Phosphoric-Carboxylic Imides. 2. Solvolytic Cleavage of the Nitrogen-Carbonyl and Nitrogen-Phosphoryl Bonds

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Received December 23, 1982

The neutral and acid-catalyzed solvolysis (hydrolysis and alcoholysis) of mixed phosphoric-carboxylic imides (1), $X_2P(O)$-NR-C(O)R′ (X = EtO, MeO, CH_2O, Et; R = H, Me; R′ = Me, Ph) has been studied and compared with the solvolytic behavior of parent phosphoric and carboxylic amides and symmetrical imides. The neutral cleavage of the P-N bond is believed to involve an oxyphosphorane intermediate. The ionization of 1 follows the amide acidity function, with half-protonation at the carbonyl oxygen atom occurring at ca. 70% D_2SO_4. The remarkable stability of the P-N bond in acidic solutions, together with the susceptibility of the N-C(O) solvolysis toward acid catalysis, is consistent with the exclusion of the N-protonation of 1 and is in accordance with carbonyl oxygen protonation and the significant electron-withdrawing effect of the *N*-phosphinyl substituent. The hydration parameter treatment was applied to the acid-catalyzed N-C(O) hydrolysis of **1d** (1, X = EtO; R = R′ = Me), and the results are compared with those obtained for the acid-catalyzed hydrolysis of *N*-methylacetamide. The acidic solvolysis of 1, with respect to both the P(O)-N and N-C(O) cleavage, lies between the extremes characterized by the respective parent amides and symmetrical imides.

In mixed diacyl systems such as acid anhydrides or imides that are derived from two different acids, selectivity in the nucleophilic cleavage depends mainly on two factors: (i) the relative electrophilicity of the acyl centers; (ii) the degree of bond breaking between the substrate and the leaving group in the rate-determining transition state. In mixed carboxylic anhydrides factor (i) is most important; for unsymmetrical pyrophosphates on the other hand, the leaving group ability determines the direction of nucleophilic attack.[1] If a reaction is (as is often the case) acid catalyzed, then an additional factor is introduced—namely the site of protonation of the substrate, i.e., the detailed structure of the reactive conjugate acid. In the case of a mixed carboxylic-phosphoric system, the situation is more complex since the substitution at each of the acyl (carbonyl and phosphoryl) centers may follow different mechanistic patterns, hence the different structure-reactivity dependence for the two cleavage pathways. Neutral acyclic carboxylic-phosphoric[2,3] and carbonic-phosphoric[4] anhydrides undergo attack by oxygen[3,4] and nitrogen[2] nucleophiles (Nu) at the carbonyl center:

$$(RO)_2P(O)OC(O)X + NuH \rightarrow (RO)_2PO_2H + NuC(O)X \quad X = R', OR' \qquad (1)$$

The relatively poor leaving ability of a carboxylate group disfavors substitution of phosphorus; the attack at the carbonyl center is facilitated by strong electron withdrawal of the dialkylphosphoryloxy substituent.[5] Following our interest in the relative reactivity of the nitrogen-carbonyl and nitrogen-phosphoryl bonds,[7] we have now studied the neutral and acid-catalyzed solvolysis of mixed phosphoric-carboxylic imides (1). System 1 can be considered as

$$X_2P(O)—NR—C(O)R'$$

1a, X = MeO; R = H; R′ = Ph
1b, X = EtO; R = H; R′ = Ph
1c, X = MeO; R = Me; R′ = Me
1d, X = EtO; R = Me; R′ = Me
1e, X = EtO; R = Me, R′ = Ph
1f, X = Et; R = Me, R′ = Me
1g, X = CH_2O; R = Me; R′ = Me

derived from carboxylic and phosphoric amides, modified at the nitrogen atom with a phosphacyl and carboxyacyl group, respectively. The solvolytic behavior of carboxylic and phosphoric amides is relatively well understood. Both systems are stable in neutral solution, but under acidic conditions they differ greatly in the reactivity of the nitrogen-acyl bond. Carboxyamides react slowly, via a tetrahedral intermediate formed by the attack of a solvent at the oxygen-protonated form of the substrate.[8] Phosphoric amides, on the other hand, react fast according to the $S_N2(P)$ direct displacement of an amine from the N-protonated substrate.[9] In an acid-catalyzed reaction, imides (1), can in principle offer three protonation sites (nitrogen and carbonyl or phosphoryl oxygens), and the protonation behavior, as well as the subsequent cleavage pathways, is difficult to predict. The crystal and molecular structure of **1a** revealed[10] secondary interactions that indicate a high electrophilicity of phosphorus together with a pronounced nucleophilic nature of the carbonyl oxygen. This observation was supported by the mass spectra of compounds 1.[11] For all compounds the N→O migration of the phosphacyl moiety yielding *O*-phosphoryl imidates, $X_2P(O)$-O-C(NR)R′, was observed, implying lability of the P-N bond and high electron density at the carbonyl oxygen. Strong resonance interactions within the -N(Me)CO- group in 1 are also indicated by the ^1H NMR and IR spectra of these substrates.[11]

Under neutral conditions the solvolysis of the P-N bond in 1 is likely to involve, due to the poor leaving group present (RNCOR′) and low nucleophilicity of the reagent (water, alcohol), a P^V intermediate.[12] In such a case the

(1) J. Emsley and D. Hall, "The Chemistry of Phosphorus", Harper and Row, London, 1976, p 329.
(2) K. Sasse, "Organische Phosphorverbindungen", G. Thieme Verlag, Stuttgart, 1964, Volume XII/2, p 566.
(3) J. L. Dever and J. J. Hodan, U.S. Patent 3 482 002 (1970); *Chem. Abstr.* **72**, 79051k (1970).
(4) D. L. Griffith and M. Stiles, *J. Am. Chem. Soc.*, **87**, 3710 (1965).
(5) The polar effect of the $OP(O)(OEt)_2$ group, as measured by the inductive and resonance constants,[6] is very close to that of chlorine atom.
(6) T. A. Modro, *Phosphorus Sulfur*, **5**, 331 (1979).
(7) T. A. Modro, *ACS Symp. Ser.*, **No. 171**, 128 (1981).
(8) T. A. Modro, K. Yates, and F. Beaufays, *Can. J. Chem.*, **55**, 3050 (1977).
(9) J. Rahil and P. Haake, *J. Am. Chem. Soc.*, **103**, 1723 (1981), and references cited therein.
(10) V. Mizrahi and T. A. Modro, *Cryst. Struct. Commun.* **11**, 627 (1982).
(11) V. Mizrahi and T. A. Modro, *J. Org. Chem.*, **47**, 3533 (1982).

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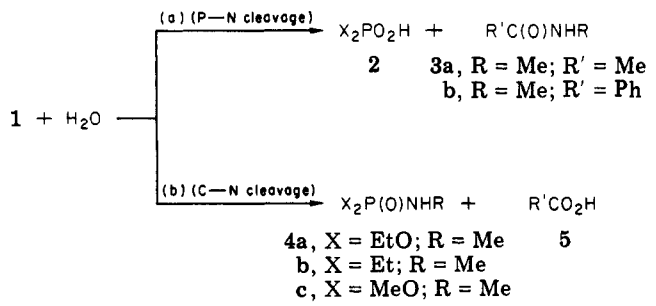
Scheme I



selectivity in the nucleophilic cleavage of 1 should be directly related to the relative electrophilicity of the two acyl centers. Under conditions of acidic catalysis, the protonation equilibria responsible for the activation of the respective nitrogen–acyl bonds would be expected to respond differently to the effects introduced by the second acyl group. The basicity of the carbonyl oxygen in 1 should not be reduced to a great extent by the phosphorylation of nitrogen,[13] but the approach of a nucleophile to this conjugate acid should be enhanced[8] by the increase in the electrophilicity of the carbonyl carbon. The N-protonation on the other hand, necessary for easy cleavage of the phosphoramidate bond,[9] would probably be almost totally suppressed because of the effect of two acyl substituents. These differences in protonation requirements could result in a greatly different response of each of the amide functions to structural modification at nitrogen, hence greatly different solvolytic behavior relative to that of the parent structures.

Results

Neutral Hydrolysis. Imides (1) can, in principle, hydrolyze according to the two pathways shown in Scheme I. Since each of the pathways yields acidic species, the autocatalytic hydrolysis of 1, as well as of the amide products 3 and 4, had to be taken into account. Although carboxylic amides are relatively stable in dilute acids,[8] hydrolysis of phosphoric amides[9] and mixed imides (1) (see following sections) is strongly susceptible to acid catalysis. For tertiary substrates (1, R = Me) product determination and rate measurements are most conveniently carried out by ^{1}H NMR spectroscopy, due to the easily distinguishable signals of the N–Me group in 1 (δ 3.05–3.25, d, J_{HP} = 6–9 Hz), 3 (δ 2.8–3.0, s), and 4 (δ 2.5–2.7, d, J_{HP} = 12 Hz). However, this technique required high substrate concentrations (0.2–0.3 M), hence very high buffer concentrations, to keep the reaction medium neutral over the course of the reaction. For practical reasons reactions were carried out in D_2O in the absence of buffers and the composition of the reaction mixture was monitored intermittently over the whole range of conversion. This enabled us to distinguish the primary products from the subsequent products resulting from further acidic hydrolysis. The hydrolytic behavior of substrates 1 is varied and covers an extremely wide reactivity range. Both secondary substrates (**1a**, **1b**) were found to be idefinitely stable in aqueous solution at 25 °C.[14] The only tertiary substrate that was also found to be indefinitely stable in D_2O at 25 °C is the phosphinic derivative **1f**. The *N*-benzoyl compound **1e** undergoes exclusive P(O)–N bond cleavage (Scheme I, pathway a) as indicated by the simultaneous appearance of *N*-methylbenzamide (**3b**) and disappearance of the substrate; the reaction is complete in 24 days. The extremely hygroscopic cyclic substrate **1g** shows the greatest hydrolytic instability; the reaction at 25 °C is complete within 7 min and the ^{1}H NMR analysis of the final product revealed that the hydrolysis proceeds with exclusive attack at phosphorus.

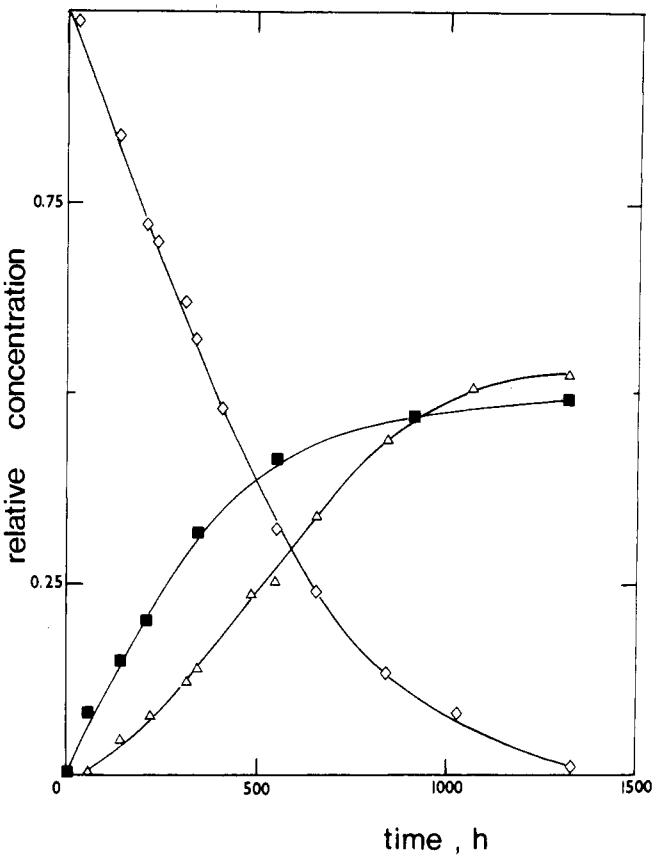


Figure 1. Variation of substrate (◇) and product (■, P–N cleavage; △, N–C cleavage) in the reaction of **1d** with D_2O at 25 °C.

The most interesting behavior is, however, exhibited by substrates **1c** and **1d**, which follow a common hydrolysis pattern, consisting of two distinct steps: (i) initially the P–N bond is hydrolyzed exclusively (formation of **3a**). (ii) After ca. 5% conversion, the simultaneous formation of acetic acid (acetyl Me, δ 2.11, s) and methylamine (NMe, δ 2.62, s) commences and proceeds at a steadily increasing rate. The variation in the concentrations of the substrate **1d** and its hydrolysis products, as a function of time, is illustrated in Figure 1.

Neutral Alcoholysis. The solvolysis of 1 by an alcohol R″OH can similarly proceed with P–N and C–N bond fission, giving two pairs of products, analogous to those shown in Scheme I, with esters $X_2P(O)OR''$ and $R'CO_2R''$ being formed instead of acids (**2** and **5**). The alcoholysis by methanol and ethanol at 25 °C was studied with imide **1c** as a substrate, and the reaction progress and the products formed were determined by GC. Both methanolysis and ethanolysis of **1c** were found to proceed with exclusive P–N bond cleavage, and both reactions followed pseudo-first-order kinetics: $-d[substrate]/dt = k_{obsd}[substrate]$.

Acidic Alcoholysis. Solvolysis of **1c** was studied in methanol and ethanol containing 0.86 M HCl using GC

(12) H. Goldwhite, "Introduction to Phosphorus Chemistry", Cambridge University Press, Cambridge, 1981, p 68.
(13) When bonded to nitrogen, phosphoryl substituents do not reduce significantly nitrogen's ability to donate its nonbonding electrons to an adjacent resonance acceptor.[6]
(14) In their preparation, **1a** and **b** are obtained by precipitation from neutral (or mildly acidic) aqueous solution.[15]
(15) A. V. Kirsanov and R. G. Makitra, *Zh. Obshch. Khim.*, **28**, 35 (1958).

Table I. Alcoholysis of 1c at 25 °C

medium	bond cleavage, %		$10^5 k_{obsd}$, s^{-1}	
	P-N	N-C	P-N	N-C
MeOH	100		0.20	
EtOH	100		0.16	
0.86 M HCl in MeOH	9	91	4.0	43.5
0.86 M HCl in EtOH	19.2	80.8	0.95	3.8

as an analytical technique. Under these conditions the cleavage of both the phosphoramidate and carboxyamide linkages was observed. The products of initial P-N cleavage are relatively unreactive in the acidic alcohol solutions (for **3a** $t_{1/2} > 2$ months), whereas the phosphoramidate formed by the N-C(O) alcoholysis of **1c** is still reactive and subsequently cleaves to the same phosphoryl ester $X_2P(O)OR''$ as that produced by the P-N bond cleavage of the mixed imide (**1c**).[16] The rate constants for the solvolysis of both amide linkages in **1c** were determined by monitoring both the appearance of *N*-methylacetamide (k_{P-N}) and the disappearance of the imide substrate ($k_{P-N} + k_{N-C}$). The product composition and observed rate constants for neutral and acidic alcoholysis of **1c** are given in Table I.

Acidic Hydrolysis. Acid-catalyzed hydrolysis of the imide system was studied in D_2O–D_2SO_4 mixtures and the tertiary phosphoric (**1d**) and phosphinic (**1f**) derivatives were selected as substrates. Selectivity and rates of hydrolysis were determined by ^1H NMR spectroscopy. Since the rate measurements require a knowledge of the hydrolytic behavior of the amide products initially formed, the hydrolysis of **3a** and **4a**, **4b** was also studied. In addition, the response of the P(O)–N and C(O)–N bond hydrolyses to medium acidity was investigated for the phosphoric (**6**) and carboxylic (**7**) imides in order to compare the hydrolytic behavior of the mixed diacylamines with their symmetrical counterparts. Phosphoric amides

$[(EtO)_2PO]_2NMe$ — **6**

RCO—NMe—COMe

7a, R = Me

7b, R = Ph

(**4a** and **4b**) were found to be too reactive for the rate measurements at 25 °C by means of the NMR technique, and, as such, a lower limit of the rate constants can, at best, be estimated: $k_{OBSD} > 5 \times 10^{-3}$ s^{-1} over the whole acidity range. In contrast, the phosphoric imide **6** was indefinitely stable under these conditions; in consequence the rate–acidity data for substrates (**4a**, **4b**, and **6**) were not available. The hydrolysis of **3a** was slow enough to allow the determination of the orientation and rates of hydrolysis of imides **1d** and **1f** by monitoring the appearance of **3a** (k_{P-N}), acetic acid (k_{N-C} for **1d**), or methylammonium ion (k_{N-C} for **1f**), as well as the disappearance of 1 ($k_{P-N} + k_{N-C}$). All hydrolyses followed pseudo-first-order kinetics over the entire acid range (1–87% D_2SO_4), and an excellent internal agreement was obtained for both substrates. The variations in the rates of hydrolysis with acid concentration are summarized in Table II, and the rate–acidity profiles are shown in Figure 2.

Ionization Behavior. Ionization ratios, *I*, were determined from the protonation induced shifts of selected signals in the ^1H NMR spectra:[17]

$$I = (\Delta\nu - \Delta\nu_B)/(\Delta\nu_{BH^+} - \Delta\nu) \quad (2)$$

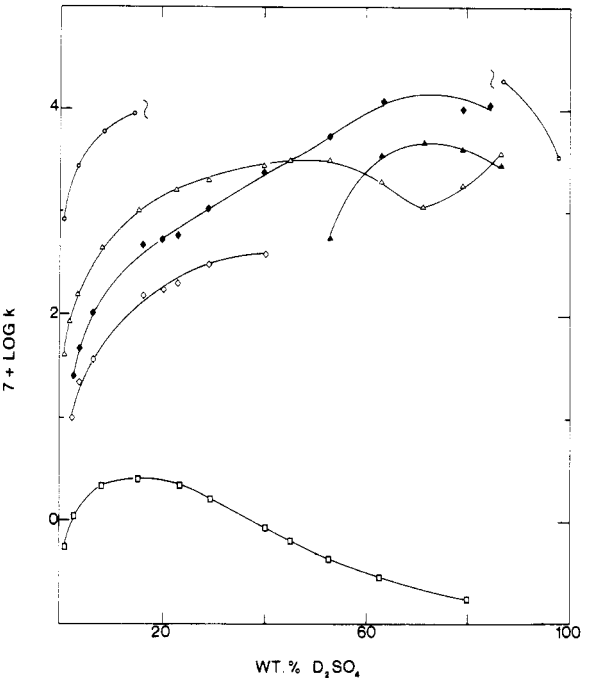


Figure 2. Rate–acidity profiles: o, N–C cleavage of **7a**; △, N–C cleavage of **1d**; ▲, P–N cleavage of **1d**; ◇, N–C cleavage of **1f**; ◆, P–N cleavage of **1f**; □, N–C cleavage of **3a**.

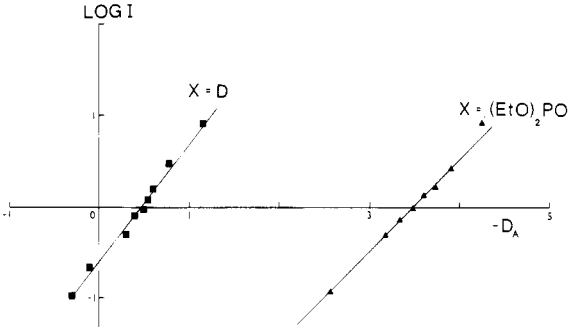


Figure 3. Ionization behavior: ■, **3a**; ▲, **1d**.

where $\Delta\nu$ is the chemical shift (relative to a standard) in a given acidic medium and $\Delta\nu_B$ and $\Delta\nu_{BH^+}$ represent chemical shifts for the free base and conjugate acid, respectively. The signals of the acetyl groups (singlets) were used as the probe signals for the ionization of the structurally related substrates **1d** and **3a**. Figure 3 gives the relationship between the ionization ratio determined and the acidity of the medium. The ionization behavior was then correlated with the amide acidity function for the D_2O–D_2SO_4 system, D_A (see Experimental Section) according to eq 3.[18] The values of the slopes, *m*, intercepts,

$$\log I = -mD_A + c \quad (3)$$

c, and the acidity function at half-protonation, $D_A^{1/2}$, of substrates **1d** and **3a** are listed in Table III.

Discussion

Neutral Solvolysis. The behavior of the five tertiary substrates (**1c–g**) in neutral media (water, alcohols) proved a useful probe for the relative reactivity of both acyl centers. With the exception of **1f**, which was found to be stable in D_2O, all remaining substrates, irrespective of the rate of hydrolysis, reacted exclusively according to pathway

(16) In 0.86 M HCl in EtOH at 25 °C, the observed rate constant for the solvolysis of dimethyl *N*-methylphosphoramidate (**4c**, X = MeO; R = Me) is k_{Obsd}(P–N) = 1.91×10^{-5} s^{-1}, i.e., twice that of **1c** under the same conditions.

(17) M. Liler, "Reaction Mechanisms in Sulfuric Acid", Academic Press, London, 1971, p 63.

(18) K. Yates, *Acc. Chem. Res.*, **4**, 136 (1971).

(19) M. Liler, *J. Chem. Soc. B*, 385 (1969).

Table II. Hydrolysis of Imides and Amides in D_2O–D_2SO_4 Mixtures (25 ± 0.5 °C)[a]

	substrates									
	1d				1f				3a	7a
D_2SO_4 % wt	P–N cleav, %	N–C cleav, %	$10^5k_{(P-N)}$, s^{-1}	$10^5k_{(N-C)}$, s^{-1}	P–N cleav, %	N–C cleav, %	$10^5k_{(P-N)}$, s^{-1}	$10^5k_{(N-C)}$, s^{-1}	$10^5k_{(N-C)}$, s^{-1}	$10^5k_{(N-C)}$,[b] s^{-1}
0.8		100		0.40						8.1
1.6		100		0.85	70.9	29.1	0.25	0.10	0.0056	11.7
3.3		100		1.5	67.5	32.5	0.47	0.23	0.011	27.5
6.4					70.5	29.5	1.09	0.46		
8.0		100		4.47					0.023	60.3
15.5		100		10.0					0.024	92.1
16.1					75.6	24.4	4.68	1.51		
20.0		100		13.8	73.8	26.2	5.13	1.82		
22.6		100		15.8	73.8	26.2	5.75	2.04	0.021	180[c]
29.2		100		19.9	78.3	21.7	10.6	2.96	0.015	210[c]
40.0		100		27.5					0.0083	*d*
40.3					86.3	13.7	24.0	3.80		
45.0		100		30.0					0.0065	*d*
52.4	15.1	84.9	5.37	30.2	100		52.6		0.0044	*d*
62.3	63.4	36.6	33.1	19.1	100		121[c]		0.0028	*d*
71.3	81.1	18.9	45.7	10.7						
79.4	68.6	31.4	38.5	17.6	100		104[c]		0.0016	*d*
83.2					100		116[c]		*e*	180[c]
86.9	44.5	55.5	25.7	32.0					*e*	190[c]
98.0									*e*	35.4

[a] Unless indicated otherwise, rate constants are reproducible to within ± 5%. [b] Corrected to a single N–C bond. [c] ± 20%. [d] $k > 5 \times 10^{-3}$ s^{-1}. [e] $k < 1 \times 10^{-8}$ s^{-1}.

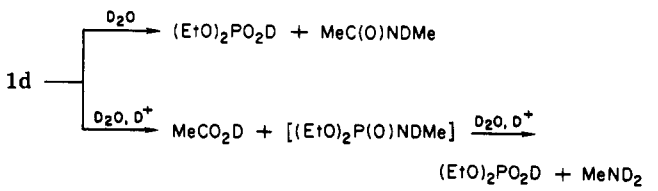
Table III. Ionization Behavior in D_2O–D_2SO_4 Mixtures (25 °C)

substrate	m	c	$D_A^{1/2}$	% acidity at half-protonation
1d	0.95	−3.31	−3.49	69.4
3a	1.25	−0.60	−0.48[a]	9.6

[a] Liler[19] reports $H_A^{1/2} = -0.72$ for 3a in H_2O–H_2SO_4 solution. Ionization data could not be obtained for substrates 4a and b and 7a and b due to their instability in aqueous acidic media.

a Scheme I, i.e., with the cleavage of the P–N bond. As demonstrated for 1c and 1d the hydrolysis course can be complicated by products arising from the subsequent acid-catalyzed reaction. Nevertheless, the initial hydrolysis of these substrates involves the exclusive attack of water at the phosphorus atom, resulting in the formation of *N*-methylacetamide and dimethyl (or diethyl) phosphate. However, the latter product, even at a yield of ca. 5%, lowers the pD of the reaction medium from 7 to ca. 2.[20] Such an increase in acidity is sufficient (see Figure 2) to change the reaction course of substrates (1c,d) from neutral P–N hydrolysis to the acid-catalyzed hydrolysis of the N–C (carbonyl) bond, resulting in the formation of acetic acid and dialkyl *N*-methylphosphoramidate; the latter product hydrolyses in a fast, acid-catalyzed step to dialkyl phosphate and methylamine (Scheme II). According to this scheme, we observed the initial fast formation of *N*-methylacetamide followed by a leveling-off period together with the delayed but rapid appearance of the acetic acid/methylamine pair (in 1:1 ratio), the concentration of the latter being, at the final stage of reaction, greater than that of the initial product of P–N bond cleavage (Figure 1). Scheme II indicates that in the absence of acid the nucleophilic attack occurs exclusively at the phosphoryl center of 1 and that acid catalysis is a prerequisite for the N–C bond solvolysis in 1. In agreement with this conclusion, the stability of the N–C bond in 1f is due to the absence of initial P–N bond cleavage of this substrate, which precludes the possibility of acid catalysis. The absence of N–C cleavage of 1e, despite the accumulation of acid in the medium caused by P–N bond hydrolysis, indicates a greater stability of an N–C(O)Ph than N–C(O)Me linkage in a mixed imide system. This result is consistent with the lower basicity of an N-substituted benzamide relative to its acetamide analogue (ΔpK_a = ca. 1),[22] resulting in a slower rate of acid-catalyzed N–C(O)Ph hydrolysis.[23]

Scheme II



The necessary presence of acidic species in order for N–C cleavage in 1 to occur is demonstrated by the results of the neutral alcoholysis. In this case, both products of the P–N bond solvolysis are neutral, and the reaction is thus not accompanied by any change in the medium acidity.

$$\text{1c} + \text{R—OH} \rightarrow (\text{MeO})_2\text{P(O)OR} + \text{MeC(O)NHMe} \quad (4)$$
$$\text{R} = \text{Me, Et}$$

As a consequence, trialkyl phosphates and *N*-methylacetamide (eq 4) are the only products of solvolysis, as determined by GC analysis of the reaction mixtures.

For the neutral solvolysis of 1 the direct S_N2 displacement at phosphorus seems unlikely for two reasons. First, the R′C(O)NR fragment has a poor leaving ability without

(20) The value of pD = ca. 2 was obtained for the 5% conversion of the initially 0.25 M solution of a substrate, taking pK_a for dialkyl phosphate as ca. 1.3.[21]

(21) D. E. C. Corbridge, "Phosphorus", Elsevier, Amsterdam, 1980, p 284.

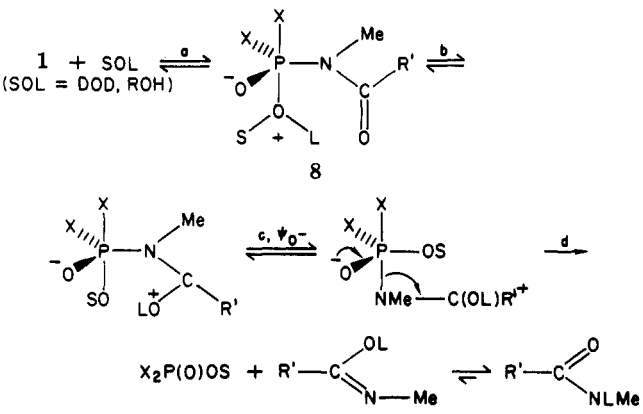
(22) R. A. Cox, L. M. Druet, A. E. Klausner, T. A. Modro, P. Wan, and K. Yates, *Can. J. Chem.*, **59**, 1568 (1981).

(23) For *N*-methylbenzamide in 5.9% H_2SO_4, at 25 °C, k_ψ(N–C) = 0.77 × 10^{-8} s^{-1}.[24] For *N*-methylacetamide under the same conditions k_ψ(N–C) = ca. 4 × 10^{-8} s^{-1}.[25]

(24) C. R. Smith and K. Yates, *J. Am. Chem. Soc.*, **93**, 6578 (1971).

(25) P. Wan, T. A. Modro, and K. Yates, *Can. J. Chem.*, **58**, 2423 (1980).

Scheme III



prior activation via a proton transfer process.[26] Second, since nucleophilic displacement is faster at a phosphinyl than at a phosphoryl center,[28] the S_N2 neutral P–N solvolysis of the phosphinic substrate (**1f**) should also be faster than that of the phosphoric derivatives (**1c,d**). However, **1f** was found to be completely inert in D_2O solution.

The neutral solvolysis of the mixed imides (**1a–g**) can, however, be plausibly explained in terms of a mechanism involving formation of the trigonal bipyramidal (tbp) intermediate (**8**) followed by proton transfer and pseudorotation, enabling P–N bond fission with the departure of the tautomeric form of the carboxylic amide (Scheme III). The proposed mechanism outlined in Scheme III adequately explains the neutral hydrolysis as well as alcoholysis of all tertiary substrates (**1c–g**). The rate-determining step of the P(O)–N bond solvolysis presumably involves the formation of the tbp intermediate (step a). The observed ca. (2×10^3)-fold increase in reactivity for the dioxaphospholan derivative (**1g**) relative to the noncyclic analogues (**1c** and **1d**) can thus be accounted for in terms of the slow step rate enhancement typifying solvolyses involving five-membered cyclic phosphates.[28] On the other hand, the phosphinic derivative (**1f**) would be expected to show much lower reactivity due to the weak apicophilicity of the ethyl groups (**8**, X = Et).[29] The weakly apicophilic ethyl and oxyanion substituents would be anchored in the equatorial positions of **8**, and since the apicophilicity of the bulky and weakly electronegative *N*-acylamino group should also be low, the activation energy for the formation of the tbp (**8**) is, in the case of substrate **1f**, relatively high.

As mentioned above, carboxamides and phosphylamides are solvolytically stable under neutral conditions. As far as the N–C linkage is concerned, we observe a retention of this solvolytic behavior in the mixed imides (**1**). However, the solvolytic instability under neutral conditions of the P–N linkage of the tertiary *N*-acyl phosphoramidates (**1c–e,g**) contrasts the behavior of their parent amide systems. The effect of an *N*-acyl substituent on the dynamics of the P(O)–N bond is probably 2-fold: it converts the nitrogen-containing function into a relatively good leaving group, and it reduces the p_π–d_π interaction between nitrogen and phosphorus, thus weakening the P–N bond and increasing the electrophilicity of the phosphorus atom. It is worthwhile to note that we did not observe the solvolysis of a P–O ester function in any of the substrates (**1**). In this respect imides (**1**) do not resemble phosphoric derivatives of urea, $MeNH–CO–NMe–CH_2–P(O)(OH)(OR)$, which easily release alcohol ROH via the intramolecular nucleophilic catalysis by the carbonyl oxygen atom.[31] Analogous catalysis in **1** would involve a four- (instead of five-) membered cyclic intermediate, and because of the strain in such a ring, the carbonyl group behaves in solvolysis rather as a proton acceptor (step b) than an internal nucleophile. The solvolytic stability of the secondary derivatives (**1a,b**) is more difficult to rationalize. All substrates (**1**) are certainly strongly hydrogen bonded in hydroxylic solvents. However, for the tertiary substrates, the hydrogen bonding can be only of the donor type (Y=O···L—O; Y = P, C; L = H, D), effectively increasing the electrophilicity of the substrate. However, the secondary imides, because of the presence of the strongly acidic N–H group,[32] would also be involved in acceptor type hydrogen bonding (N–H···O–L), increasing the electron density of the imide linkage and thus shielding the acyl centers against nucleophilic attack. The more extensive hydrogen bonding in the latter case should also result in a greater ground-state stabilization of the secondary substrates relative to the tertiary substrates.[33]

Acidic Solvolysis. Table I gives information on the response of the alcoholysis rates of the P–N and N–C bonds in **1c** to change in the acidity of the medium. Since at the acid concentration used, any nucleophilic catalysis by chloride ion should be negligible,[35] the observed changes in reactivity result primarily from the protonation preequilibrium. The individual *N*-acyl bonds in **1c** differ greatly in their sensitivity to the change of reaction medium from neutral to acidic. For the solvolysis of the P–N bond, the rate acceleration is only 20 (in MeOH) and 6 (in EtOH); the corresponding rate enhancement for the N–C bond fission is greater[36] than 4400 and 480, respectively. This result contrasts the acidity response shown by the parent amide systems; both are stable in neutral solution, but in acids, phosphoramidates show a much more dramatic increase in reactivity than their carboxyamide counterparts. The relatively poor effect of acidity on the P–N bond alcoholysis supports the view[9] that N-protonation is responsible for the fast acidic solvolysis of phosphoric amides, since in system **1** the second acyl group effectively eliminates the nitrogen atom as a competitive basic center. The remarkable sensitivity of the N–C alcoholysis rate of **1c** to the acidity of the medium clearly indicates the behavior of the carbonyl oxygen as a proton acceptor center in the preequilibrium step:

$$\mathbf{1c} + H^+ \rightleftharpoons (MeO)_2P(O)NMeC(OH)Me^+ \rightarrow TS \quad (5)$$

The rate–acidity profiles were determined in aqueous solutions for substrates **3a**, **1d,f**, and **7a** (Figure 2). The shape of the rate profile for **3a** with a rate maximum occurring at ca. 14% D_2SO_4 is typical of an A-2 carboxyamide hydrolysis.[8] The N–C hydrolysis rate of **1d** attains a

(26) The pK_a values for secondary carboxylic amides and aliphatic alcohols are similar (ca. 16),[27] and the neutral hydrolysis of the P–OR bond in alkyl phosphates is known to be slow.

(27) D. D. Perrin, B. Dempsey, and E. P. Serjeant, "pK_a Prediction for Organic Acids and Bases", Chapman and Hall, London, 1981, Appendix A.2.

(28) F. H. Westheimer, *Acc. Chem. Res.*, 1, 70 (1968).

(29) R. R. Holmes, *ACS Monogr.* No. 176, Volume II, 148 (1980).

(30) ^1H NMR spectroscopy has revealed the indefinite stability of $(RO)_2P(O)NHMe$ (R = Me, Et) in D_2O and methanol-d_4 at 25 °C.

(31) R. Kluger and P. D. Adawadkar, *J. Am. Chem. Soc.*, 98, 3741 (1976).

(32) M. K. Hargreaves, J. G. Pritchard, and H. R. Dave, *Chem. Rev.*, 70, 439 (1970).

(33) N-Methylation of $(MeO)_2P(O)NHPh$ results in a 30-fold increase in the rate of the hydrolysis of the P–N bond,[34] and the effect was interpreted in terms of solvation effects.

(34) T. A. Modro and B. P. Rijkmans, *J. Org. Chem.*, 47, 3208 (1982).

(35) M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 1*, 1294 (1979).

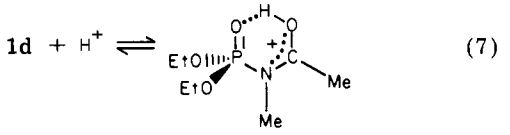
(36) Since exclusive P(O)–N cleavage is observed in neutral alcohol ($k_{\psi(N-C)} < 0.05\ k_{\psi(P-N)}$), only the lower limit of the rate acceleration could be determined.

maximum at a significantly higher acidity (ca. 52% D_2SO_4) and, as such, is more reminiscent of the profiles associated with the acid-catalyzed hydrolysis of carboxylic esters.[19] Owing to predominant P–N cleavage at higher acidity, the rate of N–C cleavage of **1f** is only determinable up to 40% D_2SO_4; the determination of a complete profile of **7a** was precluded by its hydrolytic instability in the range 25–80% D_2SO_4. However, the monotonic change in N–C(O) hydrolysis rates of **1f** and **7a**, within the observable acidity range, indicates the occurrence of their rate maxima at high acidity, as observed for **1d**. The rates of the P–N bond hydrolysis in both imides (**1d,f**) attain their maxima at ca. 70% D_2SO_4.

Rate measurements enable us to determine quantitatively (or semiquantitatively) the effect of introduction of a *second* acyl (RCO or X_2PO) substituent at nitrogen upon the dynamics of the *existing* P–N and N–C bonds of an amide. For the system MeC(O)–NMeY, the relative rates of the C(O)–N bond cleavage in 15.5% D_2SO_4 (25 °C) are 1, 23, 410, 1580, and 3780 for Y = D, $Et_2P(O)$, $(EtO)_2P(O)$, PhC(O), and MeC(O), respectively. For the P–N bond hydrolysis in the series $(EtO)_2P(O)$–NMeY (52–87% D_2SO_4, 25 °C), if the rate for the parent amide (Y = H) is taken as 1, the relative rates for the mixed (Y = MeCO) and symmetrical (Y = $(EtO)_2PO$) imides are *less* than 10^{-2} and 5×10^{-7}, respectively.[37] Therefore the introduction of a second acyl group has opposite effects upon the two amide bonds: it dramatically *stabilizes* the P–N function, whereas it significantly *labilizes* the C–N bond. Qualitatively, such results remain in excellent agreement with what could have been expected for these two acyl centers (see Introduction). Quantitative assessment of the structural effects upon the dynamics of the C–N bond hydrolysis was attempted for a pair of substrates **3a** and **1d**, i.e., for N-methylacetamide and its *N*-(diethylphosphoryl) derivative. The effect of structural change upon the reactivity in an A-2 solvolysis, $\Delta \log k_{obsd}$, is given by the effect on the preequilibrium protonation and on the rate constant k_2 for nucleophilic attack at the acyl center.[38]

$$\Delta \log k_{obsd} \cong \Delta \log k_2 + \Delta pK_{SH^+} \quad (6)$$

The strong acidity-induced low-field shifts observed for the signals of the acetyl methyl groups, together with the fact that protonation of **1d** follows the amide acidity function D_A,[39] indicate that the mixed imide **1d** parallels its precursor **3a**[41] and undergoes protonation at the carbonyl oxygen. The conjugate acid of **1d** may be internally stabilized by the phosphoryl group (structure **9**), particu-



(7)

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larly in view of the fact that monoprotonated carboxylic imides, anhydrides, and β-diketones have been proposed to exist in analogous cyclic forms.[42]

It follows from Table III that the N-phosphorylation of *N*-methylacetamide reduces the basicity of the carbonyl group by 3 log units ($\Delta pK_{SH^+} = -3$). At low acidities (up to 8% D_2SO_4), where the protonation of both substrates is not far advanced, **1d** has been found to hydrolyze 140–190 times *faster* than **3a** ($\Delta \log k_{obsd} = 2.1$–$2.3$). The ratio of the bimolecular rate constants for the slow step in the A-2 hydrolysis of **1d** and **3a** is $k_2(\mathbf{1d})/k_2(\mathbf{3a}) = 1.3 \times 10^5$–$2 \times 10^5$ ($\Delta \log k_2 = 5.1$–5.3). The observed acceleration of the slow step agrees fairly well with the effect obtained by applying the Taft equation to the hydrolysis of the nitrogen–carbonyl bond in **1d**. This approach gives the value of $\Delta \log k_2 = 5.4$,[43] i.e., $k_2(\mathbf{1d})/k_2(\mathbf{3a}) =$ ca. 2.5×10^5.

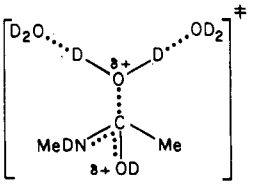
In terms of the N–C(O) bond hydrolysis, imide **1d** behaves as a carboxylic amide, whose basicity is reduced by N-phosphorylation but whose carbonyl center electrophilicity is greatly enhanced. Since the rate–acidity profile for **1d** (and for the reference compound **3a**) could be determined over a wide acidity range (0–87% and 0–80% D_2SO_4 for **1d** and **3a**, respectively), we decided to analyze these profiles in terms of one of the general theoretical treatments adopted in mechanistic studies of acid-catalyzed reactions. The *r*-parameter treatment[46] seemed to be the best approach since it gives a direct insight into the hydration changes accompanying the transformation of a protonated substrate to the transition state (slow step of the hydrolysis). We were particularly interested in the possibility of detecting any specific facilitation of the approach of water to the carbonyl center by the *N*-phosphoryl group other than polar effects transmitted within the molecular framework. Because of the low basicity of **1d**, its hydration plot up to 45% D_2SO_4 was determined from eq 8a; in stronger acids the more generalized treatment given by eq 8b was applied.[46] In eq

$$\log k_{obsd}\,(\text{N–C}) + 0.95D_A = r \log a_{D_2O} + \text{constant} \quad (8a)$$

$$\log k_{obsd}\,(\text{N–C}) - \log\left(\frac{d_A{}^m}{d_A{}^m + K_{SD^+}{}^m}\right) = r \log a_{D_2O} + \text{constant} \quad (8b)$$

8 a_{D_2O} represents activity of D_2O in D_2O–D_2SO_4 mixtures and the slope *r* is an approximate measure of the hydration requirement of the substrate → transition state step. Hydration plots for the hydrolysis of **1d** and **3a** are presented in Figure 4.

The hydration plot of **3a** consists of two straight line sections with a change of slope from 3.5 to 0.6 occurring at ca. 40% D_2SO_4. An analogous hydration plot slope change was reported[25] for the hydrolysis of *N*-ethylacetamide in the H_2O–H_2SO_4. The observed behavior is indicative of a highly hydrated (at least three solvating water molecules) A2 transition state (**10**) in a water-rich medium,



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(37) The limits of reactivities of substrates **4a** and **6** are based on the observation that the hydrolysis of **4a** is completed within less than 5 min, while **6** remains unchanged (less than 5% of reaction) over the period of at least 6 months.

(38) M. Liler, "Reaction Mechanisms in Sulfuric Acid", Academic Press, London, 1971, p 191.

(39) A log *I*-acidity function slope of 0.95–1.05 is an acceptable criterion of adherence of a base to that particular function.[40]

(40) K. Yates and J. B. Stevens, *Can. J. Chem.*, **43**, 529 (1965).

(41) R. A. McClelland and W. F. Reynolds, *J. Chem. Soc., Chem. Commun.*, 824 (1974).

(42) T. Gilles, J. C. Duplan, N. Pellisier, and E. Laurent, *J. Chem. Res. Synop.*, 8, 194 (1977), and references cited therein.

(43) Obtained takining $\rho^* = 2.48$[44] and $\sigma^*(PO_3Et_2) = 2.18$.[45]

(44) C. D. Johnson, "The Hammett Equation", Cambridge University Press, Cambridge, 1973, Chapter 3.3.

(45) D. J. Martin and C. E. Griffin, *J. Org. Chem.*, **30**, 4034 (1965).

(46) K. Yates and R. A. McClelland, *J. Am. Chem. Soc.*, **89**, 2686 (1967).

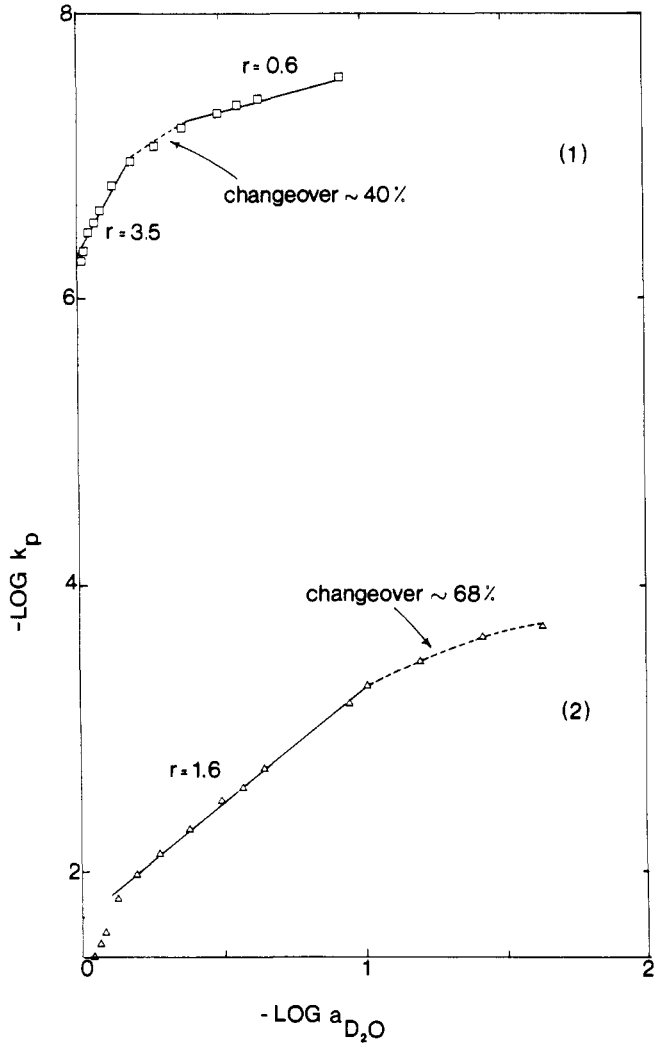


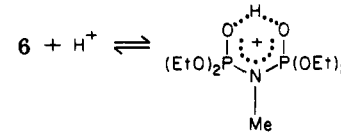
Figure 4. Hydration parameter treatment for N–C hydrolyses of **1d** (△) and **3a** (□).

changing to a mechanism involving the participation of only one water molecule in the rate-determining transition state when the availability of water is reduced.

The hydration plot for the hydrolysis of **1d** shows a similar high slope ($r \simeq 3.5$) region, but only in weakly acidic media. However, between ca. 15% and 60% D_2SO_4 an extensive linear region of slope 1.6 is exhibited, indicating a relatively poorly hydrated transition state incorporating at most two D_2O molecules. This behavior may be attributed to the formation of a transition state involving the participation of the phosphoryl group in hydrogen bonding, thus reducing the hydration requirement. In addition, a break in the linearity of the plot occurs at ca. 68% D_2SO_4; the relatively high acidity at which this break occurs is largely a consequence of the weak basicity of this substrate.[47]

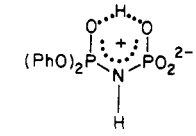
The phosphorus–nitrogen bond in imides **1**, although much less susceptible to acidic hydrolysis than that in the parent amides (**4**), undergoes hydrolytic cleavage with rates comparable to those of the N–C bond fission (Figure 2). The rate prfiles for the P–N cleavage in **1d** and **1f** are consistent with the usual $S_N2(P)$ pattern of nucleophilic displacement at the P^{IV} atom. Both profiles show broad rate maxima at ca. 70% D_2SO_4—the acidity at which the substrates exist mostly as conjugate acids. Further increase in the acid concentration does not effectively improve the leaving ability of the (protonated) *N*-methyl-*N*-acetyl group, but the simultaneous decrease in the availability of water disfavors the nucleophile–substrate transition state. As in other $S_N2(P)$ reactions, the phosphinic derivative was found to be more reactive than the phosphoric compound; the actual rate ratio for the substitution step cannot be determined because of the unknown basicity of substrate **1f**. The observed reduced reactivity of the P–N bond in **1** relative to **4** demonstrates the importance of N-protonation in activating a phosphoryl group–nitrogen linkage toward nucleophilic cleavage. However, the persistence of acid-catalyzed P–N solvolysis (albeit at a reduced rate) in systems in which direct N-protonation is precluded shows that this is not a necessary condition to labilize a P–N bond.

The rather unexpected resistance of the symmetrical phosphoric imide (**6**) to hydrolysis in aqueous sulfuric acid deserves a separate comment. We do not believe that the observed decrease in the reactivity of the P–N bond results from any dramatic changes in the substrate's basicity. Although the phosphoryl oxygen in **6** is certainly subject to a lesser basicity-strengthening effect by the neighboring nitrogen than is the carbonyl oxygen in **1**, the protonation of **6** at the acidities employed must nontheless be well advanced.[48] However, protonation of **6** should result in the formation of an internally stabilized, symmetrical quasi-phosphonium ion (**6.1**). The analysis of the electron



6.1

impact induced fragmentations of phosphoric imides (**6**) revealed[11] the extremely high inherent stability of ions of the type **6.1** in the gas phase. Any attack of an external nucleophile at **6.1** (S_N2 process) would necessarily disturb the symmetrical charge delocalization within the OPNPO framework. The relatively high stability of the monoanionic form of phosphoric imide (**11**) with respect to the unimolecular collapse[50] may be similarly attributed to the stable, zwitterionic structure.



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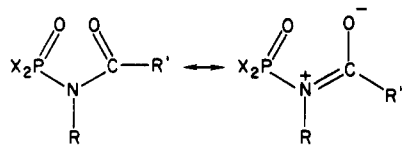
In conclusion, phosphoric–carboxylic imides (**1**) behave as reactive and versatile acylating agents. Under neutral conditions, unlike mixed anhydrides, they undergo attack by oxygen nucleophiles exclusively at the phosphoryl center. This regiospecificity undoubtedly results from the retained "carboxy–amide resonance" effect in **1** responsible for the electrophilic character of the phosphorus atom:

(47) Analogous changes in the *r*-plot slopes for carboxylic esters, which are even less basic than **1**, have been found to occur at acidities as high as 85% H_2SO_4.[19]

(48) The pK_a of **6** must be greater (less negative) than that of triethyl phosphate. Taking pK_a value for the latter as −3.7[49] it follows that in 50% D_2SO_4 more than 6% of **6** should exist as a conjugate acid.

(49) N. K. Skvortsov, C. F. Tereshchenko, B. I. Ionin, and A. A. Petrov, *Zh. Obshch. Khim.*, **46**, 521 (1976).

(50) M. Halmann, A. Lapidot, and D. Samuel, *J. Chem. Soc.*, 3158 (1961).



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As a consequence of this effect, imides (1) behave in protonation equilibrium as (carbonyl) oxygen bases, yielding a conjugate acid in which the electrophilicity of the phosphoryl and carbonyl centers are comparable, so the substrates can act as both phosphorylating and acetylating (benzoylating) reagents. In this sense, protonation of a mixed system (1) brings the P–N and C–N linkages to a level of comparable reactivity, while in the parent compounds (phosphoric and carboxylic amides) these bonds differ enormously with respect to their acidic solvolyses. This leveling effect is achieved by the simultaneous deactivation of the P–N and activation of the N–C functionalities.

Experimental Section

^{1}H NMR spectra were recorded on a 100-MHz Varian XL100 spectrometer. GC analyses were performed on a Hewlett-Packard HP 5710A model fitted with a 12.4 × 0.39 mm glass capillary packed with Silar 10c on barium carbonate. A Haake D1 thermostat and Haake L water bath were used for kinetic studies. The preparations and characterization of the substrates are described elsewhere.[11]

Alcoholysis. The stock solutions for acidic alcoholysis were prepared by passing dry HCl into anhydrous alcohol, immediately standardising by titration, and diluting appropriately with the same alcohol. The retention times of **1c** and its alcoholysis products are given in Table IV.

Kinetics. 1. Neutral Alcoholysis. The composition of a solution of substrate (0.15 mL), internal standard (0.05 mL; $(MeO)_2PO_2Et$ for methanolysis and $(MeO)_3PO$ for ethanolysis reactions), and anhydrous alcohol (5 mL) maintained at 25 °C was periodically analyzed by GC by direct injection onto the column, and concentrations (relative to the internal standard) were measured according to peak integration. Pseudo-first-order rate constants (k_ψ) obtained by following substrate disappearance and product appearance were identical; all kinetic runs were duplicated and k_ψ values found to be reproducible to a range of 2% of the average value.

2. Acidic Alcoholysis. The reaction mixture consisting of substrate, internal standard, and acidic alcohol (volumes as above) was divided into 10 equal portions, all maintained at 25 °C. The portions were quenched at various times (reactions were followed to ca. 80% completion) by neutralization to pH 7 with oven-dried K_2CO_3 and immediately analyzed by GC. Rate constants k_ψ(P–N) and k_ψ(N–C) were determined by both product appearance and substrate disappearance and final product ratio and were found to be in excellent agreement. All kinetic runs were made in duplicate using the same stock solution, all kinetic plots were found to be linear ($r > 0.999$), and rate constants calculated from duplicate runs were reproducible to a range of 3% of the average value of the two runs.

Products of alcoholysis reactions were identified by GC according to their retention times (Table IV) and by spiking the reaction mixtures with authentic samples of the products.

Hydrolysis. Aqueous acidic solutions were prepared by diluting the concentrated D_2SO_4 with D_2O, and the solutions were standardized in the usual way.

Table IV. Retention Times (t_R, min) of Alcoholysis Products of 1c

substrate	t_R	substrate	t_R
1c	9.1		
MeCONHMe	3.8	$MeCO_2Et$	*a*
$(MeO)_2PONHMe$	8.4	$(MeO)_3PO$	3.2
$MeCO_2Me$	*a*	$(MeO)_2PO_2Et$	3.6

[a] Substrate peak masked by solvent (alcohol).

Kinetics. The substrate (20–30 mg) was introduced into an NMR tube which was equilibrated in a bath at the temperature of the kinetic run (25 ± 0.5 °C). The acidic solution (0.5 mL) was transferred from a volumetric flask (also kept in the bath) and added to the substrate. The acid-catalyzed hydrolysis of **3a** ($t_{1/2} \geq 1$ month) was followed by periodically withdrawing the NMR tube from the bath and recording the spectrum at a temperature of 34 ± 1 °C (probe temperature). The hydrolyses are sufficiently slow to be unaffected by the short periods of temperature difference. Reactions of intermediate rate (30 min < $t_{1/2}$ < 24 h) were followed by periodically recording spectra at a probe temperature of 25 ± 1 °C. Faster runs ($t_{1/2}$ < 30 min) were followed by placing the NMR tubes in the probe (24 ± 1 °C) immediately after mixing and repeatedly recording the integration curve in the region containing the signals selected to monitor the reaction. Very fast runs ($t_{1/2}$ < 6 min) were repeated in triplicate and found to be reproducible to ±20%. For these runs, the reported rate constants are the average of the three runs. Slower runs were reproducible to ±5%. All runs were followed to 85–90% completion and all kinetic plots found to be linear ($r > 0.99$).

The identity of hydrolysis products was confirmed by NMR spectroscopy by spiking the reaction mixtures with authentic samples of the expected products.

pK Determinations. The central peak of the β-CH_3 triplet of the P–OEt group was used as the internal reference for $\Delta\nu$ determinations of **1d**. Methylammonium ion was used as the internal reference for $\Delta\nu$ determinations of **3a**. Measurements were made by injecting 0.01 mL of substrate into an NMR tube containing 0.5 mL of acid solution (and internal reference in the case of **3a**) and immediately recording the spectrum over the appropriate range. The range of acid concentrations contained ca. 8 samples in the region $-1 \leq \log I \leq 1$ and solutions in which the substrate is unprotonated and fully protonated. Values of $\log I$ thus obtained were plotted according to eq 3. Högfeldt and Bigeleisen[51] have found that the Hammett acidity functions H_0 and D_0 are identical in the range of 0.6 M to 12 M L_2SO_4 (L = H, D). When this argument is extended to the amide acidity function, for all solutions of concentration ≥6% D_2SO_4, $D_A = H_A$. Good straight line plots were obtained ($r > 0.995$) from which the $D_A^{1/2}$ values could be determined. Ionization ratios of **1d** and **3a** calculated from shifts in the *N*-methyl absorptions yielded less satisfactory straight lines ($r \sim 0.97$).

Acknowledgment. Financial assistance of the University of Cape Town and the Council for Scientific and Industrial Research is gratefully acknowledged. V. Mizrahi thanks African Explosives and Chemical Industries for a post-graduate scholarship.

Registry No. **1a**, 24856-23-3; **1b**, 16102-45-7; **1c**, 82134-80-3; **1d**, 13294-10-5; **1e**, 82134-81-4; **1f**, 82134-82-5; **1g**, 86550-46-1; **3a**, 79-16-3; **4a**, 6326-73-4; **4b**, 82134-83-6; **7a**, 1113-68-4.

(51) E. Högfeldt and J. Bigeleisen, *J. Am. Chem. Soc.*, 82, 15 (1960).