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SOLVENT EFFECT ON THE PROTONATION OF SOME PURINES, PYRIMIDINES AND RELATED COMPOUNDS

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ABSTRACT

Potentiometric and calorimetric data are given for the protonation at 25 °C of some purines, pyrimidines and related bases, B, in dimethylsulfoxide and water. The enthalpies of transfer from water to Me_2SO of BH^+ are found to be 32.9 ± 0.7 kJ mol^{-1} more exothermic than the transfer enthalpies of B. Correlations are reported between the free energy and enthalpy of protonation of B in both solvents and in the gas phase. These correlations are useful in predicting and assessing the validity of exprimental or calculated thermodynamic data.

INTRODUCTION

The basicity of the solvent can have a profound influence on the thermodynamics of proton transfer reactions [1]. However, except in special cases [2], the protonation free energy and enthalpy of aliphatic [3] and aromatic [4] amines appear to be little different in water than in dimethylsulfoxide (Me_2SO), even though these two widely used solvents have different basicities, in addition to their very different structural properties. We have recently reported some limited data on the protonation of some purines in various media [5]. We now present more complete thermodynamic data on the protonation of biologically important purines (Pur) and pyrimidines (Pym), and also of related compounds, in water and Me_2SO. Calorimetric as well as potentiometric and NMR determinations were carried out to supplement existing data. We have attempted to correlate protonation free energies and enthalpies in both solvents and we have also compared solution data with gas-phase proton affinities. While the diversity of the considered bases limit the possibility of interpreting the data in terms of solute–solvent interactions, the thermodynamic correlations we present are useful for predicting unavailable thermodynamic data, as well as for assessing the validity of the results of molecular orbital (MO) calculations.

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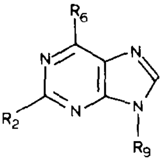
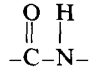
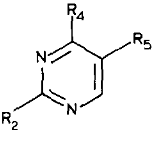
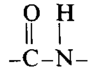
The bases considered are shown below

	Base	Abbr	R_2	R_6	R_9
	Purine	Pur	H	H	H
	Adenine	Ade	H	NH_2	H
	Adenosine	Ado	H	NH_2	ribose
	9-Methyladenine	MeAde	H	NH_2	CH_3
	N^6,*N*^{6}-Diethyladenine	Et_2Ade	H	Et_2N	H
	Hypoxanthine	Hyp	H	OH *	H
	Guanine	Gua	NH_2	OH *	H
	Xanthine	Xan	OH *	OH *	H

* Tautomerization to  $-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle H}{|}}{N}-$

	Base	Abbr	R_2	R_4	R_5	R_6
	Pyrimidine	Pym	H	H	H	H
	Cytosine	Cyt	OH *	NH_2	H	H
	Uracil	Ura	OH *	OH *	H	H
	Thymine	Thy	OH *	OH *	CH_3	H
	4-Amino-2-6-dimethylpyrimidine	Dap	CH_3	NH_2	H	CH_3

* Tautomerization to  $-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle H}{|}}{N}-$

EXPERIMENTAL

Materials

Sources of most of the compounds used were previously reported [5,6]. 7,9-Dimethylxanthine (Me_2Xan) was synthesized according to the procedure of Jones and Robins [7] and checked for purity by acidimetric titrations.

*p*K$_a$ *Determinations*

Potentiometric titrations of Me_2SO or aqueous solutions of bases ($\approx 10^4$–10^{-2} M) with standardized 0.1 M CF_3SO_3H in Me_2SO or aqueous 0.1 M HCl were carried out at 25.0 ± 0.1° C as previously reported [5]. The ionic strength was maintained constant by initially making the solution 0.10 M Et_4NClO_4 in Me_2SO or 0.10 M KCl in water. For pyrimidine, more concentrated solutions of base ($\approx$ 0.1 to 0.8 M) and acid ($\approx$ 1.0 M) were used because it is a weak base in Me_2SO. Initially, the ionic strength was 0.50 M in Et_4NClO_4.

The low pK_a value of xanthine (Xan) in Me_2SO could not be obtained by potentiometry. We recorded the ^{13}C NMR spectra of 0.07–0.08 M xanthine solutions containing increasing acid concentrations. Spectra were obtained at 28 °C with a Bruker WP-80 spectrometer operating at 20.2 Hz. ^{13}C chemical shifts were measured relative to external dioxane in D_2O (coaxial tube) taking $\delta_{Me_4Si} = \delta_{Dioxane} + 67.40$ p.p.m. [8]. Because acidic xanthine solutions developed a color on standing, NMR samples were prepared just before recording spectra, by dissolving weighed quantities of xanthine in known volumes of standardized CF_3SO_3H solutions in Me_2SO.

Calorimetric measurements

The heats of protonation of the bases were obtained at 25.00 ± 0.01 °C with a L.K.B. Model 8725-2 isoperibol calorimeter as previously described [9]. The amounts of base dissolved ($\approx 10^{-4}$–10^{-3} mol) in 100 ml of 0.1 M CF_3SO_3H in Me_2SO or aqueous 0.1 M $HClO_4$, were deduced from the weights of the glass ampoules. Hypoxanthine (Hyp) was dissolved in 0.68 M CF_3SO_3H in Me_2SO, and in aqueous 0.58 M $HClO_4$ to increase its solution rate. The heat of neutralization of pyrimidine was determined in 0.38 M CF_3SO_3H in Me_2SO. The heat of reaction of aqueous N^6,N^6-diethyladenine (Et_2Ade) with an excess of 5.8 M $HClO_4$ was measured to yield the heat of protonation of Et_2Ade after correction for the dilution of $HClO_4$.

RESULTS

Ionization constants

The values of the ionization constant, K_a, of the conjugate acids BH^+ of the bases 4-aminopyridine (Ampy), Pym, cytosine (Cyt), Et_2Ade and Me_2Xan in Me_2SO, and adenine (Ade), Et_2Ade, and Me_2Xan in water were obtained from the potentiometric titration curves. The program described previously [5] was used. Our pK_a values are valid for 0.10 M ionic strength, with the exception of Pym where $\mu = 0.50$ M. For $XanH^+$ in Me_2SO, K_a was calculated from the concentrations of H^+, Xan and $XanH^+$ at equilibrium. These concentrations were deduced from the plots of the measured ^{13}C chemical shifts against $r = [H^+]_i/[Xan]_i$ $(O \leqslant r \leqslant 10)$, where $[H^+]_i$ and $[Xan]_i$ are the initial concentrations, and from the ^{13}C chemical shifts of Xan and $XanH^+$. The pK_a values in Me_2SO and water are listed in Table 1 together with literature values for other bases [4,5,10–12]. No corrections were made for the effect of ionic strength, which would be small for such a type of reaction.

TABLE 1

Ionization constants, K_a, of BH^+ ions at 25 °C

Base (abbr)	pK_a	
	Me_2SO	H_2O
Cytosine (Cyt)	5 73 ± 0 04	4 58 [a]
Uracil (Ura)	–	−2 35 [a]
Thymine (Thy)	–	−3 08 [a]
4-Amino-2,6-dimethylpyrimidine (Dap)	6 38 [b]	6 85 [b]
Pyrimidine (Pym)	0 55 ± 0 15	1 30 [c]
4-Aminopyridine (Ampy)	−8 5 ± 0 1 [d]	9 17 [c]
2-Hydroxypyridine (Hypy)	–	0 77 [a]
Pyridine (Py)	3 45 [b]	5 17 [b]
N,N-Dimethylaniline (ϕNMe_2)	2 51 [e]	5 16 [e]
Aniline (ϕNH_2)	3 72 [e]	4 60 [e]
Purine (Pur)	1 83 [b]	2 39 [b]
Adenine (Ade)	4 06 [b]	4 34 ± 0 03
Adenosine (Ado)	3 18 [b]	3 55 [b]
9-Methyladenine (MeAde)	3 69 [b]	3 88 [b]
N^6,N^6-Diethyladenine (Et_2Ade)	3 02 ± 0 01	4 55 ± 0 03
Hypoxanthine (Hyp)	1 94 [b]	1 8 [b]
Guanine (Gua)	3 74 [b]	3 3 [b]
Xanthine (Xan)	0 52 ± 0 05	0 91 [f]
Caffeine (Caf)	–	−0 13, 0 18 [f]
7,9-Dimethylxanthine (Me_2Xan)	5 15 ± 0 03	3 08 ± 0 02
Benzimidazole (BzImid)	4 36 [b]	5 77 [b]
N-Methylimidazole (MeImid)	6 15 [b]	7 20 [b]
Imidazole (Imid)	6 26 [b]	7 14 [b]

[a] [10] [b] [5] [c] [11] [d] D Boulet, unpublished result [e] [4] [f] [12]

Protonation enthalpies and entropies

The values of the heats of neutralization of solid Ampy and Cyt in Me_2SO containing an excess of CF_3SO_3H, Q_{ns}, were plotted against the number of moles of dissolved base The slopes of the least-square lines gave the molar enthalpy of neutralization in Me_2SO, $\Delta H_{ns}(B)$, which refers to reaction (1)

$$B(1 \text{ or } c) + H^+(s \text{ or } w) = BH^+(s \text{ or } w) \tag{1}$$

Hyp and Et_2Ade dissolved slowly in acidic solutions, so that the amount of base could not be varied significantly The reported neutralization enthalpies in Me_2SO and water represent an average of two to four separate determinations The enthalpies of protonation of the bases in Me_2SO and water, $\Delta H_{ps}(B)$ and $\Delta H_{pw}(B)$, referring to reaction (2)

$$B(s \text{ or } w) + H^+(s \text{ or } w) = BH^+(s \text{ or } w) \tag{2}$$

TABLE 2

Enthalpies and entropies of protonation of B in Me_2SO and water at 25 °C

Base	$\Delta H_p^\ominus(B)$ (kJ mol^{-1})		$\Delta S_p^\ominus(B)$ (J mol^{-1} K^{-1})	
	Me_2SO	H_2O	Me_2SO	H_2O
Cyt	−30 4±0 3	−21 2 [a]	+8	+16
Dap	−42 4 [b]	−34 2 [b]	−20	+16
Pym	−7 5±1 0	+0 90±0 01	−15	+28
Ampy	−50 3±0 3 [c]	−46 1 [d]	−6	+21
Hypy	–	+0 3 [e]	–	+16
Py	−27 7 [b]	−20 3 [b]	−27	+31
ϕNMe_2	−23 8 [f]	–	−32	–
ϕNH_2	−30 8 [f]	−30 1 [f]	−32	+16
Pur	−19 5 [b]	−8 8 [b]	−31	+16
Ade	−25 8 [b]	−17 6 [b]	−9	+24
Ado	−21 0 [b]	−15 9 [b]	−9	+15
MeAde	−25 8 [b]	−19 4 [b]	−16	+9
Et_2Ade	−20 0±0 4	−19 9±0 6	−9	+20
Hyp	−19 5±1 7	−10 5 [g]	−28	−1
Gua	–	−20 6 [h]	–	−6
BzImid	−30 7 [b]	−30 0 [b]	−19	+10
MeImid	−38 8 [b]	−32 9 [b]	−12	+28
Imid	−42 4 [b]	−36 8 [b]	−22	+13

[a] [13] [b] [5] [c] D Boulet, unpublished result [d] [14] [e] [15] [f] [4] [g] [16] [h] Value obtained by subtracting $\Delta H_w^\ominus$(Gua) [6] from the average value of $\Delta H_{nw}^\ominus$(Gua) in aqueous HCl solutions for 0 18 M < [HCl] < 0 79 M [17]

were calculated by combining values of ΔH_{ns} or ΔH_{nw} with the corresponding solution enthalpies of the bases in Me_2SO and water [6], $\Delta H_s(B)$ and $\Delta H_w(B)$, obtained previously

$$\Delta H_{ps\ or\ pw}(B) = \Delta H_{ns\ or\ nw}(B) - \Delta H_{s\ or\ w}(B) \tag{3}$$

The protonation enthalpy of Pym in both solvents was obtained after correction to account for its incomplete protonation

These values of $\Delta H_{ps}(B)$ and $\Delta H_{pw}(B)$ at 0 1 M ionic strength are not likely to be very different from the $\Delta H_{ps}^\ominus$, $\Delta H_{pw}^\ominus$ values at zero ionic strength [5] These values are presented in Table 2 together with previously published data [4,5,13–17] We also give in Table 3 the enthalpies of protonation of B in the gas phase, $\Delta H_{pg}(B)$, which are equal to minus the proton affinities (PA) PA values have been reported by several groups of workers [18–25] The PA values are averages based on $PA(NH_3) = 866$ kJ mol^{-1}, $PA(Py) = 937$ kJ mol^{-1} and $PA(Me_3N) = 958$ kJ mol^{-1} Results of recent molecular orbital calculations [26–28] are also listed

The protonation entropies in Me_2SO and water, $\Delta S_{ps}^\ominus(B)$ and $\Delta S_{pw}^\ominus(B)$, respectively, are also listed in Table 2 These latter values were calculated by

TABLE 3

Enthalpies of protonation of B in the gas phase, ΔH_{pg}(B), and theoretical protonation energies (kJ mol^{-1})

Base	ΔH_{pg}(B)	Theoretical protonation energy
Cyt	−950 [a,b]	−1042 7 [c], −861 8 [d]
Ura	−887 ± 21 [b]	−798 3 [d]
Thy	−891 [a,b]	−886 2 [c], −789 7 [d]
Pym	−912 [a,e]	
Ampy	−977 [f]	
Py	−937 [a]	
ϕNMe_2	−950 [g,h]	
ϕNH_2	−901 [a,g,h]	
Pur	−929 [a,b]	
Ade	−946 [a,b]	−941 8 [d], −1008 8 [c]
Ado	−948 [b]	
Hyp	−918 ± 13 [b]	
Gua	−939 ± 9 [b]	−1023 8 [c], −910 1 [d]
BzImid	–	−957 [i]
MeImid	−974 [e,j]	
Imid	−941 [k]	

[a] [18] [b] [19] [c] [27] [d] [26] [e] [20] [f] [21] [g] [22] [h] [23] [i] [28] [j] [24] [k] [25]

TABLE 4

Enthalpies of transfer of B and BH$^+$ from water to Me$_2$SO at 25 °C (kJ mol^{-1})

Base	$\Delta H^{\ominus}_{ws}$(B) [a]	$\Delta H^{\ominus}_{ws}$(BH$^+$)
Cyt	−18 8	−53 5
Ura	−19 2	–
Thy	−15 4	–
Dap	+4 9	−28 8
Pym	+10 0	−23 9
Ampy	−7 8	−37 5
Hypy	+3 7	–
Py	+10 9	−22 0
ϕNH_2	−11 2	−37 1
Pur	−4 6	−40 8
Ade	−23 5	−57 2
Ado	−31 0	−61 6
MeAde	−19 6	−51 5
Et$_2$Ade	+5 1	−20 5
Hyp	−16 5	−51 0
Caf	+4	
BzImid	−7 7	−33 9
MeImid	+9 5	−21 9
Imid	−1 8	−32 9

[a] [6]

combining the $\Delta G^{\ominus}_{\mathrm{ps\ or\ pw}}(\mathrm{B})$ deduced from $\mathrm{p}K_{\mathrm{a}}$ with $\Delta H^{\ominus}_{\mathrm{ps\ or\ pw}}(\mathrm{B})$, according to eqns (4) and (5).

$$\Delta G^{\ominus}_{\mathrm{ps\ or\ pw}}(\mathrm{B}) = -2.303\,RT\mathrm{p}K_{\mathrm{a}} \tag{4}$$

$$\Delta G^{\ominus}_{\mathrm{ps\ or\ pw}}(\mathrm{B}) = \Delta H^{\ominus}_{\mathrm{ps\ or\ pw}}(\mathrm{B}) - T\Delta S^{\ominus}_{\mathrm{ps\ or\ pw}}(\mathrm{B}) \tag{5}$$

Enthalpies of transfer of BH$^+$

The enthalpies of transfer of BH^+ from water to $\mathrm{Me_2SO}$, $\Delta H^{\ominus}_{\mathrm{ws}}(\mathrm{BH}^+)$, were calculated by using eqn (6) relating protonation processes in both media.

$$\Delta H^{\ominus}_{\mathrm{ws}}(\mathrm{BH}^+) = \Delta H^{\ominus}_{\mathrm{ws}}(\mathrm{B}) + \Delta \mathrm{H}^{\ominus}_{\mathrm{ws}}(\mathrm{H}^+) + \Delta H^{\ominus}_{\mathrm{ps}}(\mathrm{B}) - \Delta \mathrm{H}^{\ominus}_{\mathrm{pw}}(\mathrm{B}) \tag{6}$$

$\Delta H^{\ominus}_{\mathrm{ws}}(\mathrm{B})$ and $\Delta H^{\ominus}_{\mathrm{ws}}(\mathrm{H}^+)$ are the enthalpy of transfer of B and H^+, respectively, from water to $\mathrm{Me_2SO}$. $\Delta H^{\ominus}_{\mathrm{ws}}(\mathrm{H}^+)$ was taken as -25.5 kJ mol^{-1} [1]. The $\Delta H^{\ominus}_{\mathrm{ws}}(\mathrm{B})$ values, recently reported [6], are given in Table 4 with the calculated $\Delta H^{\ominus}_{\mathrm{ws}}(\mathrm{BH}^+)$ values.

DISCUSSION

We will discuss the extensive thermodynamic data of Tables 1, 2, 3 and 4 with the help of several kinds of correlations. First, we relate free energies, $\Delta G^{\ominus}_{\mathrm{p}}$, and enthalpies of protonation, $\Delta H^{\ominus}_{\mathrm{p}}$, in each solvent in turn. Secondly, we examine the relationship between the same parameter in $\mathrm{Me_2SO}$ and water, i.e. between $\mathrm{p}K_{\mathrm{as}}$ and $\mathrm{p}K_{\mathrm{aw}}$, and $\Delta H^{\ominus}_{\mathrm{ps}}$ and $\Delta H^{\ominus}_{\mathrm{pw}}$. Finally, we look for correlations between protonation data in the gas phase and in solution.

Free energies and enthalpies of protonation in Me$_2$*SO and water*

We have plotted in Figs. 1 and 2 the free energy of protonation, $\Delta G^{\ominus}_{\mathrm{p}} = RT \ln K_{\mathrm{a}}$, against the enthalpy of protonation in $\mathrm{Me_2SO}$ and in water respectively. The corresponding correlation equations are

$$\Delta G^{\ominus}_{\mathrm{ps}} = (1.05 \pm 0.08)\Delta H^{\ominus}_{\mathrm{ps}} + (6.8 \pm 2.5) \qquad n = 16,\ r = 0.960 \tag{7}$$

$$\Delta G^{\ominus}_{\mathrm{pw}} = (0.98 \pm 0.07)\Delta H^{\ominus}_{\mathrm{pw}} - (4.7 \pm 1.8) \qquad n = 17,\ r = 0.962 \tag{8}$$

Surprisingly, the correlation lines are nearly of unit slope. This is in part due to the relatively small contribution of the $T\Delta S^{\ominus}_{\mathrm{p}}$ term to $\Delta G^{\ominus}_{\mathrm{p}}$. However, the iso-entropic behaviour ($\Delta S^{\ominus}_{\mathrm{ps}} = -23 \pm 9$ J mol^{-1} K^{-1}, $\Delta S^{\ominus}_{\mathrm{pw}} = +16 \pm 7$ J mol^{-1} K^{-1}) is only apparent because the points which do not fall on the lines, fall well outside the limit of experimental errors. Actually, data in Table 2 show that some bases have $\Delta S^{\ominus}_{\mathrm{pw}}$ values which are quite different

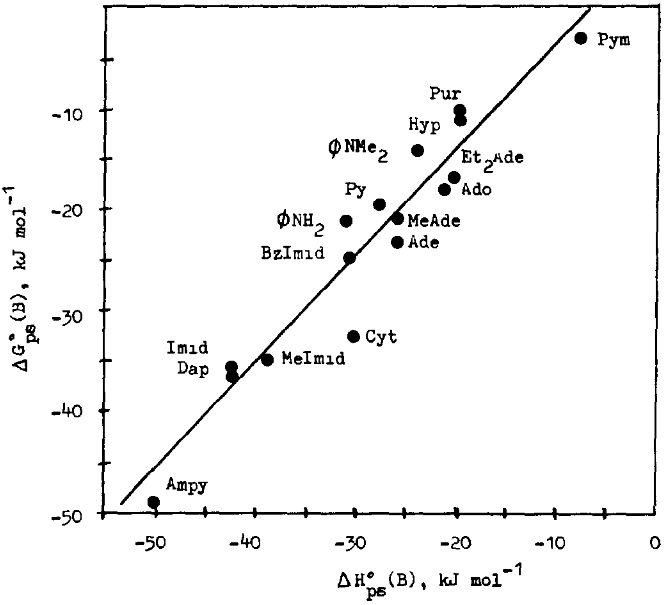


Fig 1 Free energies and enthalpies of protonation in Me_2SO at 25 °C

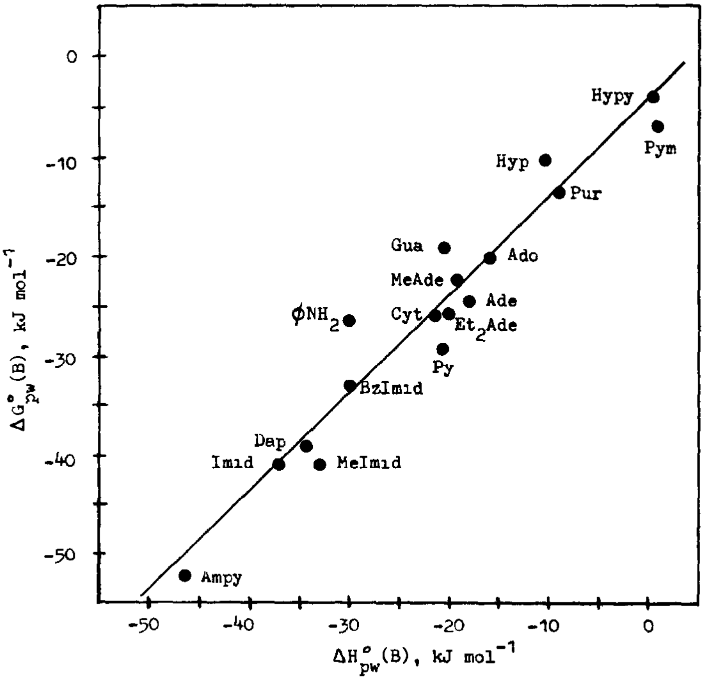


Fig 2 Free energies and enthalpies of protonation in water at 25 °C

from $+16 \pm 7$ J mol^{-1} K^{-1}, the two hydroxypurines Hyp and guanine (Gua) are examples. It is not clear why Cyt (a hydroxypyrimidine) has an unusual $\Delta S^{\ominus}_{pw}$ value but a normal $\Delta S^{\ominus}_{ps}$ value. It seems that the bases that we are considering are structurally too different to expect a better $\Delta G^{\ominus}_{p}$–$\Delta H^{\ominus}_{p}$ correlation, such as that observed in water for eleven 3- and 4-substituted pyridines, with a slope of 1.19 and $r = 0.996$ [29].

Correlation between ionization constants and protonation enthalpies in Me_2SO and water

Attempts to improve the correlation between ionization constants in Me_2SO and water, for all BH^+ conjugate acids, led us to consider different groups of bases separately. First, with the purines, pyrimidines and their derivatives, we have

$$pK_{as} = (0.95 \pm 0.05)pK_{aw} - (0.4 \pm 0.3) \qquad n = 11,\ r = 0.988 \qquad (9)$$

The bases are thus slightly less basic in Me_2SO than in water, although pyridine (Py) and Et_2Ade exhibit larger changes.

Xan, Hyp, Gua and Cyt which are tautomerized hydroxypurines and pyrimidines are better correlated through

$$pK_{as} = (1.39 \pm 0.05)pK_{aw} - (0.7 \pm 0.2) \qquad n = 4,\ r = 0.998 \qquad (10)$$

which accounts for the fact that these bases are now stronger in Me_2SO than in water.

Turning now to the protonation enthalpies, $\Delta H^{\ominus}_{ps}$ is plotted against $\Delta H^{\ominus}_{pw}$ in Fig. 3. The corresponding correlation equation which holds over a range of some 45 kJ mol^{-1} is

$$\Delta H_{ps} = (0.91 \pm 0.03)\Delta H_{pw} - (9.4 \pm 0.9) \qquad n = 12,\ r = 0.993 \qquad (11)$$

Thus the poorer correlation (eqn. (9)) obtained for the free energies (pK_a) is due to entropic factors. This time Hyp, Cyt and Py are also on the correlation line while Et_2Ade is not, but compounds with the *para*-diethylamino group are often excluded from such correlations [30]. This leaves us with only benzimidazole (BzImid) remaining well off the line.

The nearly constant difference between $\Delta H^{\ominus}_{ps}$ and $\Delta H^{\ominus}_{pw}$ (eqn. (11)) has an interesting consequence in that eqn. (6) indicates that there should be a nearly constant difference between the enthalpies of transfer of BH^+ and B. Using data for $\Delta H^{\ominus}_{ws}(BH^+)$ and $\Delta H^{\ominus}_{ws}(B)$ in Table 4, we have the following relation which covers a range of 42 kJ mol^{-1} for $\Delta H^{\ominus}_{ws}(B)$ [6]

$$\Delta H^{\ominus}_{ws}(BH^+) = (0.99 \pm 0.04)\Delta H^{\ominus}_{ws}(B) - (32.9 \pm 0.7) \qquad n = 12\ r = 0.991 \qquad (12)$$

This is a somewhat unexpected result since it means that irrespective of the nature of B, whether imidazole, pyridine, pyrimidine, or purine, the

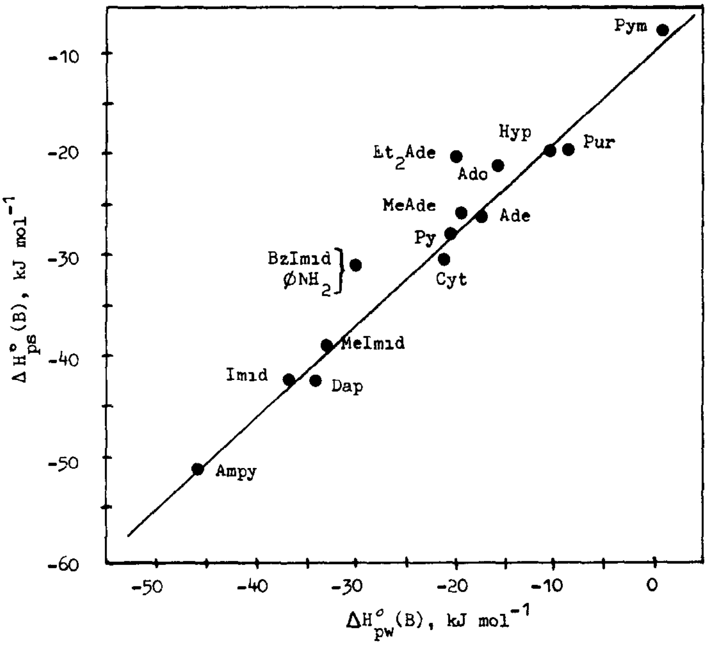


Fig 3 Correlation between protonation enthalpies in Me_2SO and water at 25 °C

addition of an H^+ on B makes the transfer of BH^+ some 33 kJ mol^{-1} more exothermic than the transfer of B Clearly this extra 33 kJ mol^{-1} exothermicity is essentially due to stronger H-bonding of BH^+ to more basic Me_2SO if we consider (i) that the electrostatic contribution to the transfer of BH^+ as calculated from the Born equation is small and of opposite sign [31] (~ 3 kJ mol^{-1} if the BH^+ ionic radius is taken as 2 5 Å) and (ii) that B is a good neutral analogue of BH^+ for cavity and related effects The 33 kJ mol^{-1} value is limited to the bases we have considered Data for two tertiary aliphatic amines, Me_3N [3] and DABCO [2], leads to a higher 48 kJ mol^{-1} extra stabilization for the transfer of BH^+ over that of B Nevertheless, since our heterocyclic nitrogen bases cannot be viewed as forming a very homogeneous series, the relation between $\Delta H^{\ominus}_{ws}(BH^+)$ and $\Delta H^{\ominus}_{ws}(B)$ expressed by eqn (6) remains puzzling, particularly since it involves transfers between water and Me_2SO, two structurally dissimilar solvents Our work in progress suggests that similar correlations are found for transfers between pairs of non-aqueous solvents

Correlation between protonation data in the gas phase and in solution

Correlations have often been established between gas-phase proton affinities and protonation enthalpies in solution, or pK_a, for series of related bases For example, with 3- and 4-substituted pyridines, but with "chem-

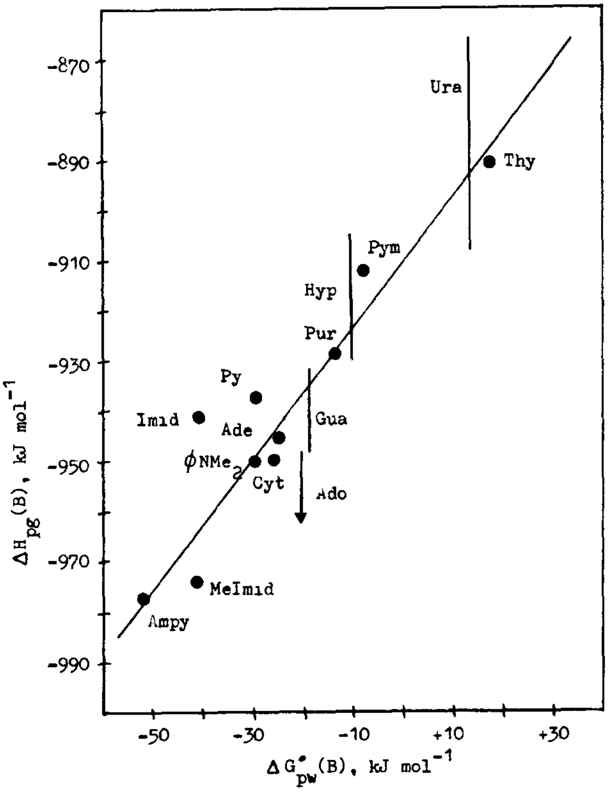


Fig 4 Correlation between protonation enthalpies in gas phase and aqueous free energies of protonation at 25° C

ically inert substituents", there is a good linear relationship between ΔH_{pg} and $\Delta H^{\ominus}_{pw}$ with a slope of 2 5 [32] We have plotted the $\Delta H_{pg}(B)$ of our bases against both their pK_a (Fig 4) and protonation enthalpies in water (because there are more data available than for the protonation in Me_2SO) The corresponding correlation equations are

$$\Delta H_{pg} = (1\ 32 \pm 0\ 13)\Delta G^{\ominus}_{pw} - (910 \pm 4) \qquad n = 9,\ r = 0\ 970 \qquad (13)$$

$$\Delta H_{pg} = (1\ 47 \pm 0\ 19)\Delta H^{\ominus}_{pw} - (916 \pm 5) \qquad n = 7,\ r = 0\ 961 \qquad (14)$$

Although these linear correlations are only fair, this is not very surprising when we consider, in particular, the diversity of H-bonding properties of our polyfunctional bases and the fact that, even with the well-behaved pyridine bases mentioned above, the data for pyridines with H-bonding substituents are eliminated from the correlation [32] Our correlation equations (eqns (13) and (14)) are of real value for predicting unknown proton affinities of bases related to our series and also for assessing the validity of some reported PA values and of some results of MO calculations For example, the quoted PA value for imidazole (Imid), 941 kJ mol^{-1}, appears to be erroneous, while some MO values for Cyt (-1043 kJ mol^{-1} [27] and -862 kJ mol^{-1} [26]) and Ade (-1009 kJ mol^{-1} [27]), which are already at odds with the experimental PA data, are definitively out of line

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