Protonation of Phosphoric Amides. Molecular Orbital Calculations on Phosphinamide, $H_2P(O)NH_2$, and Its Protonated Forms

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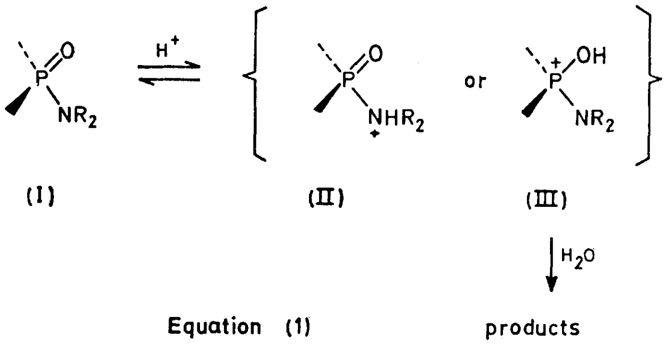
Ab initio SCF molecular orbital calculations were carried out on the amide $H_2P(O)NH_2$ (IV) and its *N*-protonated $H_2P(O)NH_3^+$ (V), and *O*-protonated $H_2P(OH)NH_2^+$ (VI) forms using optimized geometries. The total energies as well as bond lengths and angles were obtained for each individual structure. Conjugate acid (VI) was found more stable than (V). The preferred conformations of (VI) involve the *syn*- and *anti*-periplanar arrangement of the nitrogen lone pair and the POH group. In order to investigate the possibility of the intramolecular hydrogen bonding in (VI) a potential energy surface involving OH torsion and inversion at nitrogen was generated. The results obtained are related to the reactivity of phosphoric amides under acidic conditions.

THE reactivity of the P–N bond attracts considerable attention because of its involvement in the phosphorylating behaviour of *N*-phosphocreatine,[1] and the anticancer activity of the compounds of the cyclophosphamide group,[2] as well as a part of the general mechanistic [3] and stereochemical [4] studies of substitution at the phosphoryl centre. Under acidic conditions, the fundamental mechanistic problem involves the structure of the substrate conjugate acid, *i.e.* the *N*-protonated (II) or *O*-protonated (III) form of the phosphoramidonium ion:



Equation (1)

The principal difficulty in establishing the protonation behaviour of system (I) stems from its high instability in acidic solutions, so that direct investigation of the protonated species is, in most cases, not possible. This high reactivity, compared to the much greater stability of carboxylic amides, led Haake and his co-workers [3] to favour the *N*-protonated form (II) as the reactive intermediate, since *N*-protonation results in formation of the excellent leaving group (ammonia or amine), readily displaceable in the subsequent solvolysis step. It has been suggested [3] that the tetrahedral structure of (III) precludes the resonance delocalization of the positive charge responsible for the stability of the *O*-protonated carboxylic amide cations. The concept of the *N*-protonation has been also supported by studies of the effects of protonation upon the PNCH and POCH coupling constants in some phosphinic amides and esters.[5]

In our opinion, the remarkably ready acid-catalysed cleavage of (I) does not necessarily invoke *N*-protonation; the high reactivity can be a function of the electrophilicity of the phosphonium centre in (III).

On the basis of the Taft substituent constants,† the basicity of ammonia should be decreased upon phosphorylation [system (I; R = H)] at least as much as upon acylation (carboxylic amide). The dynamic n.m.r. investigations of some $P(S)NR_2$ and $P(O)NR_2$ systems [8] demonstrated significant PN torsional barriers in these compounds which was interpreted, at least partly, in terms of the p_π–d_π bonding. Such conjugative involvement of the nitrogen lone pair would, of course, result in a decrease of its availability as a proton acceptor in the proton-transfer reaction.

Even if the geometry of (III) precludes the simultaneous conjugate interaction with the nitrogen, the *O*-protonated ion can be still stabilized by the p_π–d_π back donation effect of oxygen (phosphonium–oxonium resonance structures).[9] With respect to Lewis acids, systems (I) behave as oxygen bases, giving rise to the complexes in which the phosphoryl oxygen plays the role of the electron-donor part of the molecule.[10]

In view of the above ambiguities, we decided to carry out *ab initio* SCF calculations ‡ on $H_2P(O)NH_2$ and its protonated forms using optimized geometries. The minimal (one contracted gaussian function to represent each atomic orbital) STO-3G basis set ‡ was used through this work. The molecule $H_2P(O)NH_2$ was chosen as a model for the phosphinamidate $R_2P(O)NH_2$ and phosphoramidate $(RO)_2P(O)NH_2$ systems, for which most of the experimental data regarding the acid-catalysed reactivity has been accumulated. The calculated total energies of individual structures were expected to provide information about the structural preference of the acid–base equilibrium (1). It was also hoped that the calculated bond lengths and bond angles would indicate bond orders at the phosphoryl centre and could be correlated with the reactivity of these systems.

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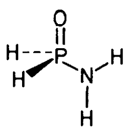
† σ^* Values for the $(RO)_2P(O)$ and $Ph_2P(O)$ groups are +2.2, and +1.7, respectively,[6] as compared to the value of +1.65 for the acetyl group.[7]

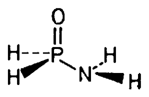
‡ All calculations were performed using a local modification of the program system Gaussian 70, W. J. Hehre, W. A. Lathan, R. Ditchfield, M. D. Newton, and J. A. Pople, Quantum Chemistry Program Exchange (Q.C.P.E.), 1973, **10**, 236. The STO-3G basis set was described in W. J. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, 1971, **51**, 2657.

RESULTS AND DISCUSSION

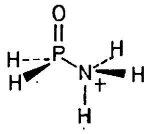
Structures and Energies.—Table 1 lists the bond-length data and total (and relative) energies for the optimized stable conformations of the unprotonated (IV), *N*-protonated (V), and *O*-protonated (VI) forms of the $H_2P(O)NH_2$ molecule.



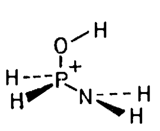
(IVa)



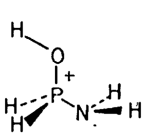
(IVb)



(V)



(VIa)



(VIb)

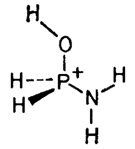
In one optimum conformation of the neutral molecule (IVa) the HNH plane bisects the HPH angle. This conformation is in agreement with crystal structure determination of some $X_2P^{III}NR_2$ and $X_2P^{V}NR_2$ systems.[11] The PO and PN bond lengths in the P^V derivatives depend upon the nature of the ligands X, which would modify the bond order of oxygen and nitrogen. For the related system, *NN*-dimethyldiphenylphosphinamidate, $Ph_2P(O)NMe_2$, the bond length values PO = 1.47 and PN = 1.67 Å have been reported.[12] While the PN bond lengths of 1.69 and 1.75 Å for (IVa) and (IVb) respectively are in reasonably good agreement, the calculated PO bond lengths of 1.59 and 1.62 Å are considerably larger than that from experiment. This may be due to the replacement of the phenyl groups at phosphorus by hydrogen, or more likely to the use of minimal basis set calculations.

The *N*-protonation [structure (V)] results in considerable lengthening of the P–N bond accompanied by a decrease in the PO distance. The former change is a consequence of the decrease in the bond order and the electrostatic repulsion between the ammonium group and the electron-withdrawing phosphoryl substituent. The same effect has been previously reported [13] for various $X-NH_2$ systems upon *N*-protonation. The shortening of the P–O bond in (V) illustrates the known effect [14] of the electronegative substituents upon the bond order of the phosphoryl group.

In the *O*-protonated structures (VIa) and (VIb) the P–O bond length has been increased and the P–N bond remained virtually unchanged relative to the neutral precursors (IVa) and (IVb). This suggests considerable phosphonium character in the P^VOH^+ system (low P–O bond order) together with the negligible participation of the nitrogen lone pair in the conjugative interaction with the adjacent quasiphosphonium centre. This conclusion is relevant to the reactivity of these systems. The high electron-deficiency at the phosphorus, together with the absence of the additional P–N bond strengthening due to the conjugative effect of nitrogen, would account for the high susceptibility of phosphorus to the nucleophilic attack of a solvent.

The calculated relative energies of the molecule (IV) and its *N*- and *O*-protonated forms are presented in Table 1. The computed total energies clearly indicate greater thermodynamic stability of the *O*-protonated forms (VI) over the *N*-protonated structure. Since the electronegativity of hydrogen and carbon are very similar, no significant change in the relative stability order should be expected for the phosphinamidate series $R_2P(O)NH_2$. In the phosphoramidate system $(RO)_2P(O)NH_2$, electronegative oxygen atoms should [15] additionally stabilize the *O*-protonated conjugate acid (relative to the *N*-protonated form). The predominant *O*-protonation was, in fact, suggested in the study of acid-catalysed hydrolysis of phosphoramidates.[16]

The barrier to rotation about the P–N bond for the *N*-protonated species (V), using rigid rotation of the NH_3^+ group, is very low (0.5 kcal mol^{-1}), corresponding to effectively free rotation. This is probably due, at least in part, to the very long calculated P–N bond reducing the interaction of the NH_3^+ group with the P=O and P–H bonds. The barrier to P–N rotation for structure (VIb) was computed to be somewhat higher (4.2 kcal mol^{-1}) from the total energy of the optimized structure (VII) (see Table 1). It is known however, that the P–N rotational barriers increase rapidly with the steric bulk of the substituents at nitrogen,[8] and restricted rotation has been observed in the conjugate acids of some *N*-alkylphosphinamidates.[17]



(VII)

Conformations of the O-*Protonated Form.*—The computed energy differences indicate that the preferred conformations of the conjugate acid of (IV) involve the *syn*- and *anti*-periplanar arrangement of the nitrogen lone pair and the POH grouping. In the *syn*-conformation (VIa) there appears to be a hydrogen bonding involving the OH proton and the nitrogen lone pair. In order to elucidate its importance two lines of action were taken. First, the molecular orbitals obtained for the optimized *syn*-geometry have been localized * and the centroids of charge $\langle r\rangle$ as well as the spatial extent $\langle r^2\rangle^{\frac{1}{2}}$ of the N lone pair determined. Secondly, the energetics of the hydrogen bonding has been investigated *via* the conformational preferences of the two *O*-protonated forms,

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* The molecular orbitals were localized by the Boys' method as given in R. C. Haddon and G. R. J. Williams, *Chem. Phys. Letters*, 1976, **42**, 453, using an extensively modified version of the BOYLOC program, D. Peeters, Quantum Chemistry Program Exchange, 1974, **10**, 330.

TABLE 1

Optimized structures and total energies of $H_2P(O)NH_2$ and its protonated forms

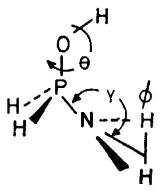
Structure	PO [a]	PN [a]	PH [a]	NH [a]	OH [a]	OPN [b]	OPH [b]	NPH [b]	PNH [b]	POH [b]	Energy (Hartrees)	Relative energy (kcal mol^{-1})
(IVa) [c]	1.59	1.69	1.40	1.01		108.0	117.0	110.0	122.0		−466.674 17	323.3
(IVb) [d]	1.62	1.75	1.39	1.02		114.0	117.0	105.0	111.0		−466.685 15	316.4
(V) [e]	1.55	1.94	1.39	1.04		116.0	114.0	100.0	113.0		−467.109 40	50.2
(VIa) [f]	1.67	1.68	1.39	1.02	0.99	110.0	109.0	111.0	118.0	106.0	−467.189 35	0.0
(VIb) [g]	1.67	1.70	1.39	1.03	0.99	110.0	110.0	109.0	113.0	108.0	−467.189 29	0.0
(VII) [h]	1.67	1.67	1.39	1.01	0.99	105.0	111.0	111.0	121.0 [i]	109.0	−467.182 62	4.2

[a] Bond lengths in Å. [b] Bond angles in °. [c] The OPNH dihedral angles were fixed at 0 and 180°, however the structure is stable with respect to the rotation about the P–N bond. [d] The OPNH dihedral angles were optimized to be ±59°. [e] One OPNH dihedral angle was fixed at 180°, and the remaining two were optimized to be ±60°. [f] The OPNH dihedral angles were optimized to be ±108°, and the HOPN angle to 0°. [g] The OPNH dihedral angles were optimized to be ±64°, and the HOPN angle to 180°. [h] Saddle point for P–N rotation. The OPNH dihedral angles were fixed at 0 and 180°. [i] Average of two angles: 116° (H *syn* to O) and 126° (H *anti* to O).

which required the generation of a potential energy surface involving OH torsion (θ) and inversion at nitrogen (γ).

The centroid of charge of the localized N lone-pair orbital is at a distance of 0.304 Å from the N nucleus, making an angle of 87° with the P–N bond. The root mean square distance of the electrons from the centroid of charge, called the 'size', is obtained [18] from the total second moment of the LMO electron distribution. The size of the lone pair is 0.745 Å but as noticed previously [18] there is an appreciable electron density within a circle of even twice the radius (1.49 Å). However, the distance of the H atom from the centroid of charge (2.34 Å) precludes the existence of any strong hydrogen bonding. This conclusion is supported by the lack of distortion of the O–H bond length or the POH angle from normal values of 0.99 Å and 105° respectively. The OPN angle of 110° is also very near the ideal tetrahedral angle.*

The rotational–inversional surface $E(\theta,\gamma)$, where θ is defined as the OH rotational angle (0° is *syn* to N) and γ is the angle the bisector of the HNH angle makes with the P–N bond (180° corresponds to a coplanar PNH_2 moiety), allows the interconversion of (VIa) and (VIb). The structure (VIa) corresponds to the point (0°, 210°), and (VIb) to the point (180°, 134°) on the (θ,γ) surface. Fifty-six points on the surface were computed for values of θ between 0 and 180°, and γ ranging between 105 and 240°. The remaining geometrical parameters were fixed at the average of the values for structures (VIa) and (VIb) with the following changes. To facilitate the use of the γ co-ordinate, the N–H bond length was replaced by the mean H–H distance (1.710 Å) and the mean distance from the centre of the H–H bisector to the N atom (0.567 Å). This also removed the difficulty of changes in the PNH angle with inversion at N, which are now automatically incorporated.



(VIII)

A surface equation of the form (2) was fitted to the

$$E(\theta,\gamma) = \sum_{i=1}^{16} c_i \cdot f_i(\theta) \cdot g_i(\gamma) \qquad (2)$$

data by stepwise least-squares regression,[19] and the individual terms are given in Table 2. The root mean square deviation of the fitted and calculated values was 0.012 kcal mol^{-1} (an average error of 0.010 kcal mol^{-1}), indicating an excellent fit.

The critical points, defined as having a zero gradient vector [equation (3)] were located on the fitted surface.

$$\left(\frac{\partial E}{\partial \theta},\frac{\partial E}{\partial \gamma}\right) = (0,0) \qquad (3)$$

The maxima and minima were determined directly using a variable metric optimization technique,[20] while the saddle points were found by minimizing the squared gradient length [21] *Sg* [equation (4)] which is zero only at

$$Sg = \left(\frac{\partial E}{\partial \theta}\right)^2 + \left(\frac{\partial E}{\partial \gamma}\right)^2 \qquad (4)$$

critical points. The co-ordinates and relative energies of all 11 critical points are given in Table 3.

Figure 1 shows the surface topology and the positions

TABLE 2

$E(\theta,\gamma)$ Surface equation for $PH_2(OH)NH_2$

Term	$f_i(\theta)$	$g_i(\gamma)$	c_i [a]
1	1.0	1.0	52.520 71
2	cos 3θ	1.0	0.309 61
3	cos 4θ	1.0	−0.029 29
4	1.0	sin γ	−1.688 14
5	cos θ	sin γ	1.987 44
6	cos 2θ	sin γ	0.403 34
7	cos 4θ	sin γ	0.020 57
8	1.0	sin 2γ	−0.543 51
9	cos 3θ	sin 2γ	−0.052 19
10	cos θ	sin 4γ	−0.043 88
11	1.0	cos γ	81.076 94
12	cos θ	cos γ	0.869 19
13	cos 2θ	cos γ	0.184 66
14	1.0	cos 2γ	29.010 30
15	cos θ	cos 2γ	−0.113 20
16	1.0	cos 3γ	2.423 39

[a] These coefficients calculate the energy in kcal mol^{-1} relative to the optimized energy for (VIa).

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* The atomic co-ordinates and the centroids of charge and sizes of the localized orbitals for (VIa) are available as a Supplementary Publication [SUP No. 22518 (3 pp)]; for details of the Supplementary Publications scheme see Notice to Authors No. 7, *J.C.S. Perkin II*, 1978, Index issue.

TABLE 3

Critical points of the $H_2P(OH)NH_2$ rotation–inversion surface

Symbol	θ (°)	γ (°)	Order [a]	E (θ,γ) [b]
m_1	0.0	217.0	0	0.01
m_2	74.0	141.0	0	0.90
m_3	180.0	137.0	0	0.21
m_4	180.0	213.0	0	3.34
s_1	0.0	147.0	1	2.02
s_2	40.0	175.0	1	2.16
s_3	114.0	138.0	1	1.12
s_4	136.0	213.0	1	3.69
s_5	180.0	190.0	1	3.70
M_1	0.0	169.0	2	2.33
M_2	132.0	189.0	2	4.14

[a] The order of the critical point is the number of negative eigenvalues of the matrix of second derivatives of the energy. Minima have order 0, saddle points have order 1, and maxima have order 2. [b] Energy calculated from equation (2), relative to the optimized structure (VIa), in kcal mol^{-1}.

of the critical points, while Figure 2 is a pseudo-three-dimensional representation of the surface. Note that there are four minima, of which two have been optimized previously: m_1 which corresponds to the *syn*-structure (VIa), and m_3 which is the *anti*-conformer (VIb). The small deviations of the locations of these minima from those optimized directly are due to the use of an average geometry for the surface. The two new minima occur at the gauche conformation (m_2, θ = 74°) and an *anti*-structure with the N–H bonds nearly eclipsing the P–H bonds (m_4).

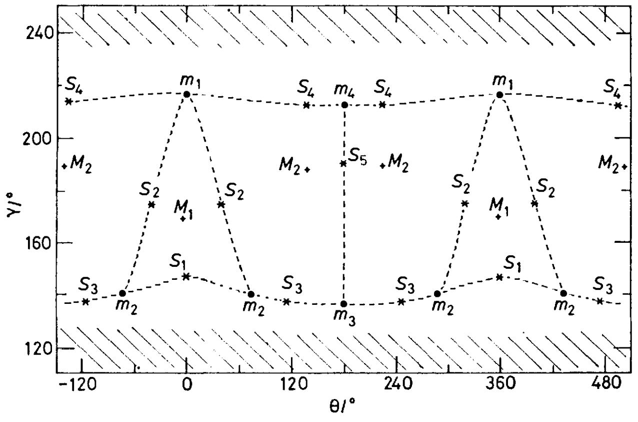


FIGURE 1 Topological map of the rotation (θ)–inversion (γ) energy surface. Minima are shown as m_1—m_4, where m_1 and m_3 correspond to the structures (VIa) and (VIb) respectively. The saddle points s_1—s_5, are the highest energy points along the dotted lines connecting the minima. The low maxima are M_1 and M_2 while the shaded areas represent rapidly increasing energy as the inversion angle becomes too small or large (the planar PNH_2 moiety has γ = 180°)

To summarize our findings we need to note a number of things. First of all, the relevant domain of the energy surface is within 4 kcal mol^{-1} of the lowest minimum indicating great stereochemical flexibility. Secondly, the *syn*- and *anti*-structures (VIa) and VIb) are nearly identical in energy. This may be rationalized, at least qualitatively, by enumerating the various possible weak interactions. As illustrated in Figure 3, structure (VIa) has a 1 lone-pair(N)–1 proton (OH) plus a 2 lone-pair(O)–2 proton(PH_2) stabilizing interaction as well as a destabilizing OH–PN bond eclipsing and near eclipsing of the PH and NH bonds. In contrast, structure (VIb) has no destablizing bond eclipsing but has a 2 proton(NH_2)–2 long-pair(O) as well as a 2 proton-$(PH)_2$–1 lone-pair(N) stabilizing interaction.

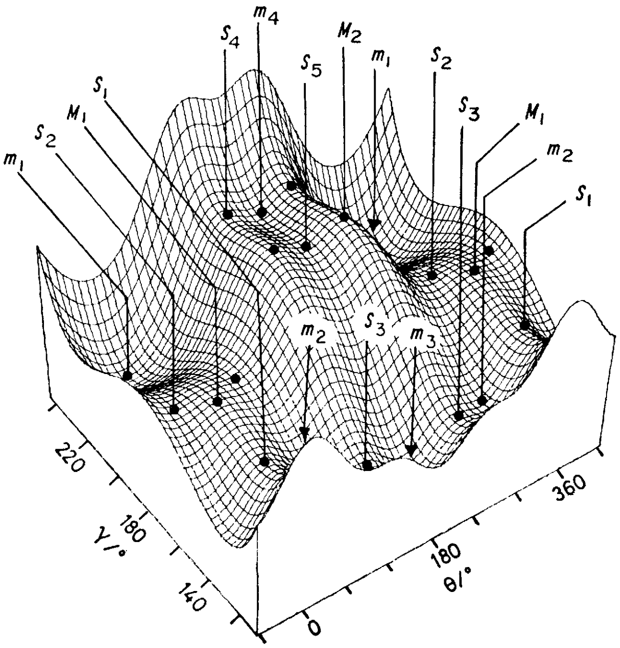


FIGURE 2 Pseudo-three-dimensional plot of the rotation–inversion energy surface. The critical points are identified as in Figure 1. The surface has reflective symmetry in the lines θ = 0°, θ = 180°, and θ = 360°

On the basis of geometrical considerations (see distances in Figure 3), one would estimate the destabilizing factors in (VIa) to be very small, and the stabilizing hydrogen-bonding interactions to be slightly stronger than in (VIb). For this reason, it is not surprising that structures (VIa) and (VIb) have nearly identical stabilities.

In order to generalize to real phosphoric amides where both the P and N are fully substituted, hydrogen bonding could only occur in structures analogous to (VIa). Consequently *syn*-conformers are expected to be some-

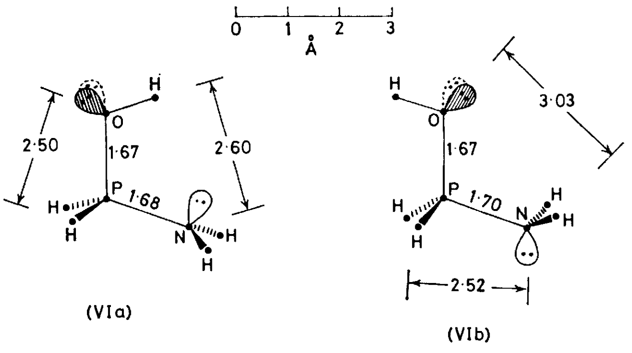
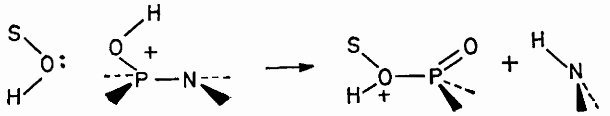


FIGURE 3 Stabilizing and destabilizing interactions in *syn*- and *anti*-*O*-protonated phosphoric amide as the consequence of geometrical parameters


(5)

(VIa)

what lower in energy than *anti*-structures. The position and heights of other critical points would also be modified, sometimes very drastically, depending on the size of the substituent. For example, upon the introduction of bulky groups at N, the minima m_2 and m_4 and the associated saddle points s_1, s_3, s_4, and s_5 would probably disappear as the maxima at M_1 and M_2 simply became intrusions of the high-energy regions (on either side of the inversion co-ordinate γ) into the valley, leaving only the minima m_1 (VIa) and m_3 (VIb), and a connecting saddle point near s_2.

The *syn*-*O*-protonated conformation (VIa) is of particular interest. The nitrogen lone pair, coplanar with the POH group, is properly oriented to serve a function of the acceptor in the oxygen→nitrogen proton transfer in the solvolysis step (equation 5). Such a proton transfer,* synchronous with the nucleophile–phosphorus bond formation and resulting in the direct formation of the energetically favourable phosphoryl function, should contribute to the lowering of the total activation energy of the reaction. In the *O*-protonated carboxylic amide the nitrogen lone pair (strongly involved in conjugative interaction with the positive centre) is orthogonal to the HOCN plane and the rate-determining step of solvolysis consists in the formation of the tetrahedral intermediate,[22] followed by the internal proton transfer to the nitrogen. Equation (5) remains also in agreement with the observed stereochemistry of the acid-catalysed solvolysis of phosphoric amides, proceeding in most cases with an exclusive (or predominant) inversion of configuration at phosphorus.[23]

[8/1071 *Received*, 8*th June*, 1978]

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* It is possible that this transfer requires the involvement of an additional solvent molecule.

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