor of ca. 500,[19] must indicate that direct S_N2 attack at methoxy carbon is slow, but faster than loss of methoxy from **9b** in non-hydroxylic solvent.

Our results demonstrate that a 2.4-fold excess of Im accelerates the aqueous methanol hydrolysis of ester **2a** by a rate factor of >50 (Figure 3), and that methanol is released in two separate pathways, one *competitive* with the formation of intermediate A (k_1, Table II) the other *from* subsequent hydrolysis of A (k_A, Table II). The fact that the rate constants and initial product composition are independent of changing pH during reaction[9] requires that free hydroxide is not the active nucleophile. Because neither methylimidazole nor its conjugate acid produced methanol under the hydrolysis conditions, we conclude that k_1 (Table II) is a measure of the rate of S_N2 attack on the methoxy carbon of **2a** by water enjoying general base catalysis by Im (i.e., **12** is the nucleophile). The very high solvolytic reactivity of imidazoyl-



12

amide **7** (and similar compounds[17]) demonstrates that it would not reach detectable concentrations under the hydrolysis conditions and, therefore, the structure of A must be **4a**-O^- rather than **4a**-Im.



4a-Im

While we cannot completely rule out the direct nucleophilic involvement of Im in the production of **4a**-O^-, the facts that **12** is the nucleophile toward carbon and that the hydrolysis is strictly first order in Im suggest **12** is also the nucleophile toward phosphorus in aqueous methanol (k_2, Table II).

Finally, a comment about the double bond in **2a**. As mentioned above, the very fast hydrolysis of phostonate **10** involved ring opening without loss of methoxy. That ring-opened intermediates **4a**-O^-, **4b**-O^-, etc. show such a high propensity to recyclize[1,2,20] attests not only to the thermodynamic stability of the oxaphospholene ring system but also to the conformation-stabilizing property of the *Z* double bond, holding the OH group in close proximity to phosphorus. In the case of **2a**, therefore, relief of ring strain must *not* be a factor in its hydrolysis.

Experimental Section

General procedures and instrumentation were as previously described[1] except that 300-MHz ^1H NMR spectra were obtained on a Nicolet NT-300 spectrometer made available by an equipment grant from the National Science Foundation. Exact mass measurement was performed on a Kratos MS-80/DS 55 mass spectrometer. Ester **2a** and chloride **8** were prepared by the published methods.[1]

Kinetic Methods. Samples of substrate (e.g., **2a**) and reagent (e.g., Im) were carefully weighed into a volumetrically calibrated NMR tube and diluted to a known volume with solvent.[6] Typical initial concentrations were $[\mathbf{2a}]_0$ = 0.48 M, $[Im]_0$ = 1.14 M. The contents were mixed by shaking, and the tube was inserted in either a thermostrated bath (±0.1 °C) or NMR probe. Periodically the ^1H NMR spectrum was recorded. Concentrations of reactants and products were determined from integration of the appropriate methoxy resonance (Table I) of **2a**, A, and methanol (the concentration of which equals that of **3**) and the known initial concentrations of reactants. *gem*-Dimethyl resonances were used in the determination of k_{Im} and methyl resonances for k_{CH_3I}. Rate constants were extracted by linear least-squares regression analysis of the appropriate rate law; correlation coefficients were ≥0.998.

Preparation of Amide 7. To a solution of 257 mg (3.78 mmol) of Im in 3.0 ml of dry methylene chloride at 23 °C was added a solution of 312 mg (1.87 mmol) of chloride **8**[1] in 3.0 mL of dry methylene chloride over 2 min. Precipitation of Im-H^+Cl^- was immediate upon addition. The mixture was stirred for 50 min and then filtered with the aid of 2 mL of methylene chloride. The filtrate was rotary evaporated (23 °C, 0.10 mm), leaving 390 mg (105%) of crude **7** as a clear colorless oil with an exceptionally clean ^1H NMR spectrum ($CDCl_3$): δ 1.67, 1.65 (singlets, 6 H), 6.24 (dd, *J* = 33.5, 8 Hz, 1 H), 7.10 (m, 2 H), 7.30 (dd, *J* = 48, 8 Hz, 1 H), 7.89 (broad s, 1 H). Confirmation of its structure came from its molecular ion (82% relative abundance) at *m/e* 198.0553 (calcd for $C_8H_{11}N_2O_2P$, 198.0558) and its methanolysis to **2a** and hydrolyses to **3**-Im; see text.

Registry No. 2a, 59474-17-8; **3**-Im, 85702-21-2; **6**, 616-47-7; **6**-H^+, 85702-23-4; **7**, 85702-24-5; **8**, 75779-67-8; imidazole, 288-32-4; methyl iodide, 74-88-4; **4a**-O^-, 85702-22-3.

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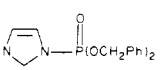

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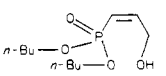
(19) Including an estimated 8-fold factor because of the temperature difference (37 °C vs. 64.5 °C).
(20) Compound **13** also cyclizes spontaneously: Machida, Y.; Saito, I. *J. Org. Chem.* **1979**, *44*, 865.



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