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# SUPERBASES IN THE GAS PHASE. PART II. FURTHER EXTENSION OF THE BASICITY SCALE USING ACYCLIC AND CYCLIC GUANIDINES

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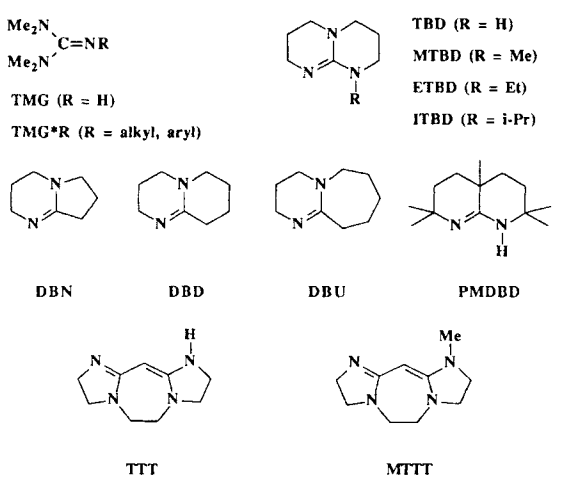
**The superbase gas-phase scale has been further extended up to proton affinities of *ca* 1080 kJ mol$^{-1}$ by use of cyclic and acyclic guanidines and vinamidines. Structural features such as Y-conjugation, vinylogy and intramolecular ionic hydrogen bonding leading to their superbasic behaviour are analysed. Solvation effects by water and acetonitrile on basicity are discussed. From a correlation p$K_a$(acetonitrile) vs gas-phase basicity, proton affinity values in the range 1070–1410 kJ mol$^{-1}$ are predicted for Schwesinger phosphazene compounds.**

## INTRODUCTION

Chemists have always been attracted by compounds with properties, such as strain energy, acidity and basicity, that exhibit extreme values. The aim of such studies is mainly to investigate possible applications, although fundamental interest in non-classical structures or even aesthetic reasons is often involved.

The design and study of very strong organic bases has long attracted interest. In particular, the guanidine moiety, which may be included in acyclic and in cyclic systems, is present in the skeleton of numerous natural (arginine, guanine) and synthetic compounds exhibiting biological activities.[1,2] Many guanidines and biguanides find wide applications in chemotherapy. They display a wide range of biological properties, from antibacterial (sulphaguanidine) to hypertensive (clonidine, guanethidine). They have also been tested as oral antidiabetics (synthalin A, synthalin B, phenformin, buformin, metformin).

Guanidines are strong organic bases.[3–5] The strength of unsubstituted guanidine and of its alkyl derivatives in solution (in water p$K_a > 13{\cdot}5$[3–6]) is comparable to that of sodium hydroxide. 1,1,3,3-Tetramethylguanidine (TMG) and its 2-substituted derivatives, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and its 7-alkyl (methyl, ethyl and isopropyl) derivatives (MTBD, ETBD and ITBD, respectively), 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN), 1,5-diazabicyclo[4.4.0]dec-6-end (DBD) 1,5-diazabicyclo[5.4.0]undec-7-ene (DBU), 3,3,6,9,9-pentamethyl-2,10-diazabicyclo-[4.4.0]dec-1-ene (PMDBD) (Scheme 1), exhibit high basicity and, in some cases, low nucleophilicity.[3–9] They have been recognized as useful for different synthetic




Scheme 1

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applications (dehydrohalogenation, Michael addition, aldol condensation).

Although some of these bases and many other guanidines are commercially available, measurement of their gas-phase basicity (*GB*) was not possible because of the lack of suitable reference bases able to exchange a proton with the conjugate guanidinium (or amidinium) cation.[10] Before we started our studies on superbasicity in the gas phase, the proton affinity (*PA*) for tetramethylguanidine (1015 kJ mol$^{-1}$)[11] was the highest *PA* for a monofunctional base reported in the basicity scale compiled by Lias and co-workers.[12] Our investigations of substituent effects on the *GB* of $N^1$,$N^1$-dimethylformamidines,[13] $Me_2NCH{=}NR$ (FDM*R, R = alkyl), have shown that the *GB* values of some amidines are close to or higher than that of tetramethylguanidine and opened the way for the extension of Lias and coworkers' basicity scale.[12] Recently, we have studied[14] a series of $N^1$,$N^1$-dimethylacetamidines, $Me_2NC(Me){=}NR$ (ADM*R, R = alkyl), -propionamidines, $Me_2NC(Et){=}NR$ (PDM*R, R = alkyl), -benzamidines, $Me_2NC(aryl){=}NMe$, and an $N^1$,$N^1$-diethylacetamidine, $Et_2NC(Me){=}NPr^n$, which allowed us to extend the gas-phase basicity scale[12] for organic compounds up to *PA* = 1050 kJ mol$^{-1}$.

In this work, we used the amidines studied previously as reference bases for carrying out gas-phase basicity measurements on guanidines. A series of acyclic 2-(substituted phenyl or alkyl)-1,1,3,3-tetramethylguanidines (TMG*R, R = 4-$ClC_6H_4$, 4-$FC_6H_4$, Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, Me, Et, $Pr^i$ and $Bu^t$), bicyclic guanidines ETBD and ITBD, and diaminovinamidines TTT and MTTT (Scheme 1) were chosen as potentially superbasic candidates. We report also the revised basicities for the bicyclic guanidines TBD and MTBD, for $Me_2NCH{=}N(CH_2)_3NMe_2$, and $Me_2NC(Me){=}N(CH_2)_3NMe_2$ and the basicity for the bicyclic amidine DBD.

We discuss here (i) the origin of the strong basicity of guanidines, (ii) the gas-phase substituent effects, (iii) an 'internal solvation' for polyfunctional compounds with flexible chains and (iv) the bulk ('external') solvation based on the correlation of the p$K_a$ vs *GB* values. These studies allow us to propose the structures that are the best candidates for a further extension of the gas-phase basicity scale and to estimate their *GB* values.

## EXPERIMENTAL

Alkyl- and aryltetramethylguanidines (TMG*Rs) were synthesized using the method of Bredereck and Bredereck.[15–17] They were obtained by reaction of 1,1,3,3-tetramethylurea with a primary amine in the presence of $POCl_3$. The aryl and alkyl derivatives were purified by vacuum distillation and preparative GC, respectively. Structures of the substituted tetramethylguanidines (TMG*R) were confirmed by 70 eV mass

Table 1. Gas-phase basicities of superbases (in kJ mol$^{-1}$): amidines and guanidines with *GB* values close to, or higher than that of tetramethylguanidine (TMG)

| Superbase | *GB*[a] | *PA*[b] | Ref. |
|---|---|---|---|
| $(Me_2N)_2C{=}N(4\text{-}ClC_6H_4)$ | 981·1 | 1013·8 | This work |
| TMG | 982·8[c] | 1017·0 | 14c |
| $Me_2NCH{=}N(CH_2)_2NMe_2$ | (982·8)[d] | (1031)[e] | 13b, 14c |
| $(Me_2N)_2C{=}N(4\text{-}FC_6H_4)$ | 983·2 | 1015·9 | This work |
| $Me_2NC(Me){=}NEt$ | 984·1 | 1016·6 | 14c |
| $Me_2NC(Me){=}NPr^n$ | 985·3 | 1017·8 | 14c |
| $Me_2NC(Me){=}NPr^i$ | 986·6 | 1019·0 | 14c |
| $Me_2NC(Me){=}N(n\text{-}C_6H_{13})$ | 988·3 | 1020·7 | 14c |
| $Me_2NC(Ph){=}NMe$ | 988·3 | 1020·7 | 14c |
| $Me_2NCH{=}N(1\text{-adamantyl})$ | 988·3 | 1020·7 | 13b, 14c |
| $Me_2NC(Me){=}N(n\text{-}C_5H_{11})$ | 989·5 | 1022·0 | 14c |
| $Me_2NC(Me){=}N(CH_2)_2OMe$ | (991·2)[d] | (1039)[e] | 14c |
| $(Me_2N)_2C{=}NPh$ | 991·6 | 1024·2 | This work |
| $Me_2NC(Et){=}NPr^i$ | 992·0 | 1024·5 | 14c |
| $Me_2NC(Et){=}N(n\text{-}C_5H_{11})$ | 992·9 | 1025·3 | 14c |
| $Et_2NC(Me){=}NPr^n$ | 992·9 | 1025·3 | 14c |
| $Me_2NC(4\text{-}MeC_6H_4){=}NMe$ | 992·9 | 1025·3 | 14c |
| $Me_2NC(Me){=}NBu^t$ | 993·9 | 1025·7 | 14c |
| DBN | 993·9 | 1025·7 | 14c |
| Arginine | | 1025·9 ± 2 | 19 |
| PMDBD | 994·3[c] | 1028·5 | 14c |
| $Me_2NCH{=}N(CH_2)_3NMe_2$ | (997·0)[d] | (1048)[e] | This work |
| $(Me_2N)_2C{=}N(4\text{-}MeC_6H_4)$ | 997·5 | 1030·1 | This work |
| $Me_2NC(Et){=}NBu^t$ | 998·3 | 1030·8 | 14c |
| DBD | 999·6 ± 2 | 1032 | This work |
| $(Me_2N)_2C{=}N(4\text{-}MeOC_6H_4)$ | 1000·8 | 1033·4 | This work |
| $(Me_2N)_2C{=}NMe$ | 1000·8 | 1033·4 | This work |
| DBU | 1002·9 | 1035·4 | 14c |
| $Me_2NC(Me){=}N(CH_2)_2NMe_2$ | (1003·5)[d] | (1052)[e] | 14c |
| $(Me_2N)_2C{=}NEt$ | 1004·6 | 1037·2 | This work |
| $Me_2NC(Me){=}N(1\text{-adamantyl})$ | 1005·8 | 1038·3 | 14c |
| TBD | 1008·3[c] | 1042·5 | This work |
| $(Me_2N)_2C{=}NPr^i$ | 1008·8 | 1041·4 | This work |
| $Me_2NC(Me){=}N(CH_2)_3NMe_2$ | (1014·2)[d] | (1064)[e] | This work |
| $(Me_2N)_2C{=}NBu^t$ | 1015·0 | 1047·7 | This work |
| MTBD | 1015·5 | 1048·1 | This work |
| ETBD | 1021·4 | 1053·9 | This work |
| ITBD | 1024·8 | 1057·3 | This work |
| TTT | >1034[c] | >1068 | This work |
| MTTT | >1045 | >1078 | This work |

[a] Gas-phase basicity (Gibbs energy scale) obtained from relative basicities measured at 338 K: no correction required to 298 K, except when entropy changes are associated with proton exchange (see footnotes c and d). Relative *GB*s are believed to be accurate to 1·5 kJ mol$^{-1}$.

[b] Proton affinity at 298 K using appropriate $T\Delta S$ term.

[c] Corrected using $\Delta S_{rot} = R \ln 2$.

[d] The 338 K experimental value is given. No temperature correction was made because of the lack of entropy data.

[e] Cyclization entropy obtained from data on diaminoalkanes was applied.

spectrometry. Bicyclic guanidines (ETBD, ITBD, DBD) and vinamidines (TTT, and MTTT) were kindly supplied by Dr R. Schwesinger.[3,18] Most of the compounds studied were stable and sufficiently volatile to be studied by Fourier transform in cyclotron resonance (FT-ICR) mass spectrometry. TTT and, to a less extent, MTTT have very low vapour pressures at the maximum practical temperature of our inlet system (*ca* 140 °C), and necessitated long stabilization periods to read their pressure and long pumping-down times (48–72 h). The procedure for the gas-phase basicity measurements was the same as that described previously.[13,14] The *GB* values for $Pr^n_3N$ and $Bu^n_3N$ were the starting points on our gas-phase basicity scale.[14c]

## RESULTS

The *GB* values of the guanidines and diaminovinamidines studied are listed in Table 1 together with the *GB* values of amidines studied previously and used as reference bases.

Proton affinities ($PA = GB + T\Delta S$) were obtained from the experimental *GB* and estimated $\Delta S$ values. In general, only the contributions from changes in symmetry on protonation were considered.[12] For compounds displaying no change in symmetry on protonation, only the translational entropy for the proton was considered ($\Delta S = 108{\cdot}9$ J mol$^{-1}$ K$^{-1}$).[20] Protonation of TMG, PMDBD, TBD and TTT produces ions with symmetry number $\sigma = 2$ leading to a $\Delta S_{rot} = R \ln 2$ correction. For the six compounds $Me_2NC(Y)=N(CH_2)_nX$ (X = OMe, $NMe_2$; $n = 2, 3$), for which internal hydrogen bonding is expected (see the Discussion), the cyclization entropy was taken as $-46{\cdot}4$ and $-61{\cdot}9$ J mol$^{-1}$ K$^{-1}$ for $n = 2$ and 3, respectively.[12b] All acyclic and cyclic derivatives of guanidines have $PA > 1000$ kJ mol$^{-1}$. The *PA* values are close to, or higher than, that of TMG, which was the strongest monofunctional organic base in Lias and coworkers' gas-phase basicity scale.[12] The *PA* values of the diaminovinamidines TTT and MTTT are higher than 1068 and 1078 kJ mol$^{-1}$, respectively, and cannot be measured with good precision because of the lack of reference bases.

In Table 1 the gas-phase basicity of arginine reported recently by Wu and Fenselau[19a] is also given. Arginine, which contains the guanidine function, has been found to be the most basic mammalian amino acid.[19] Its *PA* value, close to that of DBN, is about 60 kJ mol$^{-1}$ higher than that of histidine containing the amidine group in the imidazole ring.

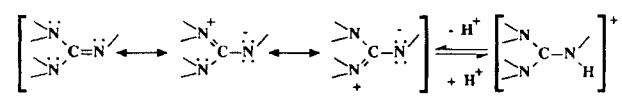
## DISCUSSION

### Superbasicity of guanidines and vinamidines

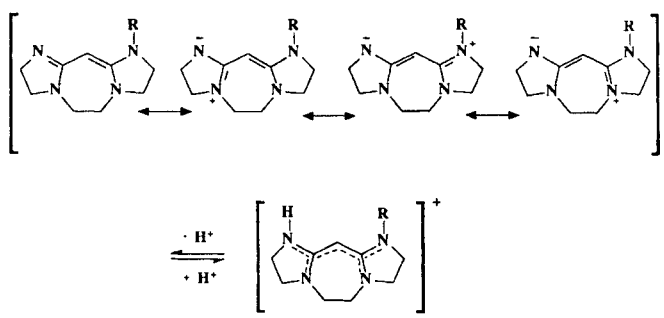
The strong basicity of guanidines originates from the stability of the guanidinium cation induced by the so-called 'cross-conjugation' or 'Y-delocalization' of the six non-$\sigma$ electrons of the guanidinium system.[4,21] The guanidinium cation is formed by protonation of the imino nitrogen atom (Scheme 2).

Comparison of the PA values obtained for guanidines with those recently reported for simple imines[22] confirms that the origin of the very high basicity of guanidines arises from the strong electron-donor effect of the amino groups. For example, the *PA* value for TMG is higher by 164 kJ mol$^{-1}$ than that for $H_2C{=}NH$. The same behaviour is observed in solution.[3–6,8,16–18,23] In water, the $pK_a$ value of TMG is higher by 6·8 $pK_a$ units than that for $Ph_2C{=}NH$.[23]

Superbasicity of the diaminovinamidines TTT and MTTT in the gas phase is the result of the reinforce-



Scheme 2



Scheme 3

ment of the basicity of the amidine function (in the imidazoline ring) by substitution with the diaminovinyl group on the amidine carbon atom (Scheme 3). In acetonitrile, the $pK_a$ values for TTT and MTTT are higher by 2·9 and 3·7 $pK_a$ units, respectively, than that for TMG.[3]

## Gas-phase substituent effects

Effects of substitution in the *para* position of the phenyl ring attached to the imino nitrogen in the TMG family (relative to unsubstituted phenyl), $\delta_X GB = GB(4\text{-}XC_6H_4) - GB(Ph)$, appear to be very close to those in the FDM series (Table 2). The same behaviour is observed for alkyl derivatives. Alkyl substituent effects (relative to methyl), $\delta_R GB = GB(R) - GB(Me)$ in the tetramethylguanidine series are similar to those in the formamidine and acetamidine series (Table 3), within experimental error (2 kJ mol$^{-1}$).

For alkyl substituents, a more quantitative comparison may be based on the Taft and Topsom analysis.[25] We have shown previously[13b,c] that alkyl substituents at the imino nitrogen atom in the FDM series act principally by the polarizability ($P$) effect. The relative basicities obey the equation

$$\delta_R GB = \rho_\alpha \sigma_\alpha + c \quad (1)$$

where $\rho_\alpha$ is the reaction constant for the $P$ effect and $\sigma_\alpha$ is the directional polarizability parameter of Taft and co-workers.[25-27]

Similar effects are observed in the TMG and ADM series. Correlations performed for the four substituents (Me, Et, Pr$^i$ and Bu$^t$) common to the three series, and separately for all substituents in the TMG series ($n = 5$), and for the six substituents (Me, Et, Pr$^n$, Pr$^i$, Bu$^t$ and 1-adamantyl) common to the FDM and ADM series are given in Table 4. Cyclopropyl, *n*-amyl and *n*-hexyl are excluded; in the FDM and ADM series, these points deviate from the $\delta_R GB$ vs $\sigma_\alpha$ correlation. For the cyclopropyl group an electron-withdrawing effect is observed. Deviations of the long-chain alkyl substituents may be explained by a coiling effect, which culminates for the *n*-amyl substituent.

When the alkyl substituent $(CH_2)_nX$ contains an electron-withdrawing group X, the gas-phase basicities depend on a combination of the $P$ and electrostatic field ($F$) effects. Additionally, for the aryl substituents a combination of the $P$, $F$ and resonance ($R$) effects should be considered. In this work, $(CH_2)_nX$ and four $4\text{-}XC_6H_4$ substituents in the ADM and TMG series, respectively, were studied. Considering the small number of substituents, the Taft and Topsom analysis[25] cannot be carried out. However, there is a good correlation between the $GB$ values of the TMG and FDM series [equation (2)], as was already observed for the $GB$ values of the ADM and FDM series [equation (3)].

$$GB(TMG^*R) = 109{\cdot}7 + (0{\cdot}929 \pm 0{\cdot}035)GB(FDM^*R)$$
$$n = 9,\ r = 0{\cdot}995,\ \text{s.d.} = 1{\cdot}2\ \text{kJ mol}^{-1} \quad (2)$$

$$GB(ADM^*R) = 88{\cdot}1 + (0{\cdot}929 \pm 0{\cdot}033)GB(FDM^*R)$$
$$n = 12,\ r = 0{\cdot}994,\ \text{s.d.} = 1{\cdot}3\ \text{kJ mol}^{-1} \quad (3)$$

Substituent effects operating in these series are the following: $P$ effect for simple alkyl groups, allowance being made for an additional coiling effect for long-chain alkyl groups and for an additional $F$ effect for the cyclopropyl group; $P$ and $F$ effects for $(CH_2)_nX$ groups, with an additional internal hydrogen bonding in the protonated form for X = OMe, $NMe_2$ with $n = 2$, and 3 (see below); and $P$, $F$ and $R$ effects for $4\text{-}XC_6H_4$

Table 2. Gas-phase aryl substituent effects: $\delta_X GB = GB(4\text{-}C_6H_4) - GB(Ph)$ in the formamidine (FDM*4-$XC_6H_4$) and tetramethylguanidine (TMG*4-$XC_6H_4$) series (in kJ mol$^{-1}$)

| X | FDM*4-$XC_6H_4$[a] | TMG*4-$XC_6H_4$[b] |
|---|---|---|
| OMe | 12·6 | 9·2 |
| Me | 7·5 | 5·9 |
| H | 0 | 0 |
| F | −7·1 | −8·4 |
| Cl | −10·9 | −10·5 |

[a] Data from Refs 13a and 24.
[b] Data from Table 1.

Table 3. Gas-phase alkyl substituent effects: $\delta_R GB = GB(R) - GB(Me)$ in the substituted formamidine (FDM*R), acetamidine (ADM*R) and tetramethylguanidine (TMG*R) series (in kJ mol$^{-1}$)

| R | FDM*R | ADM*R[a] | TMG*R[a] |
|---|---|---|---|
| H | | | −18·0 |
| Me | 0 | 0 | 0 |
| Et | 5·4[b] | 5·9 | 3·8 |
| Pr$^c$ | 3·3[b] | 0·9 | |
| Pr$^n$ | 8·2[b] | 7·1 | |
| Pr$^i$ | 9·4[b] | 8·4 | 8·0 |
| Bu$^t$ | 17·8[b] | 15·1 | 14·2 |
| *n*-$C_5H_{11}$ | 14·6[b] | 11·3 | |
| *n*-$C_6H_{13}$ | 13·2[b] | 10·1 | |
| 1-Adamantyl | 31·0[a] | 27·6 | |
| $(CH_2)_2OMe$ | 13·8[b] | 13·0 | |
| $(CH_2)_2NMe_2$ | 25·5[a] | 25·3 | |
| $(CH_2)_3NMe_2$ | 39·7[a] | 36·0 | |

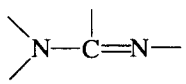
[a] Data from Table 1.
[b] Data from Refs 13b and c; small differences from the original values are due to the use of Pr$^n{}_3$N and Bu$^n{}_3$N as anchoring points in our basicity scale of superbases.[14c]

Table 4. Parameters for the regressions $\delta_R GB$s for substituted formamidines (FDM*R), acetamidines (ADM*R) and tetramethylguanidines (TMG*R) from Table 3 vs. $\sigma_\alpha$[a] [equation (1)][b]

| No. | Series | Intercept ($c$) | Slope ($\rho_\alpha$) | Correlation coefficient | Standard deviation | No. of data points |
|---|---|---|---|---|---|---|
| 1a | FDM*R | −15·7 | −43·1 ± 5·0 | 0·987 | 1·5 | 4[c] |
| 1b | ADM*R | −12·5 | −35·9 ± 4·1 | 0·987 | 1·2 | 4[c] |
| 1c | TMG*R | −12·9 | −35·1 ± 3·3 | 0·991 | 1·0 | 4[c] |
| 1d | FDM*R | −19·8 | −51·5 ± 4·1 | 0·987 | 1·9 | 6[d] |
| 1e | ADM*R | −17·0 | −44·8 ± 4·1 | 0·984 | 1·9 | 6[d] |
| 1f | TMG*R | −16·9 | −41·9 ± 2·7 | 0·994 | 1·6 | 5[e] |

[a] $\sigma_\alpha$ values from Ref. 27.
[b] In kJ mol$^{-1}$.
[c] For Me, Et, Pr$^i$ and Bu$^t$.
[d] For Me, Et, Pr$^n$, Pr$^i$, Bu$^t$ and 1-adamantyl.
[e] For H, Me, Et, Pr$^i$ and Bu$^t$.[9]

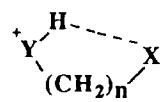
groups. The almost unit slopes indicate that similar substituent effects operate with the same intensity in guanidines and amidines. Our studies dealing with substituent effects on the basicity of compounds incorporating the



group show that the higher basicities originate in (i) the presence of an additional amino group at the functional carbon atom (guanidines) or (ii) the presence of a $(CH_2)_nNMe_2$ group at the imino nitrogen atom. Estimations carried out for TMG*$(CH_2)_nMe_2$ accordingto equation (2) give *GB* values of 1023 and 1036 kJ mol$^{-1}$ for $n = 2$ and 3, respectively. The latter *GB* value is higher than that for ITBD. In the series of 1,1,3,3-tetraethylguanidines, $(Et_2N)_2C{=}NR$, the estimated *GB* values are higher by about 10 kJ mol$^{-1}$ than those for the corresponding tetramethylguanidines series. These derivatives could permit the extension of the gas-phase basicity scale up to *PA* = 1080 kJ mol$^{-1}$ and the determination of the *PA* values for vinamidines with better precision. Vinylogues and iminologues of amidines and guanidines[28] are the next candidates for extending the gas-phase basicity scale.

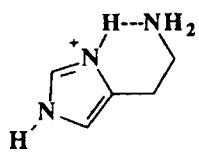
## 'Internal solvation' of amidinium (guanidinium) cation

An intramolecular stabilization of protonated polyfunctional groups, also called 'internal solvation,' has long been invoked for compounds of general formula $Y(CH_2)_nX$ (X,Y = OR, $NR_2$; R = H or alkyl; $n$ 2), for which an enhancement of gas-phase basicity has been observed.[29,30] This effect is due to cyclization by internal hydrogen bonding between the protonated functional group (Y) and an hydrogen-bond donor group (X):



We observed a similar effect for amidines $Me_2NC(Z){=}N(CH_2)_nX$ (Z = H, Me). For $n = 2$ and 3, the $\delta_R GB$ values of the corresponding compounds can be compared with those of ethyl and *n*-propyl derivatives, respectively. If we consider the electron-withdrawing effect of X, a lowered basicity should be observed. In fact, we found a strong increase in the $\delta_R GB$ values (Table 3). In the FDM series the stabilization by internal ionic hydrogen bonding was fully analysed and estimated to 23, 21 and 31 kJ mol$^{-1}$ for $(CH_2)_2OMe$, $(CH_2)_2NMe_2$ and $(CH_2)_3NMe_2$, respectively.[13c] Since the same substituent effects operate in the ADM and TMG series [equations (2) and (3)], we expect for them a stabilization by 'internal solvation' of the same order of magnitude.

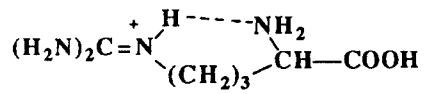
Histamine, an important biogenic molecule, also bears two potential basic sites: the pseudo-amidine (imidazole) and amino functions, separated by three carbon atoms, two of which are part of an alkyl chain. Therefore, a stable six-membered cyclic structure may be formed in the protonated form:



In the gas phase,[14c,31] the imidazole 'sp$^2$' nitrogen atom, as the site of protonation, should be preferred to the amino chain, as shown by comparison of the *GB* values for histamine[14c] (949 kJ mol$^{-1}$) and 4-

methylimidazole (915 kJ $mol^{-1}$)[32] and $PhCH_2CH_2NH_2$ (895 kJ $mol^{-1}$),[12a] taken as model compounds. In aqueous *solution*, $PhCH_2CH_2NH_2$ is more basic than 4-methylimidazole by 2·3 $pK_a$ units (13 kJ $mol^{-1}$ in Gibbs energy).[23] This reversal is due to a better solvation of the $-NH_3^+$ cation compared with $=NH^+-$. By contrast, in the gas phase, the energetically preferred imidazole nitrogen protonation (like the imino nitrogen protonation in amidines) is further favoured by 'internal solvation.' This change in histamine cation structure on going from aqueous media to the gas phase has only recently been considered in theoretical studies.[31] Structures which are less stabilized by interactions with dipolar or hydrogen-bonding solvents may play a role in the histamine behaviour in non-aqueous (lipidic) environments. The α-amino acid histidine may be considered as a carboxy derivative of histamine. The *GB* value for histidine (938 kJ $mol^{-1}$)[12a] is 23 kJ $mol^{-1}$ higher than that of the model compound 4-methylimidazole, but 11 kJ $mol^{-1}$ lower than that for histamine. The weaker basicity of histidine may be due to an electron-withdrawing effect of the COOH group. Although this interpretation seems sound, a recent semiempirical calculation[33] gives the structure with an intramolecular H-bond C=O···H−N(Im) as the most stable conformation of protonated histidine. Therefore, we suggest that the problem of histidine should be further investigated both theoretically and experimentally.

Arginine is the next example of an α-amino acid for which guanidine (preferred by the proton) and amine functions are separated by a chain of four carbon atoms. We suggest that, similarly to other examples discussed in this paper, the strong gas-phase basicity of arginine may be due to the 'internal solvation' of the guanidinium cation:



The increase in the *PA* value measured for arginine (*PA* = 1026 kJ $mol^{-1}$)[19a] is 31 kJ $mol^{-1}$, compared with that calculated by the *ab initio* method at the MP2/6–31G(d) level for the unsubstituted guanidine (*PA* = 995 kJ $mol^{-1}$) as a model compound.[21b]

The problem of internal solvation in important polyfunctional biogenic molecules with a flexible chain is still an experimental and theoretical challenge. Currently, *GB* measurements carried out by different techniques, chosen for usually unstable biogenic molecules of low volatility, are not always in good agreement with each other.[19] Molecular orbital calculations may help to solve the difficult experimental problems, but theoretical studies should take into account the potential sites of protonation with possible internal solvation, and also conformational isomerisms and the prototropic tautomerism of the amidine or guanidine −NHC(Z)=N− moieties. The proton affinities deduced from the experimental *GB* values should be based on accurate estimations of the 'entropy of cyclization.'

## Bulk ('external') solvation of amidinium and guanidinium cations

Studies of substituent effects on the basicity of amidines and guanidines in solution[3–5,16–18,34] have shown that the amino nitrogen atom is the preferred site of protonation in solution, similarly as in the gas phase.[13,14] Thus, the $pK_a$ values can be directly compared with the *GB* values.

A first comparison of basicities in solution (water[6,17,23,35,36] and acetonitrile[3,17b,18]) with those in the gas phase[12–14,24,32,37] (Table 1) for amidines (FDM*Ph, DBN, DBD, DBU), vinamidines (TTT, MTTT), guanidines (TMG*R, TBD, MTBD, ETBD, ITBD) and pseudo-amidines (imidazole, *N*-methylimidazole, benzimidazole, *N*-methylbenzimidazole, 2- and 4-dimethylaminopyridines) is shown in Figure 1.

Two kinds of behaviour can be distinguished, one for alkyl systems, which act only by the *P* effect, and the other for aromatic systems, for which a combination of *P*, *F* and *R* effects should be considered. This means that in both solvents the 'external' solvation is not identical for alkyl and aromatic derivatives. Moreover, the bulk solvation by water is different from that by acetonitrile. For acetonitrile, almost parallel regression lines, $pK_a$ vs *GB*, may be drawn for alkyl and aryl substituents (slopes 0·057 and 0·069, respectively). In water the slope of the regression line (0·017) for alkyl groups is much smaller than that for aromatic systems (0·074). For a discussion of the solvation effect on the basicity of organic compounds it is more convenient to use the direct comparison of basicity properties in solution and in the gas phase expressed in the same quantity and unit, e.g. $\Delta G$(aq) or $\Delta G$(AN) = 5·7080 $pK_a$, which represent the Gibbs free energies of deprotonation of the corresponding cation in water or in acetonitrile, and *GB* (both in kJ $mol^{-1}$). The slope of the correlation line *GB* vs $\Delta G$(aq) or $\Delta G$(AN) was defined as the solvent attenuation factor (*SAF*).[38] For the TMG*R compounds in aqueous solution, higher solvation effect is observed for alkyl (*SAF* = 10) than for aryl derivatives (*SAF* = 4).

For alkyl substituents acting only by the *P* effect, the *SAF* value represents only the polarizability attenuation factor (*PAF*). Higher *PAF* values than those for field (*FAF*) and resonance (*RAF*) attenuation factors have previously been observed for the FDM series[13c] and other nitrogen bases (amines and pyridines)[32,38,39] in aqueous solutions. However, in acetonitrile we found similar attenuation (*SAF* = 3) for alkyl and aryl derivatives. The higher *SAF* value for water than for acetonitrile, 10 vs 3, may be due to a specific solvation,

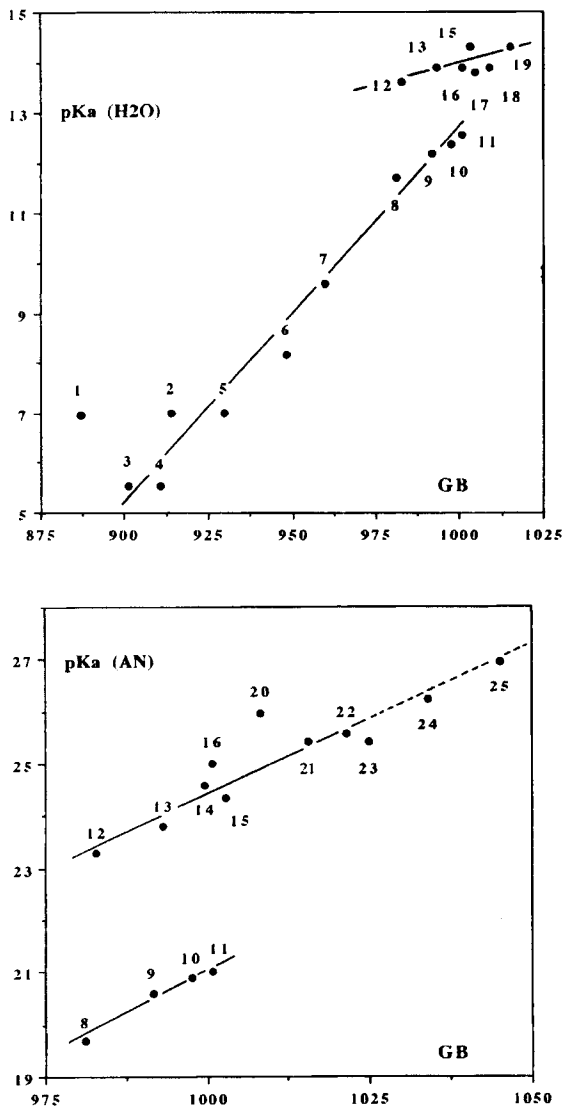
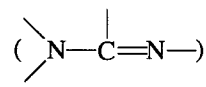


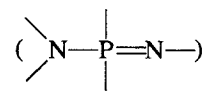

Figure 1. Comparison of the p$K_a$ values in (a) water and (b) acetonitrile with the *GB* values for pseudo-amidines, amidines, guanidines and vinamidines: imidazole (1), *N*-methylimidazole (2), benzimidazole (3), *N*-methylbenzimidazole (4), 2-(*N*,*N*-dimethylamino)pyridine (5), FDM*Ph (6), 4-(*N*,*N*-dimethylamino)pyridine (7), TMG*4-$ClC_6H_4$ (8), TMG*Ph (9), TMG*4-$MeC_6H_4$ (10), TMG*4-$MeOC_6H_4$ (11), TMG (12), DBN (13), DBD (14), DBU (15), TMG*Me (16), TMG*Et (17), TMG*Pr$^i$ (18), TMG*Bu$^t$ (19), TBD (20), MTBD (21), ETBD (22), ITBD (23), TTT (24) and MTTT (25)

varying with the basicity of the superbases (p$K_a$ > 13·5) by water, which is a stronger hydrogen bond donor solvent than acetonitrile.[40] It should be mentioned that p$K_a$s in water for superbases are subject to large uncertainties, and that their re-examination, leading to a homogeneous set of data, would be useful.

An extrapolation of the correlation line p$K_a$(AN) vs *GB* obtained for alkyl superbases [Figure 1(b)] presented in this paper can be used to consider what the *GB* values for 'hyperbasic' phosphazenes studied by Schwesinger[3c,18] in acetonitrile could be. If we assume a similar behaviour for the carbon



and phosphorus



superbases, we predict *GB* values in the range 1038–1379 kJ mol$^{-1}$ (*PA* ≈ 1070–1410 kJ mol$^{-1}$), corresponding to p$K_a$(AN) = 26–46. Similar estimates have been given by other workers.[41]

The *GB* values estimated for *tert*-butyl derivatives [1250–1379 kJ mol$^{-1}$, corresponding to p$K_a$(AN) = 39–46], which in fact represent the gas-phase acidity of the cationic form of phosphazenes ($BH^+ \rightarrow B + H^+$), are comparable with the gas-phase acidity of superacids ($AH \rightarrow A^- + H^+$), reported recently by Koppel *et al.*[42,43] Therefore, a spontaneous proton-transfer reaction between neutral organic superacids and superbases could be achieved in the gas phase:[42]

$$AH + B \rightarrow A^- + BH^+ \qquad (4)$$

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