Isolation, Structure and MO Calculational Investigations of a Highly Stable, Hydrogen-bonded Primary Amine–Phosphine Oxide Adduct, 2-Aminobenzothiazole–HMPA, $C_6H_4SC(=N)NH_2 \cdot O=P(NMe_2)_3$; a Possible Model to Explain the Carcinogenicity of HMPA (HMPA = Hexamethylphosphoramide)

David R. Armstrong,[a] Susan Bennett,[b] Matthew G. Davidson,[b] Ronald Snaith,*[b] Dietmar Stalke[b] and Dominic S. Wright[b]

[a] *Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, UK*
[b] *University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK*

Colourless needles of the 1 : 1 primary amine–phosphine oxide adduct $C_6H_4SC(=N)NH_2 \cdot O=P(NMe_2)_3$ are obtained in high yield simply by chilling a toluene solution of the two components; the solid-state structure of the highly stable adduct (which can be prepared in water, and which sublimes easily) consists essentially of dimers held by (amine) N–H···O and (amine)N–H···(heterocyclic) N hydrogen bonds.

We report the isolation and structure of a 1 : 1 adduct between 2-aminobenzothiazole $C_6H_4SC(=N)NH_2$ **1a** and hexamethylphosphoramide [HMPA, $O=P(NMe_2)_3$]. The solid adduct consists essentially of dimers, (**1a**·HMPA)$_2$, with N–H···O–P and N–H···(heterocyclic) N hydrogen bonds. It is unaffected by air or water, and it sublimes readily. Extensive *ab initio* MO calculations have been used to explore the bonding in the adduct since, to our knowledge, **1a**·HMPA is the first amine (primary or otherwise)–phosphine oxide (HMPA or otherwise) complex to be structurally characterised. This uniqueness, plus the stability of the adduct, suggest it as a model to explain the carcinogenicity of HMPA.

The adduct was first isolated by chance. In pursuing a known route[1c] to aqua complexes of metallated organic compounds,[1] the primary amine **1a** was used as the organic precursor. Previously, related compounds such as thiol **1b** and alcohol **1c** had reacted successfully with $Ca(OH)_2$ and HMPA, giving complexes of type $R_2Ca \cdot 2HMPA \cdot xH_2O$ (R = deprotonated **1b**, **1c**). However, refluxing a toluene solution of **1a** and HMPA (1 : 1 mol. equiv.) in the presence of suspended $Ca(OH)_2$ (0.5 equiv.) for 48 h failed to dissolve the solid. After filtration, cooling of the solution afforded colourless needles. Characterisation showed that these were not the expected product, $R_2Ca \cdot 2HMPA \cdot 2H_2O$ (R = deprotonated **1a**), but rather the simple 1 : 1 adduct of **1a** and HMPA.† This

† For the adduct (**1a**·HMPA)$_n$: first batch yields 42% [**1a**, HMPA, $Ca(OH)_2$ in toluene], 75% (**1a** + HMPA alone, in toluene), 70% (**1a** + HMPA in H_2O); m.p. 115–117 °; Calc. C, 47.4; H, 7.3; N, 21.3; P, 9.4. Found: C, 47.4; H, 7.5; N, 21.2; P, 9.4%; IR (Nujol) for **1a**, ν(N–H)/cm^{-1} 3400 vs and 3300 s (both sharp), for adduct, broad shoulder (3180 cm^{-1}) on Nujol bands; ^{1}H NMR (250 MHz; C_6D_6; 25 °C) δ 7.73 (m, 1H), 7.35 (m, 1H), 7.12 (m, 1H), 6.89 (m, 1H), 6.04 (s, 2H, NH_2), 2.04 (d, 18H of one HMPA) (in the ^{1}H NMR spectrum of **1a** alone, under the same conditions, the NH_2 proton resonance appears at δ 5.24).

In benzene solutions, cryoscopic relative molecular mass measurements give n values ranging from 0.87 ± 0.02 (3.0×10^{-2} mol dm^{-3}, relative to n = 1) to 0.94 ± 0.01 (5.4×10^{-2} mol dm^{-3}).

was isolated subsequently simply by dissolving the components in toluene at 50 °C, then cooling. It can indeed also be similarly prepared using water as the solvent. The adduct is also thermally stable; it sublimes intact (140 °C, 0.1 mmHg) and the monomeric molecular ion (*m/z* 330, for **1a**·HMPA·H$^+$) is intense in its FAB mass spectrum.

The crystal structure‡ of the adduct consists essentially of dimers, (**1a**·HMPA)$_2$, in which one amino-H (H2) of each amine hydrogen bonds terminally to an HMPA oxygen, whilst the second H (H1) of each amine interacts with the heterocyclic N (N1) of the other amine, giving a central [NCNH]$_2$ ring [Fig. 1(*a*)]. These dimers are further, but relatively weakly, aggregated *via* HMPA–O···aromatic CH interactions [Fig. 1(*b*)]. A data base search[2] revealed no other structures having an amine (primary or secondary) hydrogen bonded to HMPA (or to any other phosphine oxide). The only marginally related structures are of: 1:2 HMPA : barbital (5,5-diethylbarbituric acid) complex, unstable in air, and having two 'rather strong' NH···O–P hydrogen bonds (N···O distances of 281, 284 pm);[3] a 1:2 HMPA–S_7NH adduct (N···O *ca.* 280 pm);[4] and a 1:1 HMPA–biphenylene-1,8-diol adduct (O···O distances 260, 261 pm).[5] For (**1a**·HMPA)$_2$, the key hydrogen bonds are short, reflecting its stability. Those distances involving HMPA, O(1)···H(2) 194(4) pm and O(1)···N(2) 278.3(5) pm, approach the criteria suggested[6] for strong hydrogen bonds (*ca.* 275 pm for O···N in O···H–N systems); the O(1)H(2)N(2) angle is 169.9(1.1)°. The central interactions effecting dimerisation [Fig. 1(*a*)] are clearly rather weaker [distances, N(1)···H(1a) 232(5) pm, N(1)···N(2a) 301.4(5) pm; the N(1)H(1a)N(2a) angle is 168.9(1.1)°], whilst the HMPA···aromatic CH interactions causing yet further association [Fig. 1(*b*)] are weaker still [estimated O(1a)···(H(3b) distance, 234.0(5) pm; O(1a)···C(3b), 332.1(5) pm].

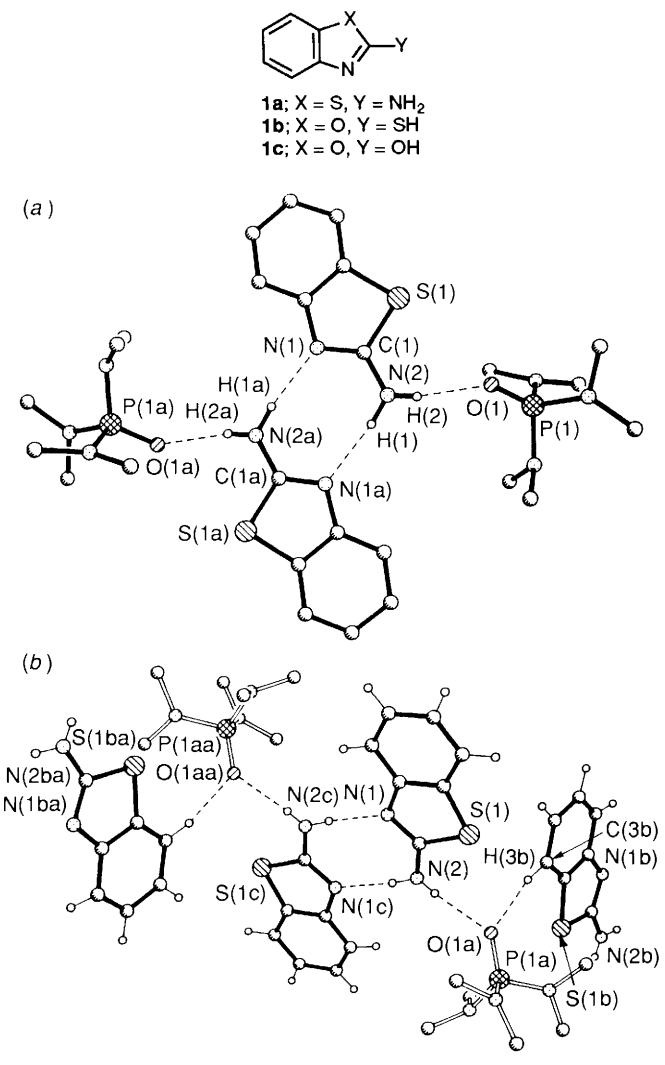
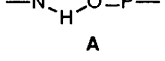


Fig. 1 (*a*) Basic dimeric structure of the 1:1 adduct $C_6H_4SC(=N)NH_2$·O=P(NMe$_2$)$_3$, **1a**·HMPA; (*b*) further intermolecular association of (**1a**·HMPA)$_2$

In benzene solutions, cryoscopic measurements show that (**1a**·HMPA)$_n$ exists mainly as a monomer (n = 1) (though slight further dissociation into the separate components is apparent).† Such monomer formation reflects in part the relative weakness of N(2)H(1) ··· N(1a) interactions in the solid. However, other features, and estimates of the energies involved, have come from *ab initio* MO calculations§ on models for a **1a**·HMPA monomer and for a dimer. The models for a monomer included adducts of HC=CHSC(=N)NH$_2$ **1a**′ with O=P(NH$_2$)$_3$ and of **1a** itself with O=PH$_3$. Structures **A** with a *double* hydrogen bridge were examined first [*cf.* Fig. 1(*a*); cleavage of H(1)···N(1a), then both H(2) *and* H(1) interacting with O(1)]. However, during attempted optimisation of dibridged forms, the phosphine oxide moves, possibly owing to N···O repulsions or possibly to introduce secondary interactions (see below). A *single* N–H···O interaction results, allowing two isomers for each model; the NH···O unit can be *cis* to the amine ring N or *cis* to the ring S. Typical results are shown in Fig. 2 for (*a*) **1a**·O=PH$_3$, *cis* to N, and (*b*) **1a**·O=PH$_3$, *cis* to S. The calculated adduct formation energies (ΔE, the decrease in energy on bringing together the two components) are 55.3 and 42.3 kJ mol^{-1} for the *cis*-N and *cis*-S species, respectively. The difference is due to the *cis*-N isomer having, over and above the (N)H···O–P interaction, a *secondary* interaction between the P atom (charge, +0.85) of O=PH$_3$ and



A

‡ *Crystal data* for (**1a**·HMPA): $C_{13}H_{24}N_5OPS$, M = 329.4, monoclinic, space group $P2_1/c$, a = 823.90(10), b = 1767.7(3), c = 1215.3(2) pm, β = 96.75(2)°, U = 1.758 nm^3, Z = 4, D_c = 1.245 Mg m^{-3}, μ = 0.27 mm^{-1}, 4359 measured reflections, 4140 uniqe, 2705 observed reflections ($F_o > 4\sigma F_o$), $2\theta_{max}$ = 55°, R = 0.071, R_w = 0.092 [$w^{-1} = \sigma^2(F) + 0.0002F^2$], 199 refined parameters, data to parameter ratio = 13.6:1, largest difference peak: 0.69 e$^-$ nm^{-3} × 10^2, largest difference hole: −0.28 e$^-$ nm^{-3} × 10^2. Data were collected on a Stoe-Siemens diffractometer using graphite-monochromated Mo-Kα radiation (λ = 71.073 pm) at 193 K. The attempted data collection at lower temperature failed owing to a solid–solid phase transition at *ca.* 183 K. The structure was solved by direct methods and refined by full-matrix least-squares techniques (SHELXTL Plus, G.M. Sheldrick, Universität Göttingen). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in calculated positions, except for hydrogen atoms H(1) and H(2) involved in the hydrogen bonds, whose coordinates were freely refined. Atomic coordinates, bond lengths, bond angles and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ *Ab initio* MO calculations: 6-31G basis set with d orbitals on P and S atoms,[7] using the program GAMESS.[8] Geometries were freely optimised except that, since for **1a**′ adducts a plane of symmetry resulted from optimisation even when using no constraints, a plane of symmetry was assumed for **1a** adducts. The total energies (in a.u.) calculated for the optimised structures mentioned in the text are: O=PH$_3$ −417.284250; O=P(NH$_2$)$_3$ −582.442838; **1a** −774.838967; **1a**′ −622.225046; **1a**·O=PH$_3$, *cis*-N isomer −1192.144363; **1a**·O=PH$_3$, *cis*-S isomer −1192.139387; **1a**′·O=P(NH$_2$)$_3$, *cis*-N isomer −1204.695505; **1a**′·O=P(NH$_2$)$_3$, *cis*-S isomer −1204.688360; **1a**′·O=PH$_3$, *cis*-N isomer −1039.530375; **1a**′·O=PH$_3$, *cis*-S isomer −1039.524718; (**1a**′)$_2$ with NH···N links −1244.472272; (**1a**′)$_2$ with NH···S links −1244.451432; (**1a**′·O=PH$_3$)$_2$, *cis*-N isomer, NH···S links −2079.061885; (**1a**′·O=PH$_3$)$_2$, *cis*-S isomer, NH···N links −2079.066569.

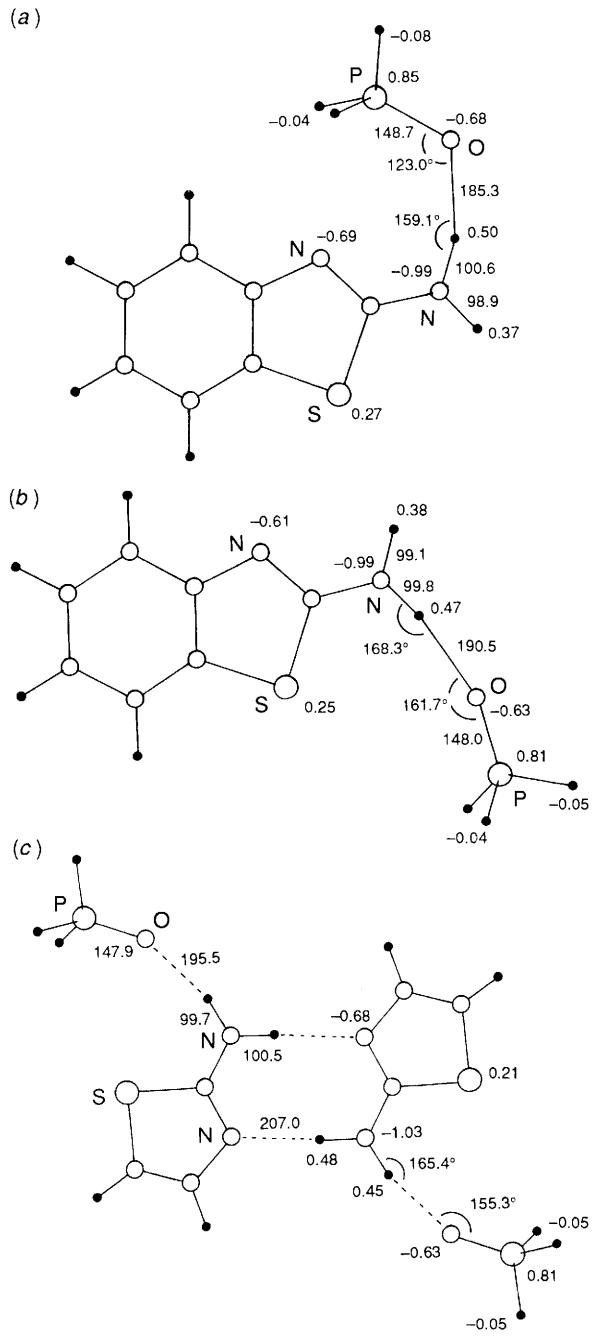


Fig. 2 *Ab initio* MO optimised geometries (bond lengths in pm, angles in °) and atomic charges: (*a*) **1a**·O=PH_3, *cis*-N isomer; (*b*) **1a**·O=PH_3, *cis*-S isomer; (*c*) (**1a**′·O=PH_3)$_2$ with NH ··· N links and the NH ··· O unit *cis* to S

the *heterocyclic* N (charge, −0.69; *cf.* that on S +0.25 in the *cis*-S isomer) of **1a**. To introduce this further bonding, the H···O–P angle is only 123.0° for the *cis*-N isomer (*cf.* 161.7° for the *cis*-S one). For **1a**′·O=P(NH_2)$_3$, more pronounced secondary interactions occur, and for both isomers (though more so for the *cis*-N one). For the *cis*-N species, ΔE = 72.4 kJ mol^{-1}, ∠H···O–P = 132.6°, and the interaction involves one H (charge +0.48) of O=P(NH_2)$_3$ and the heterocyclic N (charge −0.67) of **1a**′. For the *cis*-S species, ΔE = 53.6 kJ mol^{-1}, H···O–P = 159.3°, and the interaction occurs between one N (charge −0.97) of O=P(NH_2)$_3$ and the heterocyclic S (charge +0.22) of **1a**′.

Seemingly in conflict with the above results, in solid (**1a**·HMPA)$_2$ the NH···O link is *cis* to S. However, this then leaves the ring N [N(1), Fig. 1(*a*)] free to engage in hydrogen bonding to give the dimer. One expects only a low dimerisation energy for *cis*-N monomers, since NH···S interactions should be weak. This is confirmed by further MO calculations§ on dimers of **1a**′ [(**1a**′)$_2$ with NH···N attachments and with NH···S ones] and on dimers of **1a**′·O=PH_3 adducts {(**1a**′·O′=PH_3)$_2$ with NH···N links so NH···O is *cis* to S [Fig. 2(*c*)] and with NH···S ones so NH···O is *cis* to N}. For (**1a**′)$_2$, the dimerisation energies are 58.2 kJ mol^{-1} for the NH···N species, but a mere 3.3 kJ mol^{-1} for the NH···S one. Even more strikingly, whilst the *cis*-N isomer of monomeric **1a**′·O=PH_3 is favoured over the *cis*-S one (ΔE = 55.6 and 40.6 kJ mol^{-1}, respectively), this preference is reversed on forming the dimers, (**1a**′·O=PH_3)$_2$: the dimerisation energies are 2.9 kJ mol^{-1} for the *cis*-N, NH···S bonded dimer and 45.0 kJ mol^{-1} for the *cis*-S, NH···N bonded one. The calculations thus rationalise the structural features of solid (**1a**·HMPA)$_2$, in that, overall, the *cis*-S, NH···N bonded dimer is favoured by 12.1 kJ mol^{-1}. They predict that, on forming the solution monomer, the amine would rotate so that H(1) (*cis* to N), not H(2) (*cis* to S) [Fig. 1(*a*)], is involved in NH···OP interactions. They also estimate the energies of the two sorts of strong hydrogen bonding found in the solid: 42.3 kJ mol^{-1} for the NH···OP interaction (ΔE for the *cis*-S form of **1a**.O=PH_3, assuming no secondary interactions) and 22.5 kJ mol^{-1} for the NH···N bond [half the dimerisation energy for (**1a**′·O=PH_3)$_2$, formed from *cis*-S monomers].

The structure and stability (especially towards water) of the **1a**·HMPA adduct suggest a model to help explain the carcinogenicity of HMPA. Amine **1a** has similarities to the natural bases along DNA: A, G and C have *exo*-NH_2 groups and ring N and/or NH units, whilst T has ring NH units. Hydrogen bonds between base pairs (A→T, C→G), individually weak, but numerous, impart the high stability essential for preservation of genetic information. Clearly, strong and competitive complexation of HMPA to these amines would severely hinder replication of such information. More generally, the formation of such a strong adduct as **1a**·HMPA reflects the dipolar (ylidic) nature of HMPA, whose O–P bond is better described by O^-–P^+ than by O=P. We are investigating other ylide adducts with P^+–E^-···H–X interactions (E^- = CH_2^-, NH^-, O^-, S^- and X = N, O, S *etc.*).

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