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ORIGINAL PAPER

The decomposition of α-aminophosphine oxides to phosphonic acid derivatives (P^{III})

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Abstract Aminophosphine oxides and aminophosphonates are, in general, very stable compounds. However, following phosphorus–carbon bond cleavage in aqueous acidic media these compounds sometimes decompose to phosphonic acids derivatives (P^{III}). Despite some controversy in the literature, careful analysis supported by theoretical studies leads to the conclusion that decomposition to P^{III} derivatives proceeds via an elimination reaction.

Keywords P–C bond cleavage · Aminophosphine oxides · Reaction mechanism

Introduction

α-Amino organophosphine oxides, phosphinates, and phosphonates (Scheme 1) are relatively stable due to the stability of the carbon–phosphorus (P–C) bond. Under some circumstances, however, they readily decompose [1–4, A. Kiersnowska, M. Doskocz, R. Gancarz, manuscript in preparation]. Extensive mechanistic studies in solution as well as in enzyme have been performed for the P–C bond breaking reactions [5, 7]. Theoretical studies have also been attempted [4, 5, 7]. In general, in pentavalent tetracoordinated organophosphorus compounds, there are three possible mechanisms of P–C bond breaking (presented schematically in Scheme 2 [1]). The first example represents the homolytic breaking of the bond. The second reaction corresponds to heterolytic bond cleavage with formation of phosphoric acid derivatives (P^{V}). In the case of aminophosphonates, two alternative mechanisms: dissociative S_N1@P-and associative S_N2@P have been proposed [A. Kiersnowska, M. Doskocz, R. Gancarz, manuscript in preparation; 8]. The third possibility leads to P^{III} products. Decomposition of α-aminophosphonates according to the third mechanism has long been observed (Scheme 3a) [1]. Recently, the proposed mechanism has been supported by theoretical predictions (Scheme 3b) [4]. The most favourable mechanism consists of protonation of the amino group, proton transfer through the hydrogen bond [NH···O(P)], and P–C bond cleavage leading to the protonated imine and derivatives of H-phosphonate (Mechanism I). We believe that the above scheme is general, and that similar mechanisms should be expected for other phosphoryl compounds including phosphinates and phosphine oxides.

In their study on the decomposition of pirydyl aminophosphino oxides to P^{III} derivatives, Goldeman et al. [2] observed retention of the configuration at phosphorus in the case of substrates with a stereogenic phosphorus atom. These authors proposed a new alternative mechanism for the elimination (Mechanism II), namely electrophilic attack of the proton on the phosphorus atom (S_E2@P). This mechanism is shown in Scheme 4 [2]. The present work is an attempt to verify the alternative mechanisms presented above, based on high level theoretical models.

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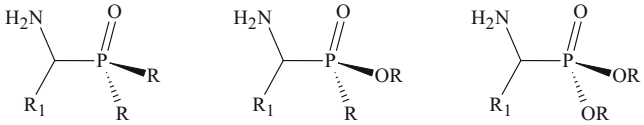


Scheme 1 Structures of α-aminophosphine oxides, α-aminophosphinates, and α-aminophosphonate

Computations

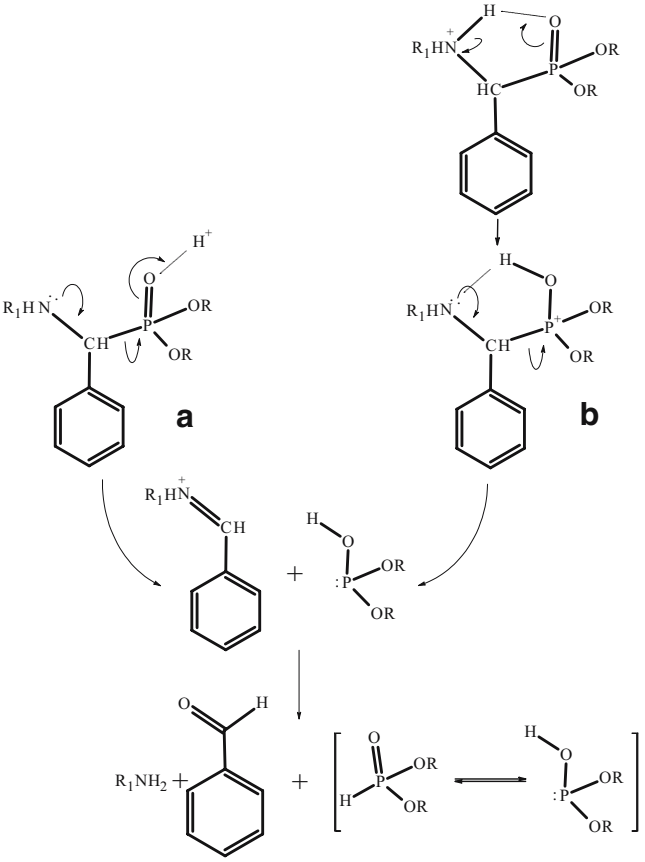
All structures were optimised at the density functional theory (DFT) level utilizing Becke's three-parameter hybrid functional B3LYP [9] and the standard 6-31G(d) basis set. No symmetry constraints were imposed during the optimisation process and the structures were verified by frequency calculations. Atomic charges were calculated by applying the following methods: Mulliken, natural bond orbital (NBO), Chelp, and ChelpG [10]. For all structures, the solvation energy (ΔG_{solv}) was calculated according to Barone and Cossi's implementation of the polarisable conductor solvent model (CPCM) [11]. Calculations were performed using the Gaussian 03 program [12], and results were visualised by applying the GaussView 3.09 package [13].

Results and discussion

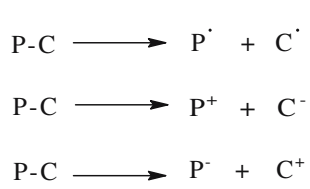
In Mechanism I for aminophosphonates, the key step constitutes the protonation of the phoshoryl oxygen and decomposition of the resulting intermediate (Scheme 3). Mechanism II assumes an attack by a proton or some other electrophile (e.g. H_3O^+) on the positively charged phosphorus atom (Scheme 4) [2]. In order to verify the proposed mechanisms, we performed an analysis of the protonation equilibrium for aminophosphino oxides and the charge distribution in all possible individuals that decompose to P^{III} derivatives.

Protonation sites

In acidic solution, α-aminopirydylphosphine oxides can exist as neutral molecules, or in single-, double-, or triple-protonated form, all being in dynamic equilibrium (Scheme 5). The energies of protonation for each site, calculated according to the thermodynamic cycle defined in Scheme 6, are given in Table 1. The main monoprotonated structure comprises the isomer protonated on pirydyl nitrogen (structure B). The G structure is energetically preferred between double protonated moieties. The pKa values for the dissociation of the single proton in the water solvent are 0.2 (H), 1.0 (F), 1.6 (E), 2.7 (D), 2.9 (G), 4.7 (C), and 5.4 (B). The corresponding values for methanol are 0.04 (H), 0.4 (F), 1.4 (E), 2.6 (G), 2.7 (D), 4.7 (C), 5.5 (B). The above data correlate reasonably with measured results for the acid α-*N*-butyloamino(4-pirydylo) methylophosphonate: pK^{NH3}=3.79, pK^{PyH}=9.18 [14]. The double-protonated structures on the amine nitrogen and phosphoryl oxygen, and triple-protonated structures are the strongest acids. The weakest acids are aminophosphino oxides protonated on both nitrogen atoms. The differences between acidity in water and methanol are negligible.



Scheme 3 Protonation–elimination reaction of α-aminophosphonates resulting in phosphonic acid derivative (P^{III}) product formation, as proposed by Gancarz [1], path (**a**) and Doskocz [4], path (**b**)

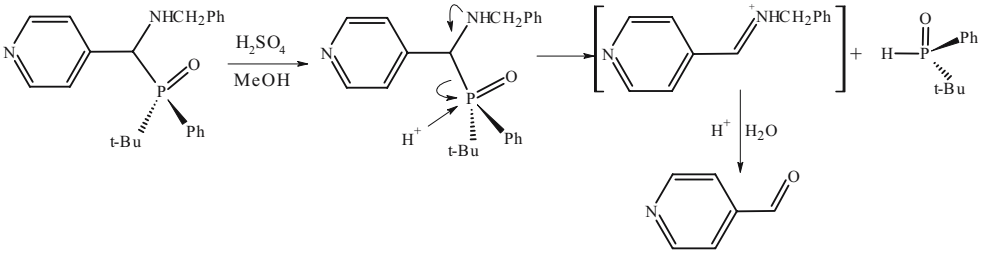


Scheme 2 Possible mechanisms of P–C bond cleavage

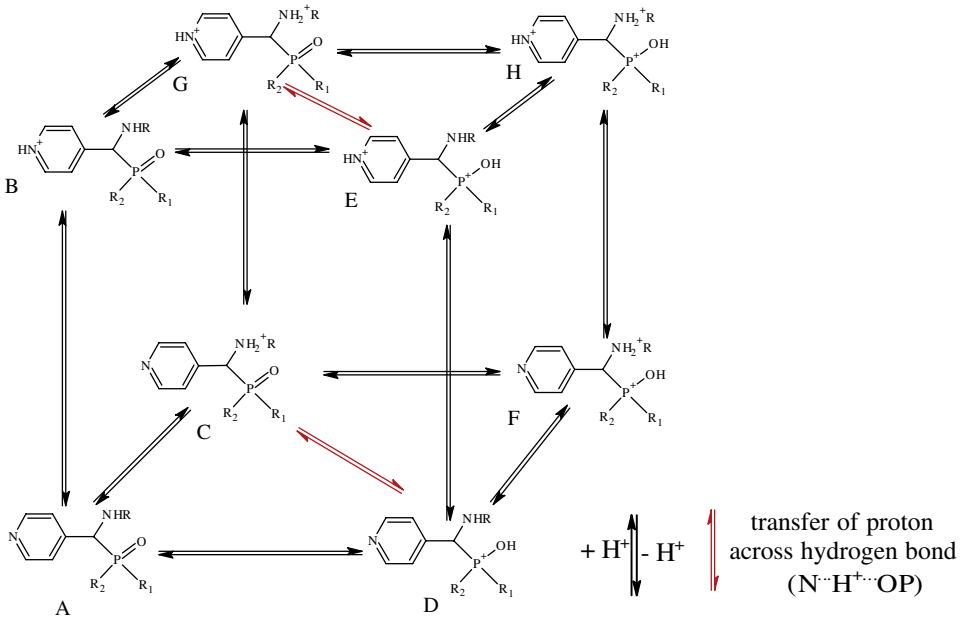
Charge distribution in molecule

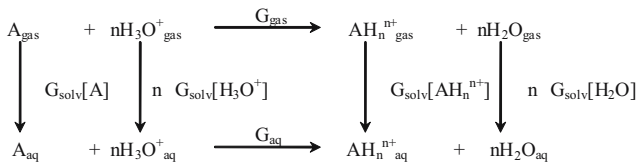
In the phosphoryl group (P=O), oxygen is negatively charged while the phosphorus atom carries a positive charge (Table 2). The charge separation in the case of phosphoryl compounds is higher compared to that of carbonyl compounds, e.g. the atomic charge on the carbonyl C amounts to 0.453, 0.556, and 0.261 electrons

Scheme 4 The mechanism of decomposition of pyridylaminomethanephosphine oxides to P^{III} derivatives by electrophilic attack by the proton on the tetracoordinated phosphorus atom [2]



Scheme 5 Protonation equilibria in aminophosphinooxides





Scheme 6 Thermodynamic scheme defining the free enthalpy of multiple (n=1,2,3) protonation of molecule A

Table 1 Energy of multiple protonation of molecule A calculated according to Scheme 6

Structure	ΔE	Δ(E+ZPE)	ΔG	ΔG_{aq}	ΔG_{MeOH}
D	−63.8	−63.8	−62.8	−14.6	−14.7
B	−67.8	−67.8	−66.9	−29.7	−29.8
C	−72.6	−72.6	−70.7	−25.8	−25.5
E	−64.4	−64.4	−62.4	−38.1	−37.4
G	−69.8	−69.8	−66.5	−45.3	−44.3
F	−47.0	−46.9	−46.1	−31.1	−27.9
H	16.4	16.4	17.9		

ΔE Electronic energy, *Δ(E+ZPE)* electronic energy corrected for the zero point energy, *ΔG* free enthalpy at 293 K, ΔG_{aq} free enthalpy including solvent effects of water, ΔG_{MeOH} methanol
Values in kcal mol^{-1}

Table 2 Charge distribution for selected atoms in different protonated forms of aminophosphine oxides

Structure	Method	Atom				
		P	O	N-py	PC-N-H	P-C-H
A	Mulliken	0.914[a]	−0.598	−0.409	−0.568	−0.254
	NBO	2.026	−1.092	−0.454	−0.708	−0.406
	Chelp	0.956	−0.697	−0.566	−0.660	0.179
	ChelpG	0.494	−0.557	−0.606	−0.532	−0.038
C	Mulliken	0.892	−0.604	−0.379	−0.654	−0.290
	NBO	2.007	−1.080	−0.421	−0.632	−0.401
	Chelp	1.098	−0.645	−0.521	0.113	−0.364
	ChelpG	0.637	−0.551	−0.555	−0.082	−0.098
D	Mulliken	0.930	−0.657	−0.382	−0.632	−0.247
	NBO	1.992	−0.999	−0.373	−0.733	−0.423
	Chelp	0.902	−0.433	−0.551	−0.427	0.135
	ChelpG	0.582	−0.443	−0.581	−0.488	−0.020
B	Mulliken	0.910	−0.593	−0.544	−0.579	−0.256
	NBO	2.022	−1.081	−0.483	−0.705	−0.405
	Chelp	0.916	−0.635	−0.263	−0.581	0.102
	ChelpG	0.587	−0.557	−0.304	−0.476	−0.315
F	Mulliken	0.910	−0.666	−0.355	−0.648	−0.254
	NBO	1.983	−1.006	−0.393	−0.633	−0.388
	Chelp	0.895	−0.558	−0.502	0.123	−0.003
	ChelpG	0.499	−0.471	−0.522	−0.084	−0.086
E	Mulliken	0.927	−0.642	−0.536	−0.634	−0.250
	NBO	1.996	−0.987	−0.467	−0.738	−0.387
	Chelp	0.891	−0.386	−0.132	−0.480	0.038
	ChelpG	0.591	−0.422	−0.272	−0.563	−0.075
G	Mulliken	0.929	−0.606	−0.536	−0.647	−0.293
	NBO	2.013	−1.080	−0.467	−0.628	−0.405
	Chelp	0.940	−0.649	−0.098	0.148	−0.219
	ChelpG	0.727	−0.581	−0.255	−0.178	−0.312
H	Mulliken	0.913	−0.658	−0.528	−0.669	−0.269
	NBO	1.985	−1.006	−0.456	−0.663	−0.399
	Chelp	1.075	−0.606	−0.126	0.093	0.039
	ChelpG	0.596	−0.533	−0.259	0.109	−0.268

NBO Natural bond orbital
[a] Charges in electrons

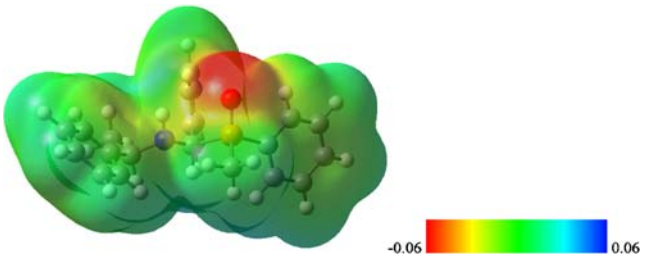


Fig. 1 Molecular electrostatic potential (MEP) surfaces for structure A. The colour code for electrostatic potential surfaces uses *blue* and *red* to indicate the most negative and positive electrostatic potentials, respectively. Surface potential is displayed at an electron density of $0.002e/a_o^3$, which is the volume surrounding more than 95% of the total electron density and is near the van der Waals surface [11]. Potential in kcal mol^{-1}

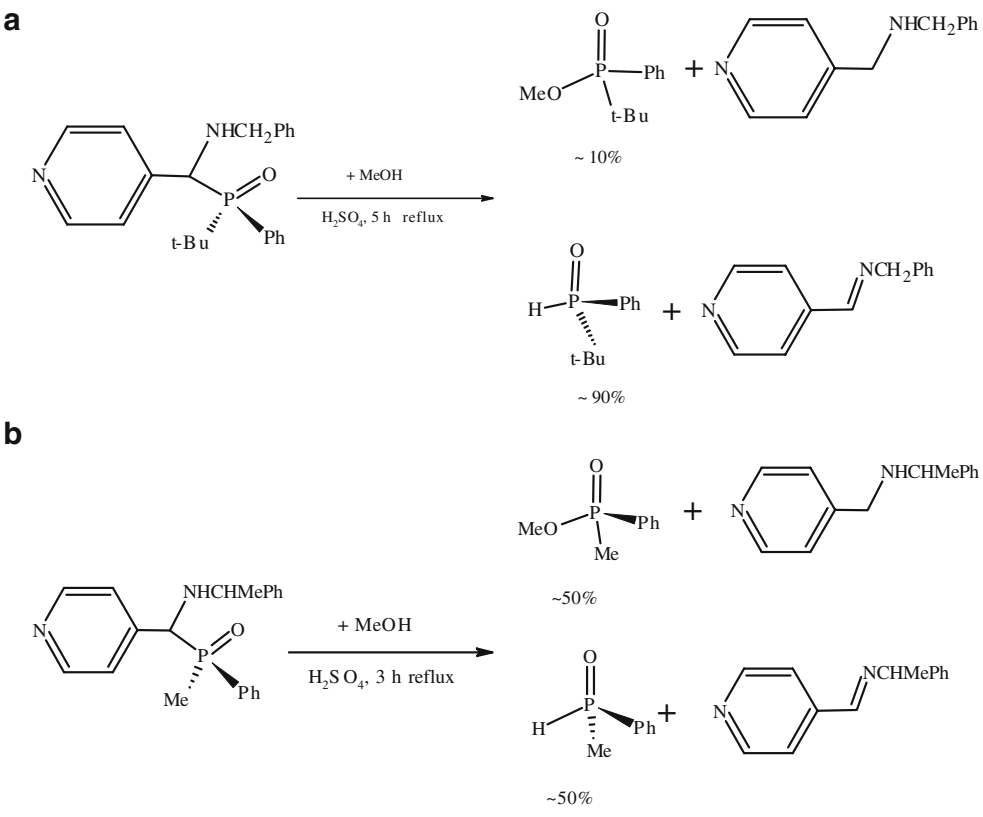
in acetone, acetic acid, and acetaldehyde, respectively. Electrophilic attack on the carbonyl carbon is of low probability, and thus seems even less probable in the case of phosphorus. The molecule possesses two amine nitrogens and, as was shown above, at least one of them is protonated. In the case of such a complex, the attack by the proton, or rather the hydronium ion, is retarded by both these factors—the positively charged molecule as a whole, and the shielded positively charged phosphorus atom. In this case, the proton would rather interact with the much more basic and readily available phosphoryl oxygen atom [15, 16].

The charge distribution for protonated moieties indicates that phosphorus is highly positively charged in all cases. Consequently, an electrophilic attack on the tetracoordinated phosphorus is highly improbable. The same conclusion can be drawn from inspection of the molecular electrostatic potential (MEP) [17] maps. An example of an MEP, for the non-protonated structure, is given in Fig. 1.

Stereochemistry

Mechanism II, which involves a proton attack directly on the P atom, was proposed because of the observed retention of configuration at phosphorus in the case of the decomposition of aminophosphino oxide, with a stereogenic phosphorus atom [2]. However, the expected stereochemistry on phosphorus, after elimination via Mechanism I should also be retention of configuration, since elimination to P^{III} products leads to phosphonate with a trivalent tricoordinated phosphorus atom. Its transformation to the tetracoordinated form proceeds with retention of configuration due to the high barrier of inversion. In this case, the barrier is expected to be in the range of 30 kcal mol^{-1} [8]. In the case of a small barrier, Mechanism II should also lead to racemisation, even if the decomposition is stereospecific. Mechanism II is also of low probability due to steric reasons. Attack by the proton from the most sterically hindered site, namely the site of the C–P bond, is proposed. Based on our recent calculations, the most probable path of decomposition is one similar to that proposed for the decomposition of

Scheme 7 The influence of substituents of phosphorus on yields of products [2]



aminophosphonates [4], where the first step consists of protonation of the aminophosphino oxide, followed by transfer of the proton from the protonated amine group to the phosphoryl oxygen. This makes the phosphoryl fragment a good leaving group. After P–C bond cleavage, the trivalent tricoordinated neutral phosphonate fragment is detached and further transformed to pentavalent tetracoordinated H-phosphonate with retention of configuration.

Bulky group effect

Boduszek et al. [2] reported that replacement of the *t*-butyl ligand attached to the phosphorus in aminophosphino oxide by a methyl group decreases the amount of the compound being decomposed to P^{III} derivatives from 90% to 50% (Scheme 7). This finding fits with Mechanism I for the decomposition of aminophosphonates to P^{III} derivatives [1]. The *t*-butyl group prevents protonation of the amine nitrogen and thus facilitates decomposition to P^{III}.

Conclusions

Our calculations indicate that, in the neutral substrate, the phosphorus atom is positively charged, whereas the phosphoryl oxygen is characterised by negative charge. Such an electron density distribution makes the phosphoryl oxygen vulnerable to protonation in acidic medium and, as a consequence, makes the whole phosphoryl fragment a relatively good leaving group. The elimination starts from the form that is protonated on the phosphoryl oxygen. For electronic or steric reasons, the equilibrium is shifted towards this form in aminophosphine oxides. Due to P–C bond cleavage, trivalent tricoordinated phosphorus acid (III) derivatives [4] are formed, with retention of configuration on phosphorus. Thus, careful consideration of the proposed mechanisms, namely: (1) elimination via the $S_N1@P$ process, and (2) assuming electrophilic attack of a proton on the positively charged phosphorus atom, indicates that for the more basic or sterically crowded aminophosphonates the first mechanism is much more appropriate.

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