# Base Strengths of Substituted Tritylamines, *N*-Alkylanilines, and Tribenzylamine in Aqueous Solution and the Gas Phase: Steric Effects Upon Solvation and Resonance Interactions

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The dissociation constants of the conjugate acids of *N*-tritylacetamide (**1h**; $pK_{BH^+}$ = 3.81) and *N*-benzyl-*N*-methyl-4,4′,4′′-trimethoxytritylamine (**4i**; $pK_{BH^+}$ = 9.86) have been measured in aqueous acetonitrile at 25 °C and at other temperatures to determine the enthalpies and entropies of reaction. For **1h**, $\Delta H^{\ominus}$ = 40.7 kJ·mol$^{-1}$ and $\Delta S^{\ominus}$ = 64 J·K$^{-1}$·mol$^{-1}$, and for **4i** $\Delta H^{\ominus}$ = 9.1 kJ·mol$^{-1}$ and $\Delta S^{\ominus}$ = −159 J·K$^{-1}$·mol$^{-1}$. In addition, gas-phase base strengths at 25 °C (*GB* values in kJ·mol$^{-1}$) of $TrNH_2$ (**1a**; 902.1), TrNHPh (**1c**; 926.3), TrNHAc (**1h**; 929.7), $TrNHC_6H_4(o\text{-}NO_2)$ (**1i**; 895.0), $DMTrNH_2$ (**3a**; 921.3), $DMTrNHCH_2CO_2Me$ (**3b**; 879.1), and $DMTrNH(p\text{-}NO_2Bn)$ (**3d**; 886.6) have been determined by ICR measurements. The *GB* of TrNHAc corresponds to protonation at oxygen and B3LYP/6-31G* calculations indicate that the *N*-protonated isomer is 46.4 kJ·mol$^{-1}$ less stable, i.e. the *GB* value for *N*-protonation is 883.3 kJ·mol$^{-1}$. Correspondingly, the literature *GB* value of 857.6 5 kJ·mol$^{-1}$ for *N*-methylacetamide corresponds to protonation at oxygen, and B3LYP/6-31G* calculations indicate that the *N*-protonated isomer is 58.1 kJ·mol$^{-1}$ less stable, i.e. the *GB* value for *N*-protonation of MeNHAc is 799.5 kJ·mol$^{-1}$. The *GB* of PhNH(*t*Bu) (**5**; 920.1 kJ·mol$^{-1}$) has been measured and compared with values for other *N*-alkylanilines, PhNHR, including PhNHTr; the results indicate that the increasing *GB* values as R increases in size are due solely to the increasing polarisability of R. This indicates that the increasing solution base strength of PhNHR as R increases in size is a solvation effect and is not due to decreasing resonance interactions between the nitrogen lone-pair and the phenyl ring. Similarly, the base-strengthening effect in solution of the (substituted) trityl in TrNHZ, where Z is an alkyl with an electron-withdrawing group, is shown to be due to solvation phenomena as it is absent in the gas phase; for one such compound, $TMTrNHCH_2CO_2Me$ (**4b**; $pK_{BH^+}$ = 9.30), $\Delta H^{\ominus}$ = 17.9 kJ·mol$^{-1}$ and $\Delta S^{\ominus}$ = −118 J·K$^{-1}$·mol$^{-1}$. In contrast, the difference in solution base strengths between MeNHAc ($pK_{BH^+}$ = −0.56) and TrNHAc ($pK_{BH^+}$ = 3.81) is attributed, at least in part, to a reduced base-weakening resonance interaction between the lone pair on N and the acetyl group in TrNHAc, as the effect is also evident in the gas phase. The *GB* value for tribenzylamine (**6**) has also been measured (965.2 kJ·mol$^{-1}$) and is unexceptional; this indicates that the low base strength of **6** in aqueous solution ($pK_{BH^+}$ = 4.90 at 25 °C) is a solvation effect which is expressed mainly through an abnormally large positive entropy of reaction ($\Delta S^{\ominus}$ = 76 J·K$^{-1}$·mol$^{-1}$), the value of $\Delta H^{\ominus}$ (50.5 kJ·mol$^{-1}$) being only slightly larger than normal for tertiary amines.



## Introduction

The trityl group (triphenylmethyl, Tr) and its methoxy-substituted analogues [4-monomethoxy- (MMTr), 4,4′-dimethoxy- (DMTr), and 4,4′,4′′-trimethoxytrityl (TMTr); Figure 1] have been widely used in synthesis as protecting groups for hydroxyl and amino functions.[1] We have reported previously that (substituted) tritylamines under acidic conditions, where they are present as the corresponding (substituted) tritylammonium cations, undergo deamination reactions, and that these are specific acid catalysed.[2,3] This was an exceptional finding as the tritylammonium cation has no basic site at the reaction centre to accept a proton, and a mechanism involving intermediate ion-molecule pairs was proposed. Methoxy substituents at the *para* positions of the phenyl groups are, as expected, rate enhancing, and these rate effects are observed in both the catalysed and uncatalysed reaction channels. Remarkably, however, R substituents on the nitrogen have much more dramatic effects upon the deamination rate constants, and these effects

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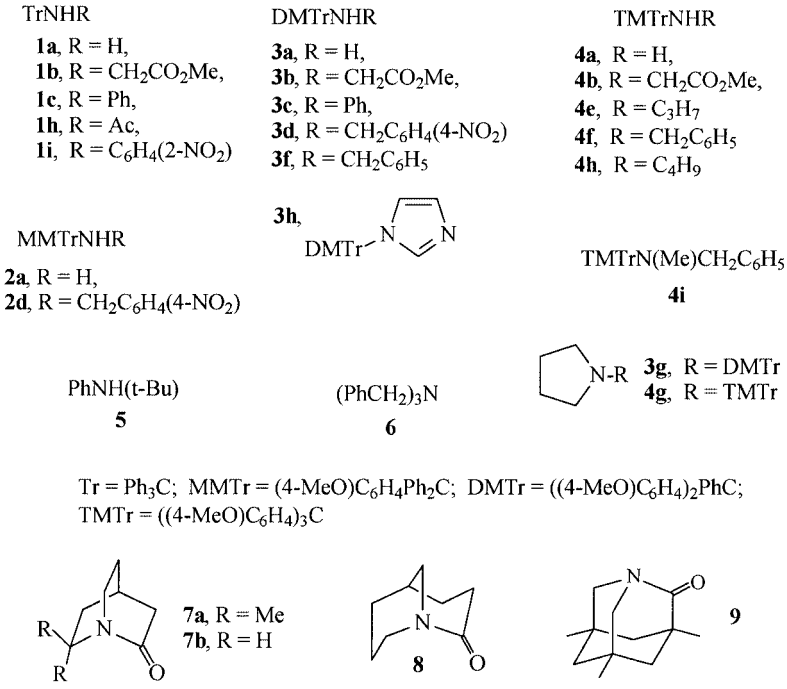


Figure 1. Structures of substituted amines used as protection

are not very sensitive to the nature of R.[4] In addition to these kinetic effects, we have also observed unexpected base strengths in a range of substituted tritylamines.[5] For example, *N*-tritylarylamines are strong bases like alkylamines rather than weak bases like arylamines, and substituents in the aromatic ring of the arylamine have very little effect upon the base strength. We speculated whether the base strength of a substituted *N*-tritylalkylamine was directly related to the rate constants for its deamination, but this appears not to be the case.[4] Nevertheless, it seems improbable that, for example, there is no connection at all between the large rate enhancements in the deaminations of *N*-tritylarylamines and their unusually high base strengths, both being characteristic of the same structural features. We have now taken a step back to investigate whether the anomalously high base strengths of some substituted tritylamines are due to intrinsic steric or electronic molecular effects, or peculiarities arising out of aqueous solvation phenomena.[6]

We also became aware of the anomalously low base strength in aqueous solution of tribenzylamine $Bn_3N$ ($pK_{BH^+} \approx 5$ compared with values of about 10 for typical trialkylamines).[7,8] Here also, we sought to establish whether this anomaly is an intrinsic molecular effect (steric or electronic) or due to aqueous solvation phenomena (whilst acknowledging that solvation itself is subject to steric constraints).[6,9,10] For selected substituted tritylamines and related compounds, and for tribenzylamine, therefore, we have measured base strengths in the gas phase for comparison with results in solution. And, to establish whether unusual base strengths in solution are entropy or enthalpy effects, we have measured equilibrium constants for some proton-transfer equilibria at different temperatures.

The modern measure of base strength in aqueous solution is the $pK_{BH^+}$, i.e. the $pK_A$ of the conjugate acid of the base, and this may be related by a familiar thermodynamic relationship to the standard molar free energy, $\Delta G^{\ominus}$, for the proton transfer reaction between the protonated base and water (the solvent), usually at 298 K [Equation (1)].[11,12]

$$BH^+ + H_2O \rightleftarrows B + H_3O^+; \Delta G^{\ominus} \quad (1)$$
$$\Delta G^{\ominus} = -RT\cdot\ln K_A; K_A \text{ of } BH^+ = K_{BH^+} \text{ of B}; \Delta G^{\ominus} = 2.303\ RT\cdot pK_{BH^+}$$

In the gas phase, however, base strengths are conventionally expressed as *GB* values where *GB* is the negative of the free energy of reaction between the base and proton; i.e. it is the free energy of deprotonation of the conjugate acid of the base in the gas phase, usually at 298 K, and values are always positive.[10,13]

$$BH^+ \rightleftarrows B + H^+; \Delta G^{\circ} = GB \text{ of B} \quad (2)$$

Direct comparison between gas phase and solution is further complicated by the conventions that in the gas phase the standard state is the pure gas at 1 atm (and the thermochemical standard state superscript is used) whereas in solution an activity of 1 mol·dm$^{-3}$ is usually more convenient for solutes and mol fraction of unity for the solvent (and the defined standard state superscript is used). Occasionally, the molal scale is used for solutions but, for dilute aqueous solutions at 25 °C, the numerical difference between molal and molar values is minute.[14] In this report, we are comparing *differential* effects within the gas phase with *differential* effects in solution, rather than making di-

  

rect comparisons of *absolute* base-strength values in the two phases; consequently, there is no need to convert reactions in the two phases to a common standard state. However, it is occasionally convenient to convert solution $pK_{BH^+}$ values into standard free energies, and these are referred to as *SB* values, where $SB = \Delta G^{\ominus}$ [Equation (1)]; so, *SB* is the standard molar free energy for proton transfer from the protonated base to water in aqueous solution, usually at 25 °C, the standard state for solutes being an activity of 1 mol·dm$^{-3}$, and values are positive for bases stronger than water.

It is well-known that the dissociation of some acids in solution is dominated by entropy effects; for example, for a wide range of polar-substituted carboxylic acids $\Delta H^{\ominus} \approx 0$ and substituent effects are due to changes in the strongly negative $\Delta S^{\ominus}$.[12] In the case of sterically hindered alkyl-substituted carboxylic acids, however, small changes in acid strength are due to complex entropic and enthalpic solvation effects for both the neutral acid and its conjugate base, the anion.[15] For dissociation of protonated amines, $\Delta H^{\ominus}$ values are usually moderately positive (typically 40−50 kJ·mol$^{-1}$), but $\Delta S^{\ominus}$ values may vary widely (though most are negative in the range −5 to −30 J·K$^{-1}$·mol$^{-1}$).[8] In order to identify causes of particular effects in some of the present cases, we have measured p*K* values at different temperatures in order to resolve *SB* values [$\Delta G^{\ominus}$, Equation (1)] into $\Delta H^{\ominus}$ and $\Delta S^{\ominus}$ components. In contrast, structural effects upon gas-phase base strengths are invariably energy (enthalpy) effects, and it is seldom necessary to resolve the *GB* term [$\Delta G°$, Equation (2)] into the proton affinity (PA) and the entropy of proton transfer.[13]

## Results and Discussion

### Preparations and Methods

Most amines were available from our previous studies;[2−5] additionally, *N*-*tert*-butylaniline (**5**) and *N*-tritylacetamide (**1h**) were prepared by methods based upon literature descriptions,[16,17] and their spectral and other properties were in agreement with assigned structures.[16−19] The new compound *N*-(4,4′-dimethoxytrityl)imidazole (**3h**) was also prepared in the obvious way from imidazole and dimethoxytrityl tetrafluoroborate.[4] Our methods for base-strength measurements in solution have already been described and require no further comment.[4,5] Our gas-phase measurements followed conventional ICR (Ion Cyclotron Resonance) practice,[20] and aspects of the method have already been described.[21] The *GB* values of amides have been calculated at the B3LYP/6-31G* level of theory using the Gaussian 98 program suite to obtain separate values for protonation at nitrogen and at oxygen.[22] Our computed result for protonation of *N*-methylacetamide at oxygen (867.5 kJ·mol$^{-1}$) is in satisfactory agreement with the literature experimental *GB* value (857.6 kJ·mol$^{-1}$). Experimental results for substituted tritylamines are given in Table 1, and in Table 2 for other compounds; computational results are given below these tables.

### Base Strengths of Substituted Tritylamines

Simple alkylamines have $pK_{BH^+}$ values in the region of 9−11.[8,11,14] The results in Table 1 for the base strengths of $TrNH_2$ (**1a**), $MMTrNH_2$ (**2a**), $DMTrNH_2$ (**3a**), and $TMTrNH_2$ (**4a**) in aqueous solution containing acetonitrile confirm that: (i) all are typical values for simple alkylamines, (ii) the modest differences between the solvent compositions have minimal effect, and (iii) the methoxy substituents have no appreciable effect. In contrast, *GB* values for simple primary amines, $RNH_2$, increase from the value for methylamine with increasing molecular weight (Table 2). If we consider the sequence of primary amines $RNH_2$ for R = Me, Et, *n*Pr, *n*Bu, Bn, cyclohexyl, and *n*-$C_{10}H_{21}NH_2$, i.e. an arbitrary sequence of primary amines with hydrocarbon residues of increasing molecular weight, an upper limit for *GB* of about 900 kJ·mol$^{-1}$ is indicated (Table 2).[13] That this is largely a polarisability effect is indicated by the ap-

Table 1. Base strengths of substituted tritylamines in aqueous acetonitrile and in the gas phase[a]

| Base | $pK_{BH^+}$ (% $CH_3CN$) | *GB* (kJ·mol$^{-1}$) |
|---|---|---|
| $TrNH_2$ (**1a**) | 9.2(16)[b] 25 °C | 902.1 |
| $TrNHCH_2CO_2Me$ (**1b**) | 10.1(22)[c] | – |
| TrNHPh (**1c**) | – | 926.3 |
| TrNHAc (**1h**) | 3.81(37)[d] 25 °C | 929.7[e] |
| $TrNHC_6H_4(2\text{-}NO_2)$ (**1i**) | – | 895.0[f] |
| $MMTrNH_2$ (**2a**) | 9.3(10)[c] | – |
| $MMTrNH(p\text{-}NO_2Bn)$ (**2d**) | 10.5(38)[c] | – |
| $DMTrNH_2$ (**3a**) | 9.5(28)[b] | 921.3 |
| $DMTrNHCH_2CO_2Me$ (**3b**) | 9.7(21)[c] | 879.1 |
| DMTrNHPh (**3c**) | 8.9(39)[c] | – |
| $DMTrNH(p\text{-}NO_2Bn)$ (**3d**) | – | 886.6 |
| DMTrNHBn (**3f**) | 9.9(30)[g] | – |
| *N*-DMTr-pyrrolidine (**3g**) | 8.7(21)[c] | – |
| *N*-DMTr-imidazole (**3h**) | 7.5 (37)[h] 25 °C | – |
| $TMTrNH_2$ (**4a**) | 9.3(26)[b] | – |
| $TMTrNHCH_2CO_2Me$ (**4b**) | 9.30(15)[i] 25 °C | – |
| $TMTrNHC_3H_7$ (**4e**) | 9.7(26)[b] | – |
| TMTrNHBn (**4f**) | 9.4(32)[b] 25 °C | – |
| *N*-TMTr-pyrrolidine (**4g**) | 8.2(21)[c] | – |
| $TMTrNHC_4H_9$ (**4h**) | 9.7(21)[c] 22 °C | – |
| TMTrN(Me)Bn (**4i**) | 9.86(20)[j] 25 °C | – |

[a] $pK_{BH^+}$ values of the bases, i.e. the $pK_A$ values of the conjugate acids, were measured in acetonitrile/water solution at 21 °C, ionic strength ($NaClO_4$) = 1 mol·dm$^{-3}$ unless otherwise indicated; the volume % of acetonitrile is given in brackets. *GB* values are at 298 K. [b] Ref.[5] [c] Ref.[4] [d] Present work. $\Delta H^{\ominus}$ = 40.7 kJ·mol$^{-1}$ and $\Delta S^{\ominus}$ = 64 J·K$^{-1}$·mol$^{-1}$. [e] Corresponds to protonation at oxygen; B3LYP/6-31G* calculations indicate that the *N*-protonated isomer is 46.4 kJ·mol$^{-1}$ less stable, i.e. *GB* = 883.3 kJ·mol$^{-1}$ for *N*-protonation. [f] Corresponds to protonation at the amino nitrogen; B3LYP/6-31G* calculations indicate that the *O*-protonated isomer is 23.0 kJ·mol$^{-1}$ less stable, i.e. *GB* = 872.0 kJ·mol$^{-1}$ for protonation at an oxygen of the nitro group. [g] Ref.[3] [h] Approximate value. [i] Present work. $\Delta H^{\ominus}$ = 17.9 kJ·mol$^{-1}$ and $\Delta S^{\ominus}$ = −118 J·K$^{-1}$·mol$^{-1}$. [j] Present work. $\Delta H^{\ominus}$ = 9.1 kJ·mol$^{-1}$ and $\Delta S^{\ominus}$ = −159 J·K$^{-1}$·mol$^{-1}$.

  

Table 2. Base strengths of other amines in aqueous solution and in the gas phase[a]

| Base | $pK_{BH^+}$ | *GB* ($kJ \cdot mol^{-1}$) |
|---|---|---|
| $MeNH_2$ | 10.65[b] | 864.5 |
| $EtNH_2$ | 10.68[b] | 878.0 |
| $nPrNH_2$ | 10.57[b] | 883.9 |
| $nBuNH_2$ | 10.64[b] | 886.6 |
| $BnNH_2$ | 9.34[c] | 879.4 |
| $tBuNH_2$ | 10.68[c] | 899.9 |
| *cyclo*-$C_6H_{11}NH_2$ | 10.58[b] | 899.6 |
| *n*-$C_{10}H_{21}NH_2$ | ca. 10.6 | 896.5 |
| MeNHAc | −0.56[d] | 857.6[e] |
| $PhNH_2$ | 4.63[f] | 850.6 |
| PhNHMe | 4.85[c] | 890.1 |
| PhNHEt | 5.12[c] | 892.9 |
| PhNH(*i*Pr) | 5.77[c] | – |
| PhNH(*t*Bu) (**5**) | 7.0[g] | 920.1 |
| $Me_3N$ | 9.80[b] | 918.1 |
| $Et_3N$ | 10.72[b] | 951 |
| *n*-$Pr_3N$ | 10.66[b] | 960.1 |
| $nBu_3N$ | 9.93[b] | 967.6 |
| $Bn_3N$ (**6**) | 4.90[h] | 965.2[i] |

[a] $pK_{BH^+}$ values of the bases are the $pK_A$ values of the corresponding alkylammonium ions; all results are at 298 K. *GB* values are at 298 K and taken from reference 12 except where otherwise indicated. [b] Ref.[14] [c] Ref.[11] [d] $\Delta H^{\ominus} = -2.9\ kJ \cdot mol^{-1}$ and $\Delta S^{\ominus} = 1.3\ J \cdot K^{-1} \cdot mol^{-1}$.[35] [e] Experimental value corresponding to protonation at oxygen (see ref.[13]); our B3LYP/6-31G* calculations give a value of $867.5\ kJ \cdot mol^{-1}$ and indicate that the *N*-protonated isomer is $58.1\ kJ \cdot mol^{-1}$ less stable, i.e. the *GB* value for *N*-protonation, based upon the experimental result for *O*-protonation, is $799.5\ kJ \cdot mol^{-1}$. [f] Ref.[34] [g] Ref.[43] [h] Present work by interpolation from results at other temperatures in 12% acetonitrile/water; $\Delta H^{\ominus} = 50.5\ kJ \cdot mol^{-1}$ and $\Delta S^{\ominus} = 76\ J \cdot K^{-1} \cdot mol^{-1}$; see also ref.[7] [i] Present work.

preciably larger value for *tert*-butylamine ($899.9\ kJ \cdot mol^{-1}$) than for *n*-butylamine ($886.6\ kJ \cdot mol^{-1}$). We appear to be observing, therefore, the asymptotic value for the *GB* of alkylamines, $RNH_2$, with $TrNH_2$ (*GB* = $902.1\ kJ \cdot mol^{-1}$) and it seems unlikely that the difference between this value and the appreciably higher result for $DMTrNH_2$ (*GB* = $921.3\ kJ \cdot mol^{-1}$) is due simply to the changed molecular weight/polarisibility attributable to the addition of two methoxy substituents. More likely, the induced positive charge at the carbon to which the protonated nitrogen is bonded in the conjugate acid is stabilised by delocalisation of electron density from the two *para*-methoxy substituents. This is entirely compatible with our report that protonation of the nitrogen of the parent tritylamine leads to elongation of the C−N bond and some planarisation of the central carbon;[4] it represents a mixing of resonance and polarisation electronic effects normally regarded as separate. On this basis, we predict that $TMTrNH_2$ will have a slightly larger *GB* value, and that the result for $MMTrNH_2$ will lie between those for $TrNH_2$ and $DMTrNH_2$.

From a consideration of intrinsic molecular properties alone, addition of an inductively electron-withdrawing alkyl substituent onto the nitrogen of a tritylamine would be expected to reduce the gas-phase base strength, even though the molecular weight is increased. In agreement with this expectation, *GB* values for DMTrNH(*p*-$NO_2$Bn) (**3d**) and $DMTrNHCH_2CO_2Me$ (**3b**) are 886.6 and 879.1 $kJ \cdot mol^{-1}$ compared with 921.3 $kJ \cdot mol^{-1}$ for $DMTrNH_2$ (**3a**; Table 1). This effect is not observed in aqueous solution, however, where $TrNHCH_2CO_2Me$ (**1b**), MMTrNH(*p*-$NO_2$Bn) (**2d**), $DMTrNHCH_2CO_2Me$ (**3b**), and $TMTrNHCH_2CO_2Me$ (**4b**) are all strong bases ($pK_{BH^+}$ values of 10.1, 10.5, 9.7, and 9.3, respectively; Table 1), comparable with DMTrNHBn (**3f**), $TMTrNHC_3H_7$ (**4e**), $TMTrNHC_4H_9$ (**4h**), and TMTrNHBn (**4f**) ($pK_{BH^+}$ values of 9.9, 9.7, 9.7, and 9.4, respectively; Table 1). Looked at the other way round, $NH_2CH_2CO_2Me$ ($pK_{BH^+} = 6.84-7.59$ depending upon the experimental conditions)[8,23] and *p*-$NO_2BnNH_2$ ($pK_{BH^+} = 8.50$)[24] are both weaker bases than simple alkylamines in water on account of the electron-withdrawing effects of the methoxycarbonyl and the nitrophenyl groups, but addition of the trityl appears to cancel these inductive base-weakening effects in solution. In other words, introduction of the sterically demanding *N*-Tr group increases the base strengths of $NH_2CH_2CO_2Me$ and *p*-$NO_2BnNH_2$ in solution. This is unlikely to be a molecular strain effect as this is invariably base-weakening for monoamines.[25] The effect is parallel with, though larger than, increased steric hindrance enhancing the base strength of alkyl-substituted carboxylate and (in methanol) phenolate anions,[15,26] bases of a different charge type, where the effect was attributed to steric hindrance of solvation of the (anionic) bases. In contrast, increased steric hindrance leads to reduced solution base strength in ketones,[27] pyridines,[28] piperidines,[29] and anilines,[30] where the effect has been attributed to steric hindrance of solvation of the (cationic) conjugate acid, though it may be expressed through either the enthalpy or the entropy of dissociation. There is clearly an unresolved paradox here: in some cases increased steric hindrance leads to enhanced base strength, and in others to reduced base strength.

For **4b**, a representative member of this group of compounds of enhanced base strength through steric hindrance, the $pK_{BH^+}$ was measured at different temperatures to give $\Delta H^{\ominus} = 17.9\ kJ \cdot mol^{-1}$ and $\Delta S^{\ominus} = -118\ J \cdot K^{-1} \cdot mol^{-1}$ for the reaction of Equation (1). These results are broadly similar to those for TMTrN(Me)Bn (**4i**, Table 1), which has a similar $pK_{BH^+}$ at 25 °C, but characteristically different from results for simple secondary amines of similar base strength where $\Delta H^{\ominus}$ is typically about $50-60\ kJ \cdot mol^{-1}$ and $\Delta S^{\ominus} = -12$ to $-30\ J \cdot K^{-1} \cdot mol^{-1}$.[8] The relatively low positive enthalpy and large negative entropy of reaction are compatible with a greater increase in solvation for Equation (1) with base **4b** than with simpler analogues of similarly high base strength. So, compared with more typical amines, B, **4b** (like **4i**) must be unusually strongly solvated or its protonated form, $BH^+$, unusually weakly solvated.

### Base Strengths of *N*-Alkylanilines PhNHR

Arylamines are generally weaker bases in water than alkylamines and this is ascribed to the delocalisation of the lone pair on nitrogen into the arene ring, i.e. a resonance effect. However, for *N*-alkylanilines, PhNHR, the base

  

strength increases from $pK_{BH^+}$ = 4.63 for aniline through $pK_{BH^+}$ = 4.85, 5.12, 5.77, 7.0, and 8.9 (corresponding to a range of 23.1 kJ·mol$^{-1}$ in *SB* values) as R increases from R = Me, Et, *i*Pr, *t*Bu, to DMTr (Tables 1 and 2), and PhNHDMTr is virtually as strong a base as a simple alkylamine. We suggested previously that the increasing steric bulk of R increasingly inhibits the delocalisation of the lone pair from nitrogen into the benzene ring,[4] a previously identified phenomenon,[30] in which case the same trend should be observed in the gas phase. For aniline, *GB* is only 850.6 kJ·mol$^{-1}$ compared with 899.6 for cyclohexylamine, a primary alkylamine of similar molecular weight but without the resonance possibility, and the *GB* then increases along the series 890.1, 892.9, and 920.1, to 926.3 for PhNHR for R = Me, Et, *t*Bu, and Tr (Tables 1 and 2). However, this increase in *GB* (36.2 kJ·mol$^{-1}$) with increasing size of R in PhNHR is only about the same as the increase in *GB* along the series $RNH_2$ for R = Me, Et, *n*Pr, *n*Bu, cyclohexyl, and Tr (37.6 kJ·mol$^{-1}$) which can only be due to the increasing polarisability of R. It appears, therefore, that there is no evidence of an attenuation of the base-weakening resonance effect in PhNHR in the gas phase as R increases in size from Me to trityl. In accord with this interpretation, introduction of an *ortho*-nitro substituent into *N*-tritylaniline (**1c**) to give **1i** causes an appreciable reduction in *GB* from 926.3 to 895.0 kJ·mol$^{-1}$ (Table 1).[31] The effect in solution, therefore, must be a sterically induced solvation phenomenon. And, here again, it is base-strengthening, as for alkyl-substituted carboxylate and (in methanol) phenolate anions,[15,26] rather than base-weakening as in ketones,[27] pyridines,[28] piperidines,[29] and ring-alkylated anilines.[30]

### Base Strengths of *N*-Acetylamines

The base strengths of amines in solution are generally much reduced by acetylation, and the site of protonation is usually oxygen rather than nitrogen.[32] For example, $pK_{BH^+}$ = 0.61 for acetanilide compared with 4.63 for aniline ($\delta SB$ = 22.9 kJ·mol$^{-1}$),[33,34] and −0.56 for *N*-methylacetamide compared with 10.65 for methylamine ($\delta SB$ = 64.0 kJ·mol$^{-1}$).[35,14] In line with our observations above, *N*-tritylacetamide ($pK_{BH^+}$ = 3.81, Table 1) is not as weak a base as *N*-methylacetamide, but is still much weaker than tritylamine ($pK_{BH^+}$ = 9.2). It compares with, and supports, the result ($pK_{BH^+}$ = 5.3) estimated by Pracejus for 6,6-dimethyl-1-azabicyclo[2,2,2]octan-2-one (**7a**), an amide whose bicyclic structure prevents appreciable resonance between the nitrogen and the carbonyl.[36] This difference of 4.37 in $pK_{BH^+}$ values between *N*-tritylacetamide and *N*-methylacetamide corresponds to $\delta SB$ = 24.9 kJ·mol$^{-1}$, and makes *N*-tritylacetamide one of the strongest carbonyl bases known (assuming protonation is at the oxygen rather than at the nitrogen).[37] We found that $\Delta H^{\ominus}$ = 40.7 kJ·mol$^{-1}$ for *N*-tritylacetamide in Equation (1) (see also footnote d to Table 1), a result not dissimilar from values for much more strongly basic amines,[8] and it is only the substantially positive $\Delta S^{\ominus}$ value of 64 J·K$^{-1}$·mol$^{-1}$ [corresponding to desolvation in Equation (1)] which leads to *N*-tritylacetamide being less basic than a simple amine. Thermochemical data for proton-transfer reactions of amides in solution are sparse, however, and results in water have to be obtained indirectly, for example by acidity function techniques in concentrated acids. For three substituted benzamides, Ar-$CONH_2$, which have typically low $pK_{BH^+}$ values of −1.54 to −2.49 in water at 25 °C, $\Delta H^{\ominus}$ = −1 to −4 kJ·mol$^{-1}$ and $\Delta S^{\ominus}$ = 25−36 J·K$^{-1}$·mol$^{-1}$.[38] For a range of acylated methylamines, RCONHMe, $\Delta H^{\ominus}$ ranges between 0 and −10.9 kJ·mol$^{-1}$, and $\Delta S^{\ominus}$ between 20.9 and −6.7 J·K$^{-1}$·mol$^{-1}$, with the values for MeNHAc ($pK_{BH^+}$ = −0.56) being $\Delta H^{\ominus}$ = −2.9 kJ·mol$^{-1}$ and $\Delta S^{\ominus}$ = 1.3 J·K$^{-1}$·mol$^{-1}$.[35] It appears, therefore, that the enhanced base strength of *N*-tritylacetamide in solution is expressed both in exceptional enthalpy and entropy terms compared with normal amides.

In the gas phase, as in solution,[32] protonation of amides occurs at oxygen rather than nitrogen (Figure 2). Calculations at the B3LYP/6-31G* level, indicated below Tables 1 and 2, lead to *GB* values for MeNHAc (799.5 kJ·mol$^{-1}$) and TrNHAc (883.3 kJ·mol$^{-1}$) for protonation at nitrogen, i.e. TrNHAc is a stronger gas phase base by 83.8 kJ·mol$^{-1}$. The free-energy diagrams for protonation of TrNHAc and MeNHAc are combined in Figure 3 with superposition of the levels for the two *N*-protonated species for which there can be no resonance in the functional group. If we assume that the difference in *GB* values of 37.6 kJ·mol$^{-1}$ between methylamine and tritylamine is due to the increased polarisability of the alkyl residue on the nitrogen that becomes protonated (see above), and that this may be transferred to other pairs of compounds bearing identical structural

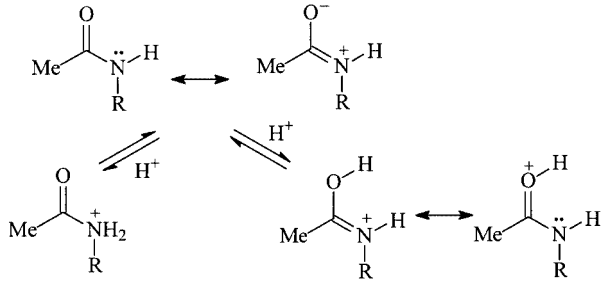

Figure 2. Resonance in acetamides and their conjugate acids

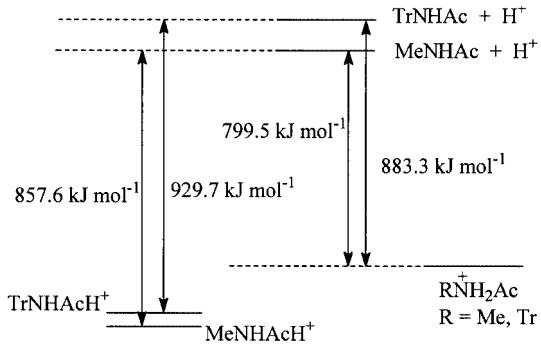


Figure 3. Combined free-energy diagrams for protonation of TrNHAc and MeNHAc in the gas phase

  

features, the higher *GB* value of TrNHAc compared with MeNHAc for *N*-protonation, which is not attributable to the increased alkyl polarisability, drops to 46.2 kJ·mol$^{-1}$. We suggest that this, or an appreciable proportion of it, is the difference in gas-phase base-strength between TrNHAc and MeNHAc for *N*-protonation due to a reduced resonance interaction between the lone pair on nitrogen and the acetyl group in TrNHAc. The resonance energy (RE) in normal amides is about 85 kJ·mol$^{-1}$,[39] so the reduction being proposed here is not more than about 50%. Such a reduction would not be expected to be detectable in the IR stretching vibration of the carbonyl bond as 1-azabicyclo-[3.3.1]nonan-2-one (**8**), whose cage structure leads to a reduction in RE of about 60%, still has an amide carbonyl vibration at 1680 cm$^{-1}$,[40] i.e. within the normal range for a tertiary amide. The value for *N*-tritylacetamide is 1655 cm$^{-1}$, i.e. fairly normal for a secondary amide in accord with a proposed reduction in RE of up to about 50%. In contrast, the CO stretching band for the unstable 1-azabicyclo[2.2.2]octan-2-one (**7b**) and its alkylated derivatives, which have almost no RE, has been estimated to be at 1733 cm$^{-1}$;[39] the experimental value for the stable 1-azaadamantanone (**9**) is 1732 cm$^{-1}$.[41]

A similar analysis for *O*-protonatation is more complicated for two reasons. First, resonance is feasible in both the *O*-protonated and the unprotonated forms; indeed, as it does not involve charge separation, one might expect (in the absence of other effects) a greater degree of resonance in the *O*-protonated form. Secondly, less than 37.6 kJ·mol$^{-1}$ due to the polarisability difference between Me and Tr in amines may be transferable because, in *O*-protonation, the alkyl residue is not now on the atom suffering protonation. We observe that, for *O*-protonation, TrNHAc is more basic than MeNHAc by 72.1 kJ·mol$^{-1}$ (results under Tables 1 and 2, illustrated in Figure 3). It follows, therefore, that, depending upon how much of the 37.6 kJ·mol$^{-1}$ is transferable, the difference in gas-phase base-strength at oxygen between TrNHAc and MeNHAc attributable to reduced resonance stabilisation in the *O*-protonated species lies between 11.7 and 49.3, i.e. between about 12 and 50 kJ·mol$^{-1}$. This resonance effect will contribute towards the base strength of TrNHAc being greater than that of MeNHAc in solution considered above, i.e. $\delta pK_{BH^+} = 4.37$. However, in view of the sterically induced solvation effects identified above for other *N*-tritylamine derivatives, it would be surprising if there were not a similar contribution here also.

### Other Tritylamines

Substituted *N*-trityl tertiary amines [*N*-DMTr-pyrrolidine (**3g**), *N*-TMTr-pyrrolidine (**4g**), and TMTrN(Me)Bn (**4i**)] are comparable in base strength with simple secondary amines and other tertiary amines (Table 1), so addition of an *N*-trityl group to a secondary amine has no base-enhancing effect when the secondary amine is already strongly basic. For TMTrN(Me)Bn, however, the positive $\Delta H^{\ominus}$ is numerically small (9.1 kJ·mol$^{-1}$) and $\Delta S^{\ominus}$ unusually large and negative (−159 J·K$^{-1}$·mol$^{-1}$). So, although $\Delta G^{\ominus}$ ($pK_{BH^+}$) is unexceptional, it is the result of untypical component terms. Experimental difficulties allowed determination of only an approximate result for *N*-(4,4′-dimethoxytrityl)imidazole (**3h**, $pK_{BH^+} = 7.5$, 25 °C, 37% aqueous acetonitrile). The provisional conclusion is that the *N*-trityl group has a minor base-strengthening effect upon imidazole, a base of moderate strength in solution ($pK_{BH^+} = 6.99$ for imidazole),[8] compared with no effect for strongly basic primary and secondary alkylamines, and a large base-strengthening effect for weakly basic arylamines, alkylamines, and acetamide. These matters warrant further exploration since the steric features introduced by the trityl group are the same in all cases.

### Base Strength of Tribenzylamine (6)

The anomalously low base strength of tribenzylamine (**6**) in aqueous solution has been known in the literature for many years ($pK_{BH^+}$ ca. 5 compared with ca. 9 for typical trialkylamines).[7,8,11] It is also known to be a very weak hydrogen-bond acceptor, so weak that the π-systems of the phenyl groups, rather than the lone pair on nitrogen, are the basic site.[42] Our new result of $pK_{BH^+} = 4.90$ at 25 °C in 12% acetonitrile/water confirms the modest solvent effect. We have now measured its base strength in the gas phase for comparison with other trialkylamines. First, we note in Table 2 the increasing base strengths of simple alkylamines, $RNH_2$, with increasing polarizabilty of the R groups (864.5, 878, 883.9, and 886.6 kJ·mol$^{-1}$ for R = Me, Et, *n*Pr, and *n*Bu).[13] The result for benzylamine is 879.4 kJ·mol$^{-1}$, i.e. it lies between $EtNH_2$ and $nPrNH_2$ in base strength in the gas phase. We also observe a gradual increase in base strength with the size of R in simple trialkylamines, $R_3N$ (918.1, 951, 960.1, and 967.6 kJ·mol$^{-1}$ for R = Me, Et, *n*Pr, and *n*Bu). Our result of 965.2 kJ·mol$^{-1}$ for $Bn_3N$ puts it between tripropylamine and tributylamine. It appears that there is nothing exceptional about the base strength of $Bn_3N$ in the gas phase, and the abnormal result in aqueous solution must, therefore, be a solvation effect. By measuring its $pK_{BH^+}$ over the temperature range 7.9 to 45.4 °C, we have determined $\Delta H^{\ominus}$ and $\Delta S^{\ominus}$ for Equation (1) (Figure 4). The

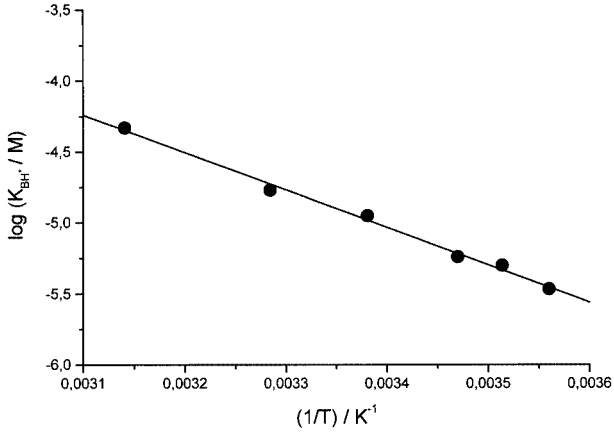


Figure 4. van′t Hoff plot for $pK_{BH^+}$ of tribenzylamine in 12% aqueous acetonitrile

  

substantial positive enthalpy of reaction ($\Delta H^{\ominus}$ = 50.5 kJ·mol$^{-1}$) is typical of results for simple alkylamines, though perhaps slightly large, but the large positive entropy of reaction ($\Delta S^{\ominus}$ = 76 J·K$^{-1}$·mol$^{-1}$) is abnormal; for comparison, $\Delta H^{\ominus}$ = 47.4 and 54.3 kJ·mol$^{-1}$, and $\Delta S^{\ominus}$ = −4 and −3 J·K$^{-1}$·mol$^{-1}$, for dibenzylamine (p$K_{BH^+}$ = 8.52) and benzylamine (p$K_{BH^+}$ = 9.35).[8] Clearly, the large positive entropy of deprotonation of $Bn_3NH^+$ is principally what causes tribenzylamine to be so anomalously weak a base in aqueous solution. This cannot be due to abnormal intrinsic entropic differences between protonated and unprotonated forms otherwise the reduced base strength would also have been seen in the gas phase. We conclude, therefore, that either $Bn_3N$ is exceptionally weakly solvated, or that $Bn_3NH^+$ is unusually strongly solvated, and it is the shedding of solvent molecules in the deprotonation of $Bn_3NH^+$ which causes $\Delta S^{\ominus}$ to be so positive (and, correspondingly, $\Delta H^{\ominus}$ to be somewhat more endothermic) and $Bn_3N$ such a weak base. The evidence that $Bn_3N$ is a very weak hydrogen-bond acceptor suggests that it is the free base which is weakly solvated rather than the conjugate acid which is strongly solvated.[42]

## Experimental Section

***N-tert*-Butylaniline (5):**[16,43] *n*-Butyllithium (Aldrich, 100 mL of a 2.5 mol·dm$^{-3}$ solution in hexanes, 0.25 mol) was added by cannula dropwise to magnetically stirred *tert*-butylamine (Avocado, 98%, 500 mL) under a stream of nitrogen in a three-necked flask at −78 °C. After the initially formed suspension cleared, the temperature was allowed to rise first to −50 and then to 0 °C as another suspension formed. Iodobenzene (Avocado, 98%, 10 mL) was added over 10 min by syringe whereupon the colour changed to yellow and the solid dissolved; the reaction was allowed to warm to room temperature as a solid reappeared. Analysis by TLC after ca. 40 min indicated no iodobenzene, so a further amount (5 mL) was added (total = 28 g, 0.137 mol). After 1 h, further analysis indicated the presence of iodobenzene; water (10 mL) was added dropwise after a further 12 h and the reaction was worked up in the normal way to give a crude oil (18 g) which was fractionally distilled at oil-pump pressure to give the product as a colourless oil [b.p. 54−55 °C; 14.0 g, 0.094 mol, 69%. $^1$H NMR: $\delta$ = 1.25 (s, 9 H), 3.31 (br., exchangeable, 1 H), 6.6−6.7 (m, 3 H) 7.0−7.1 (m, 2 H) ppm] which was stored under nitrogen.

***N*-Tritylacetamide (1h):**[17−19] Sulfuric acid (96%, 0.2 mL) was added to a stirred solution of trityl alcohol (0.84 g, 3.23 mmol) in acetonitrile (10 mL). The clear red solution was heated gently for 1 h then allowed to cool and the stirring was continued for several days, after which time water was added and the precipitated colourless solid (0.92 g, 3.06 mmol, 95%) was filtered at the pump and washed with copious amounts of water; a sample for measurements was recrystallised from aqueous ethanol. M.p. 215.5−216 °C (ref.[17−19] 206.5−207.2, 211, 218−219 °C). $^1$H NMR: $\delta$ = 2.06 (s, 3 H, Me), 6.68 (br, 1 H, NH), 7.2−7.4 (m, 15 H, arom) ppm. $^{13}$C NMR: $\delta$ = 24.63 (Me), 70.57 (C-N), 127.00 (C4′), 127.91 (C3′,5′), 128.66 (C2′,6′), 144.68 (C1′), 169.0 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3250 (br), 3200 (sh), 1655 (s), 1533 (m), 1491 (m), 1447 (m), 745 (m), 700 (s) cm$^{-1}$.

***N*-Dimethoxytritylimidazole (3h):** A solution of dimethoxytrityl tetrafluoroborate (0.300 g, 0.769 mmol) in dichloromethane (5 mL) was added dropwise to a stirred solution of imidazole (0.16 g, 2.35 mmol) in dichloromethane (5 mL).[4] After about 5 min, the reaction mixture was added to water (ca. 25 mL) and worked up in the normal way to give a pale-yellow oil which gave crystals from diethyl ether/pentane (1:1). Recrystallisation from heptane gave colourless crystals (160 mg, 0.432 mmol, 56%). M.p. 115−116 °C. $^1$H NMR: $\delta$ = 3.82 (s, 6 H, OMe), 6.8−7.45 (m incl. AA′BB′q, 16 H, arom) ppm. $^{13}$C NMR: $\delta$ = 55.27 (OMe), 74.41 (C-N), 113.17 (C3,5) 121.55 (Im), 127.81 (C4′), 127.91 (C3′,5′), 128.2 1 (Im), 129.53 (C2′,6′), 131.00 (C2,6), 134.89 (Im), 138.93 (C1), 143.12 (C1′), 159.02 (C4) ppm.

**Solution Base-Strength Measurements:** Base-strength determinations in solution were made in the conventional way usually both by titration of the free base against standard acid and by titration of the conjugate acid of the base against standard sodium hydroxide, as described previously.[4] Microcal Origin (Microcal Software Inc.) was used to analyze the potentiometric data. Multiple determinations were usually made at each of a range of temperatures for each compound in a cell thermostatted by water circulating from a thermostatted water bath. Average p$K_{BH^+}$ values are as follows: TrNHAc (**1h**; 37% acetonitrile/water): 3.81 (298 K), 3.60 (308 K), and 3.26 (323 K); TMTrN(Me)Bn (**4i**; 20% acetonitrile/water): 10.01 (283 K), 9.95 (289 K), 9.87 (302 K), 9.83 (316 K), 9.79 (323 K); $TMTrNHCH_2CO_2Me$ (**4b**; 15% acetonitrile/water): 9.53 (283 K), 9.30 (298 K), 9.25 (303 K), 9.17 (318 K); $Bn_3N$ (**6**; 12% acetonitrile/water): 5.47 (281 K), 5.30 (285 K), 5.24 (288 K), 4.95 (296 K), 4.77 (305 K), 4.33 (318 K).

**Gas-Phase Base-Strength Measurements:** An Extrel FTMS 2001 Fourier transform mass spectrometer was used for base-strength measurements in the gas phase.[21] An experiment was initiated by a 5 ms pulse of an electron beam (20 eV) through the ICR cell in which the total pressure of the bases was maintained at lower than $1 \times 10^{-6}$ Torr. The proton-transfer equilibrium was achieved within several hundred ms of the initiation of the reaction (depending on the pressure of the neutrals), and the equilibrium constant for each proton-transfer reaction was evaluated from $K = [B_o][BH^+]/[B][B_oH^+]$. The relative abundances of ions $BH^+$ and $B_oH^+$ were determined by the relative intensities of ICR mass spectra at equilibrium. The pressures of the neutral reactants were measured by a Bayard−Alpert-type ionization gauge applying appropriate correction factors to correct the gauge readings for the different ionization cross-sections of the various compounds,[44] and experiments were performed at several ratios of partial pressures and at different overall pressures. The arithmetic means of the values of $K$ were used to calculate $\Delta G^{\circ}$, the average uncertainty being ±0.8 kJ·mol$^{-1}$ in most cases, and each value was measured with two reference bases. Gas-phase basicity values for reference compounds were taken from the literature.[13] Ion-eject experiments using the SWIFT technique[45] were also carried out to ensure proton-transfer reactions occurred. For compounds of low volatility investigated in this study, the solid sample direct-inlet system was used and all vacuum chamber systems were kept at 60−80 °C.

**Calculations:** Conformational searches were carried out using the Spartan 02 program (Wavefunction Inc.) and several lowest-energy conformers were further optimized at the RHF/3-21G* level of theory to identify each global minimum. Finally, the geometries were fully optimized at the B3LYP/6-31G* level with normal convergence using the Gaussian 98 program.[21] Vibrational normal-mode analyses were performed at the same level to ensure that each optimized structure was a true minimum on the potential energy sur-

  

face and to calculate the thermal correction needed to obtain the Gibbs free energies. The zero-point energies used for the thermal correction were unscaled.

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