Gas Phase Basicities of 1,3-Benzazoles: Benzimidazole, Benzoxazole, Benzothiazole, Benzoselenazole and Benzotellurazole

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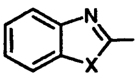
The gas phase basicities of the title compounds have been experimentally determined by means of Fourier transform ion cyclotron resonance spectroscopy (FTICR). The experimental results have been analysed further using the PM3 semiempirical MO method.

As part of a programme on the investigation of the gas phase properties of heteroaromatic systems, we required structural information on the effect of heteroatoms on the gas phase basicities (GB) of azoles.[1,2] The gas phase proton basicity, GB, of a given base, B, is the negative of $\Delta G_{\mathrm{H^+}}(\mathrm{g})$, the standard free-energy change for reaction (1).

$$\mathrm{B(g)} + \mathrm{H^+(g)} \longrightarrow \mathrm{BH^+(g)} \quad \Delta G_{\mathrm{H^+}}(\mathrm{g}) \qquad (1)$$

The proton affinity of B, PA, is defined as the negative of $\Delta H_{\mathrm{H^+}}(\mathrm{g})$ for reaction (1). One of the most complete series of heteroaromatic systems is represented by 1,3-benzazoles **1** and **2**, where X = NH (**a** series), O (**b** series), S (**c** series), Se (**d** series) and Te (**e** series).[3]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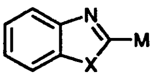
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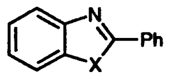
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We report here the experimental determination (by FTICR) of the gas phase basicities of compounds **1b**, **1c**, **2b**, **2c**, **2d** and **2e**. That of **1a** was estimated previously as ΔGB = −24.2 kcal mol^{-1},[4] where ΔGB is the gas phase proton basicity using ammonia as the reference base through reaction (2) and defined in eqn. (3).

$$\mathrm{B(g)} + \mathrm{NH_4^+(g)} \rightleftharpoons \mathrm{BH^+(g)} + \mathrm{NH_3(g)} \quad \Delta\Delta G_{\mathrm{H^+}}(\mathrm{g}) \quad (2)$$

$$\Delta \mathrm{GB} = -\Delta\Delta G_{\mathrm{H^+}}(\mathrm{g}) = \mathrm{GB(NH_3)} - \mathrm{GB(B)} \quad (3)$$

To discuss these values we have followed two procedures. The first one is purely empirical and is based on similarity criteria frequently used in linear free energy relationships (LFER).[2,6] For compounds **1a**, **1b**, **2b**, **1c**, **2c**, **2d** and **2e** (seven points) both the gas phase and solution basicities (the water pK_as in Table 1) are known or could be estimated. A plot of one against the other shows a linear relationship which can be expressed as eqn. (4).

$$\Delta\mathrm{GB/kcal\ mol^{-1}} = -11.66 - 2.7215\,\mathrm{p}K_a, \quad R = 0.95 \quad (4)\dagger$$

The FTICR technique does not lead directly to the PA values. In our case, a very satisfactory estimate of the PA values for 1,3-benzazoles **1** and **2** can be obtained as follows: the FTICR experiments provide the $\Delta\Delta G_{\mathrm{H^+}}(\mathrm{g})$ values. Using eqn. (5) and

$$\Delta\Delta G_{\mathrm{H^+}}(\mathrm{g}) = \Delta\Delta H_{\mathrm{H^+}}(\mathrm{g}) - T\Delta\Delta S_{\mathrm{H^+}}(\mathrm{g}) \qquad (5)$$

recalling the definitions of GB and PA leads to eqn. (6), where

$$\Delta\mathrm{GB} = \Delta\mathrm{PA} + T\Delta\Delta S_{\mathrm{H^+}}(\mathrm{g}) \qquad (6)$$

the $\Delta\Delta S_{\mathrm{H^+}}(\mathrm{g})$ term pertains to reaction (2). For the series of compounds examined in this work, the value of $\Delta\Delta S_{\mathrm{H^+}}(\mathrm{g})$ is nearly constant, as it is mostly determined by changes in the symmetry numbers, σ, of the various species involved in this reaction.[1,7] It follows that a comparison between the experimental GB values and the theoretically calculated PAs (Table 2) is meaningful. For $\mathrm{NH_3}$ and $\mathrm{NH_4^+}$, $\sigma = 3$ and 12, respectively. For B and $\mathrm{BH^+}$, $\sigma = 1$ in all cases, except for **1a** and **2a** for which $\sigma(\mathrm{B}) = 1$ and $\sigma(\mathrm{BH^+}) = 2$. Further details are given in ref. 1.

Combination of these values of the entropy changes with the experimental values of GB and PA for $\mathrm{NH_3}$, respectively 195.6 and 204.0 kcal mol^{-1} leads to the PA values. The calculations have been carried out using the PM3 Hamiltonian.[8] The results of these calculations are summarized in Table 2.

Since it has been described,[3] that in the case of 2-phenylbenzotellurazole **3e**, treatment with methyl iodide can lead either to the N3-methyl cation **4e** or to the Te1-methyl

Table 1 Basicity of 1,3-benzazoles **1** and **2** (X = NH, O, S, Se, Te)

Compound	X	pK_a(BH$^+$)[a]	PA[b]	pK_a(BH$^+$)[c]
1a	NH	—	223.8	5.56
2a	NH	—	226.7	6.19
1b	O	6.70	210.2	−0.13
2b	O	7.30	214.1	*0.55*
1c	S	7.87	211.3	1.2
2c	S	8.63	214.9	*2.06*
1d	Se	8.03	208.1	*1.38*
2d	Se	8.87	212.5	*2.34*
1e	Te	—	214.7	—
2e	Te	10.10	219.6	*3.74*

[a] Experimental values in acetonitrile solution at room temperature.[5] [b] PM3 calculated values using PA[H$^+$] = 367.2 kcal mol^{-1}. [c] Experimental values in water [the italicized values have been estimated from the values in acetonitrile by means of the equation pK_a(water) = −7.746 + 1.1368 pK_a(CH$_3$CN) calculated using the points corresponding to compounds **1b** and **1c**].

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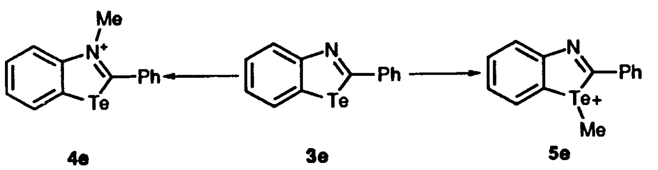
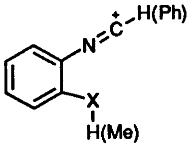
† 1 cal = 4.184 J.



4e **3e** **5e**

cation **5e** (although in the latter case $AgClO_4$ is necessary as a promotor), we have calculated the stability of both possible cations in the case of compounds with X = NH, O, S, Se and Te.

The cation resulting from protonation or methylation on N3 is always more stable than that resulting from protonation or methylation on X1. Moreover, according to the PM3 calculations, the optimized geometries for the cations resulting from protonation or methylation on X1 corresponds to the open-chain structure **6** except in the case of X1 = NH.



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It is clear that in all cases, the most stable cations (ring or open-chain compounds) are those corresponding to protonation or methylation on N3. Meot-Ner *et al.*[10] (see also ref. 11) estimated that of the two possible cations resulting from the protonation of oxazole, the *O*-protonated is 41 kcal mol^{-1} less stable than the N3-protonated one; in Table 2 this difference is reduced to 10 kcal mol^{-1} but the structure of the *O*-protonated oxazole is a ring compound according to MP2/6-31G(d,p) calculations and an open-chain compound according to PM3 calculations.

A representation of GB *vs.* PA (protonation on N3, Table 2) is possible for compounds **1a**, **1b**, **2b**, **1c**, **2c**, **2d** and **2e**. To provide a more extensive range of examples, we have added three more compounds, imidazole **R1**, 1-methylimidazole **R2** and 1-methylbenzimidazole **R3**, whose GBs were known (the results of our calculations are reported in Table 3). The result (Fig. 1) is very satisfactory taking into account the great variety of X1 atoms (NH > O > S > Se > Te) and rings (1,3-azoles and 1,3-benzazoles). Eqn. (7) corresponds to the ten points.

Table 2 Results of the PM3 calculations on 1,3-benzazoles **1** and **2** (all values in kcal mol^{-1})

Compound	$\Delta H_f°(B)$	$\Delta H_f°(BH^+)$[a]	$\Delta H_f°(BH^+)$[b]	PA[a,c]	GB[a,d]
1a	47.77	191.19	220.07	223.8	219.8
2a	37.69	178.20	207.42	226.7	—
1b	15.94	172.95	182.10[e]	210.2	205.4
2b	6.94	160.07	168.30[e]	214.1	209.4
1c	54.07	209.93	236.35[e]	211.3	210.5
2c	46.61	198.89	224.40[e]	214.9	214.4
1d	41.93	201.01	237.17[e]	208.1	—
2d	30.84	185.53	222.83[e]	212.5	214.5
1e	70.81	223.34	248.73[e]	214.7	—
2e	59.42	207.01	234.62[e]	219.6	215.9

[a] Corresponds to the cation protonated on the N3 nitrogen atom. [b] Corresponds to the cation protonated on the X1 atom. [c] Theoretical values of PA calculated using $\Delta H_f°(H^+) = 367.2$ kcal mol^{-1}. [d] Experimental values of GB calculated as $GB = -\Delta G_{H^+}(g) = GB(NH_3) - \Delta GB$ (see the text) using $GB(NH_3) = 195.6$ kcal mol^{-1}.[9] [e] The resulting cation corresponds to an open-chain structure (see the text).

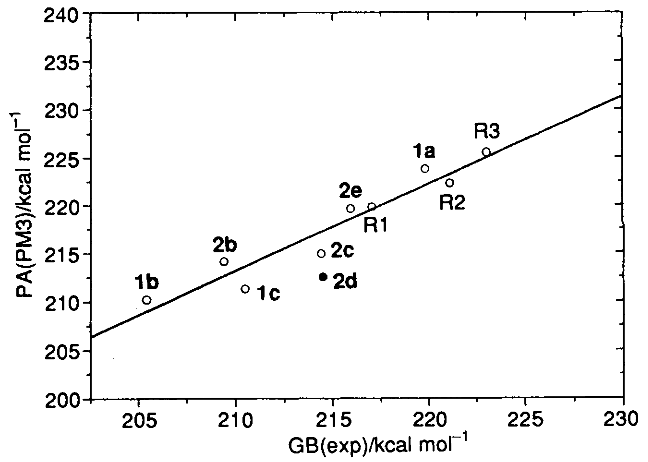

Fig. 1 A plot of GB *vs.* PA (protonation on N3)

$$PA\ (\text{kcal mol}^{-1}) = 19.7 + (0.92 \pm 0.14)\ GB\ (\text{kcal mol}^{-1}),\quad R = 0.92 \qquad (7)$$

The point which shows the maximum deviation is 2-methylbenzoselenazole **2d**: if this point is excluded the correlation becomes, eqn. (8). The line in Fig. 1 corresponds to eqn. (8) (point for **2d** is in black).

$$PA\ (\text{kcal mol}^{-1}) = 22.5 + (0.91 \pm 0.10)\ GB\ (\text{kcal mol}^{-1}),\quad R = 0.96 \qquad (8)$$

We have also calculated the effect of methylation on a series of compounds carrying a phenyl substituent at the 2-position: 2-phenylbenzimidazole **3a**, 2-phenylbenzoxazole **3b**, 2-phenylbenzothiazole **3c**, 2-phenylbenzoselenazole **3d** and 2-phenylbenzotellurazole **3e**. The numerical results are reported in Table 4; the two main conclusions are, first, that the cation resulting from the methylation on the N3 atom, **4**, is always more stable than the cation resulting from the methylation on X1, **5**; and second, that on going from **3** to **4**, the 2-phenyl substituent experiences a rotation of 20–40° out of plane [torsion $(BMe^+) = 21.1° + 1.414$ torsion (B), $n = 5$, $R = 0.98$].

Experimental

Materials.—The compounds studied in this work are reported in ref. 5.

ICR Spectrometry.—Gas phase basicities (GB) were determined from equilibrium proton-transfer reactions conducted in a modified Bruker CMS-47 FTICR mass spectrometer.[13–15]

Table 3 Experimental and calculated (PM3) values of reference azoles (all values in kcal mol^{-1})

Compound	$\Delta H_f°(B)$	$\Delta H_f°(BH^+)$[a]	PA(PM3)[a]	GB[a,b]
Imidazole, **R1**	31.31	178.69	219.8	217.0
1-Methylimidazole, **R2**	29.84	174.69	222.3	221.1
1-Methylbenzimidazole, **R3**	46.30	187.97	225.5	223.0

[a] Corresponds to the cation protonated on the N3 nitrogen atom. [b] From ref. 4 (values multiplied by 1.07).

Table 4 Results of the PM3 calculations (all values in kcal mol^{-1})

Compound	$\Delta H_f°$(B)	$\Delta H_f°$(BMe$^+$)[a]	$\Delta H_f°$(BMe$^+$)[b]	MA[a,c]	Torsion (B) (°)[d]	Torsion (BMe$^+$) (°)[a,d]
3a	71.60	207.19	239.25	126.2	32.8	64.5
3b	41.84	187.53	206.72	116.1	7.9	29.4
3c	81.21	228.43	247.61	114.6	24.9	61.7
3d	61.85	210.67	230.09	113.0	0.9	26.3
3e	88.56	231.98	256.09	118.4	5.1	24.8

[a] Corresponds to the cation methylated on the N3 nitrogen atom. [b] Corresponds to the cation methylated on the X1 atom. [c] Methyl cation affinity calculated using $\Delta H_f°(CH_3^+)$ = 261.8 kcal mol^{-1}.[12] [d] Value of the dihedral angle between the 2-phenyl substituent and the 1,3-benzazole ring.

Table 5 Experimental determination of the gas phase basicities of selected benzazoles. The nominal temperature is 333 K (all values in kcal mol^{-1})

Compound	Standard	ΔGB(std)[a]	$\delta\Delta G_{H^+}$(g)	ΔGB	ΔGB(av)
1b	$HCONMe_2$	−8.5	−1.28	−9.78	
	Bu^t_2S	−10.7	0.98	−9.72	−9.8 ± 0.2
	$MeNH_2$	−10.5	0.38	−10.12	
	$H_2C{=}CHCH_2NH_2$	−8.5	−1.15	−9.65	
2b	3-chloropyridine	−12.3	−1.52	−13.82	
	pyridazine	−13.6	−0.16	−13.76	−13.8 ± 0.1
	$PrNH_2$	−15.1	1.22	−13.88	
1c	pyridazine	−13.6	−1.50	−15.10	
	$PrNH_2$	−15.1	0.32	−14.78	−14.9 ± 0.2
	$C_6H_5CH_2NH_2$	−14.2	−0.55	−14.75	
2c	pyridine	−18.8	−0.07	−18.87	
	neopentylamine	−17.4	−1.11	−18.51	−18.8 ± 0.2
	Bu^tNH_2	−19.0	0.13	−18.87	
2d	pyridine	−18.8	−0.25	−19.05	
	neopentylamine	−17.4	−1.30	−18.70	−18.9 ± 0.2
	Bu^tNH_2	−19.0	0.05	−18.95	
2e	pyridine	−18.8	−1.64	−20.44	
	tert-pentylamine	−20.5	0.26	−20.24	−20.3 ± 0.1
	2-methoxypyridine	−19.5	−0.79	−20.29	

[a] Values from ref. 7, multiplied by 1.07 as indicated in the text.

Working conditions were similar to those already described,[16] the nominal cell temperature being *ca.* 333 K. These FTICR measurements provide the standard free-energy change, $\delta\Delta G_{H^+}$ (g), for proton-transfer reaction (1) in the gas phase between a given base, B, and a reference compound, B_{ref} [reaction (9)].

$$B(g) + B_{ref}H^+(g) \underset{K_p,\delta\Delta G_{H^+}(g)}{\rightleftharpoons} BH^+(g) + B_{ref}(g) \quad (9)$$

The reversibility of reaction (9) was systematically confirmed by means of double resonance experiments. GB values can be obtained by combining $\delta\Delta G_{H^+}$(g) data with GB of the reference bases.

The experimental gas phase basicities for the reference bases used in this work are the values from Professor Taft's laboratory published in ref. 7.[4] These values have been compared with those given in the most recent high pressure mass spectrometry (HPMS) determination of GBs and proton affinities, PAs, carried out under extremely careful temperature monitoring.[17] The correlation between GBs at 333 K (our nominal working temperature) obtained from ref. 17, for 18 bases ranging from water to dimethylamine, and Taft's data is exceptionally good: r = 0.9997, sd = 0.34 kcal mol^{-1}. The slope is 1.07 ± 0.02 at the 99% level. Taft's values have been multiplied by this factor throughout.

Gas Phase Basicities.—Table 5 presents the results of proton-transfer equilibria (1) between the different compounds considered and a series of standard reference gases. The values of $\delta\Delta G_{H^+}$(g) given in Table 5 are defined as shown in eqn. (10).

$$\delta\Delta G_{H^+}(g) = -RT\ln K_p \quad (10)$$

All GBs are referenced to ammonia [reaction (2)]. ΔGB (av) is the average of the ΔGB values obtained through eqn. (11),

$$\Delta GB = \Delta GB(std) + \delta\Delta G_{H^+}(g) \quad (11)$$

where ΔGB(std) pertains to reaction (12).

$$B_{ref}(g) + NH_4^+(g) \rightleftharpoons B_{ref}H^+(g) + NH_3(g) \quad (12)$$

Computational Details.—Structures and energies were obtained by means of the PM3 semiempirical method,[8] as implemented in the SPARTAN 3.0 and MOPAC 6.0 packages of programs.[18] The proton affinities at this level were calculated taking the heat of formation of the proton as 367.2 kcal mol^{-1}.[9] The corresponding methyl cation affinities were calculated taking as the heat of formation of the methyl cations the experimental value of 261.8 kcal mol^{-1}.[12] The results of PM3 computations are reported in Table 2 (series **1** and **2**) and in Table 4 (series **3**).

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