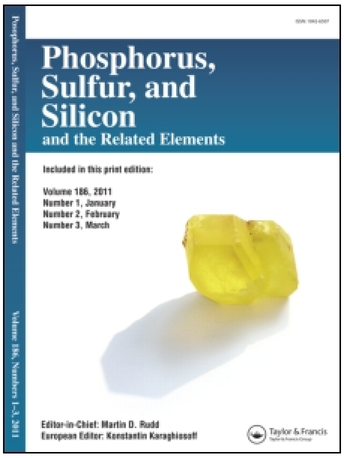

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SHORT COMMUNICATION
Gas Phase Basicity of Hexamethylphosphotriamide (HMPT) and Phosphinoxide Derivatives

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Gas phase basicities are determined by Ion Cyclotron Resonance (ICR) mass spectrometry for the six organophosphorus compounds $OP(NMe_2)_{3-x}Me_x$ $x = 0$ to 3, $OP(nPr)_3$ and $OP(OEt)_3$. All values are in the range 209–219.3 kcal · mol^{-1}, and their variation with structure is examined. The site of protonation (O or N?) is briefly discussed, and arguments are presented which favour O-protonation.

In order to ascertain a better knowledge of the biological behavior of organic phosphorus (V) compounds, the acid hydrolysis of the P—N bond has attracted considerable interest in recent years. However, the controversy concerning the site of protonation, viz. O- vs N-protonation, is still remaining.[1] As reported in two recent publications, some insight has been given onto the basic behavior of hexamethylphosphotriamide (HMPT, **4**), which behaves as a strong Lewis base[2] but also as a very weak Brønsted base.[3] We want to present data on the gas phase basicity of a series of phosphine oxide derivatives B^1, compounds **1–6**, obtained from the determination of the equilibrium constant K_{eq} for the proton transfer reaction (1), where B^2 stands for reference compounds of known basicity.[4]

$$B^1H^+ + B^2 \rightleftarrows B^2H^+ + B^1 \qquad (1)$$

The experiments were conducted in an ion cyclotron resonance (ICR) spectrometer which was operated in the same conditions as described previously.[5] Reaction (1) was observed for reaction times up to 1 s. Determination of the concentrations of the neutrals B^1 and B^2 and of the ions B^1H^+ and B^2H^+ at equilibrium yields the equilibrium constant K_{eq} for reaction (1).[4] Neutral concentrations were determined from the pressure measurements of an ionization gauge directly connected to the vacuum can of the instrument. In order to translate the gauge readings into concentrations, we estimated the ionization cross sections σ as follows: in a first step, the polarizabilities α of the neutrals were calculated (in Å^3) from the molar refraction $R = (n^2 - 1)M/(n^2 + 2)d = \frac{4}{3}\pi N_A \alpha$, where n is the refractive index, M the molar mass and d the density. Taking into account the proportionality[6] between σ and $(\alpha + 1)$, the ratio of ionization cross sections was thus approximated as the

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TABLE I

Physical constants for the phosphine oxides B^1 = OPXYZ and for the reference bases B^2

B^1	X	Y	Z	M	d_{25}	n_D^{25}	α_{calc}	Ref.
1	Me	Me	Me	92.08	—	—	9.9	a
2	Me	Me	NMe_2	121.12	1.0109	1.4556	12.90	b
3	Me	NMe_2	NMe_2	150.17	1.0159	1.4567	15.95	c
4	NMe_2	NMe_2	NMe_2	179.20	1.0196	1.4563	18.95	d
5	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	176.24	—	—	21	e
6	OEt	OEt	OEt	182.16	1.064	1.4035	16.58	d

B^2	M	d_{20}	n_D^{20}	α_{calc}	Ref.
$EtNH_2$	45.09	0.6829	1.3663	5.87	f
$n\text{-}PrNH_2$	59.11	0.7173	1.3870	7.69	f
$t\text{-}BuNH_2$	73.14	0.6958	1.3784	9.61	f
Me_3N	59.11	0.6709	1.3631	7.77	f, g
Et_2NH	73.14	0.7056	1.3864	9.66	f
$n\text{-}Pr_2NH$	101.19	0.7400	1.4050	13.28	f

[a] Value for α estimated from the values for compounds **2–4**.
[b] Results not yet published.
[c] Taken from Ref. 3.
[d] Taken from Ref. 14.
[e] Estimated value for α, physical properties not available.
[f] Handbook of Chemistry and Physics, CRC Press Inc. (1978).
[g] Values at 0°C.

TABLE II

Free energy changes in the equilibrium proton transfer reaction: $B^1H^+ + B^2 \rightleftarrows B^1 + B^2H^+$

B^1	B^2	$GB(B^2)^a$	ΔG_r	$GB(B^1)^b$
1	$EtNH_2$	208.7	0.5	209.4
	$n\text{-}PrNH_2$	210.1	−0.6	
2	$t\text{-}BuNH_2$	212.9	0.7	213.6
3	Me_3N	216.5	0.2	216.7
4	$n\text{-}Pr_2NH$	219.2	0.1	219.3
5	Me_3N	216.5	0.05	216.7
	Et_2NH	216.9	−0.1	
6	$EtNH_2$	208.7	0.05	209.2
	$n\text{-}PrNH_2$	210.1	−0.5	

[a] kcal · mol^{-1}, values taken from Ref. 4.
[b] ± 0.2 kcal · mol^{-1}, deviation on the experimental determination of ΔG_r.

ratio for (α + 1). The resulting values are summarized in Table I. Table II reports the values for the free energy changes $\Delta G_r = -RT \cdot \ln K_{eq}$ from which the values for the gas phase basicity $GB(B^1) = GB(B^2) + \Delta G_r$ are obtained.

In order to discuss the problem of O- vs N-protonation in HMPT **4**, it is useful to consider the effect of sequentially substituting methyl groups in **1** by dimethylamino groups as realized along the series of compounds **1–4**. Compound **1** undoubtedly protonates on the oxygen atom to form a phosphonium ion which can be resonance stabilized, $(CH_3)_3P^+\text{—}OH \leftrightarrow (CH_3)_3P{=}\overset{+}{O}H$. Replacing methyl by dimethylamino groups results in an increase in basicity of 4.2, 3.1 and 2.6 kcal · mol^{-1} for the first, second and third substitution step, respectively. While there exists no identical substitution pattern in the literature to be compared with our data, analogous situations show a similar trend, i.e. an increase in basicity is observed with increasing substitution. These trends reflect the significant role played by polarization forces between the charged center and the substituents.[4] It has also been shown that dipolar forces play a minor role on gas phase properties[7] (however they seem to predominate in long-range intramolecular interactions[5]). It might also be anticipated that the possibility for resonance structures such as $>N^+{=}\underset{/\backslash}{P}{-}OH \leftrightarrow >N{-}\underset{/\backslash}{P^+}{-}OH \leftrightarrow >N{-}\underset{/\backslash}{P}{=}\overset{+}{O}H$ contribute to the stability of the protonated species $2H^+$, $3H^+$ and $4H^+$. However, the basicity data obtained for compound **5** which does not allow for such resonance structures in its protonated form seems to dismiss the contribution of resonance stabilization. In the case of **5** only the stabilizing contribution by polarization of the alkyl groups has to be considered. These effects can be evaluated by considering the basicity values[4] for $MeNH_2$ (GB = 205.7 kcal · mol^{-1}), n-$PrNH_2$ (210.1), Me_2NH (212.3), n-Pr_2NH (219.2), Me_3N (216.5) and n-Pr_3N (225.6 kcal · mol^{-1}). It can be seen from these data that replacing Me by n-Pr is not an additive effect, but the concomittant increase in basicity drops from 4.4 kcal · mol^{-1} down to about 3.5 and 3.0 kcal · mol^{-1} when replacing one, respectively two and three Me by n-Pr groups. For the phosphine oxides, an average value of 2.4 kcal · mol^{-1} is found for this effect when going from **1** to **5**.

An estimate of the qualitative ordering of basicities for compounds **4** and **6**[8] can be attempted from the molecular properties of the model systems represented by $H_2N{-}\underset{/\backslash}{P^+}{-}OH$ and $HO{-}\underset{/\backslash}{P^+}{-}OH$ which correspond to the oxygen protonated forms of substituted phosphine oxides. From the bond distances P—O = 1.58 Å[9] and P—N = 1.68 Å[10] and from the group polarizabilities for OH (α = 1.01 Å^3) and NH_2 (α = 1.71 Å^3, see Ref. 11), it is possible to deduce the values for the charge-induced dipole potential energy, $V_{\text{ch-id}} = -\alpha q^2/2r^4$, where q is the unit charge and r the distance between the charge and the center of the dipole (here identified with the atom, in order to simplify the calculations). Using these parameters, absolute values of 27 kcal · mol^{-1} and 35.5 kcal · mol^{-1} for the $HO{-}P^+$, respectively $H_2N{-}P^+$, systems are found for the stabilization energy $V_{\text{ch-id}}$, in qualitative agreement with the ordering of basicities, GB (**6**) < GB (**4**). Similar arguments can be used to understand the order GB (**6**) < GB (**1**).

Our data thus seem to indicate that phosphine oxide derivatives, including HMPT **4**, exhibit preferential protonation on the oxygen atom. However the effect of substitution by additional alkyl groups in the presently studied compounds cannot be taken fully into account by the oversimplified arguments presented above. Further experiments on the basicity of phosphine oxide derivatives are planned together with parallel calculations on the stability of these protonated systems by molecular orbital *ab initio* methods.

COMPOUNDS

1 and **5**, supplied by Ventron GmbH, were used as received. The phosphinic amide **2** was obtained by reacting dimethylamine with $OPMe_2Cl$[12] in benzenic solutions; other experimental conditions and the techniques for purification have been already published.[13] The synthesis of **3** is described in Ref. 3 and purification of **4** and **6** in Ref. 14.

Gas phase chromatography (Carbowax 20M) indicates a purity greater than 99%, except for **2** which contains *ca.* 1.7% of an impurity with a close retention time, probably resulting from an interchange reaction during preparation and purification. Although the mechanism of *in vivo* carcinogenesis by HMPT **4** is not clearly known,[15] it can be induced by inhalation as proven in the case of rats;[16] moreover, other phosphoramides are also potential carcinogens.[17] However, no risk may exist at the microdose level used in the present experiments.

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