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Gas-phase structural (internal) effects in strong organic nitrogen bases

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epoc ABSTRACT: Gas-phase basicities (*GB*) of strong organic bases containing the imino group were re-examined in the light of the re-evaluated *GB* values for the reference bases given in a recent compilation of Hunter and Lias. Structural (internal) effects which influence the basicity are discussed and general relations for the *GB* prediction are proposed for simple alkyl amidines and guanidines. These relations were used for estimation of cyclization and intramolecular H-bonding effects. Copyright © 2000 John Wiley & Sons, Ltd.
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KEYWORDS: organic nitrogen bases; gas-phase structural (internal) effects; gas-phase basicity

INTRODUCTION

Systematic gas-phase studies on strong organic bases containing the imino group started about 10 years ago.[1,2] A great number of cyclic and acyclic nitrogen compounds have been investigated: amidines, guanidines and vinamidines. Their gas-phase basicities (*GB*s) have been measured and results reported in a series of papers.[1–12] Recently, we studied phosphazenes and biguanides reported as the strongest organic bases known in solution.[13,14] However, the *GB* values could be determined with satisfactory precision only for three phosphazenes.[12] Lack of the appropriate reference bases rendered *GB* measurements impossible for other phosphazenes and biguanides.

In a search of structures having basicity comparable to that of phosphazenes and biguanides, structural (internal) effects in strong nitrogen bases have been re-examined. For this analysis, all amidines, guanidines, vinamidines, phosphazenes and biguanides (Scheme 1) studied previously have been considered. Their *GB* values have been revised according to the re-evaluated *GB* values for the reference bases given in a recent compilation of Hunter and Lias,[15] and a complete set of self-consistent data are presented. Gas-phase substituent effects have been analysed according to simple similarity models.[16]

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RESULTS AND DISCUSSION

Gas-phase basicity (*GB*)

Deprotonation reactions in the gas phase for conjugated acids of nitrogen bases are very endoergic,[15,17–19] and thus the *GB* corresponding to the Gibbs free energy change of the deprotonation reaction (1) is impossible to determine in a direct experiment. Fortunately, the relative basicity (ΔGB) can easily be obtained from the equilibrium constant (K) of the proton-transfer reaction (2) between two bases, one (B) with unknown *GB* value and the other (B_0), taken as reference base, for which the *GB* value was determined earlier. The *GB* value of the base B can be determined from Eqn. (3)

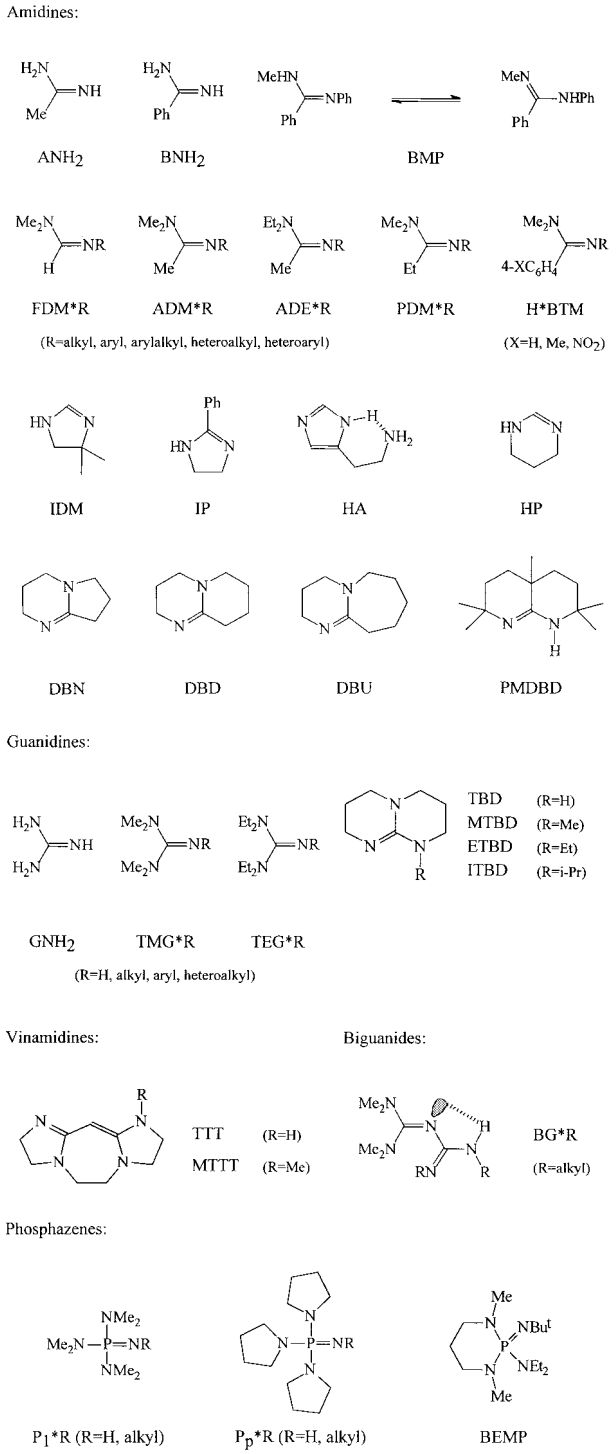
$$BH^+ \rightleftharpoons B + H^+ \quad (1)$$

$$BH^+ + B_0 \rightleftharpoons B + B_0H^+ \quad (2)$$

$$GB(B) = GB(B_0) - \Delta GB = GB(B_0) + RT\ln K(2) \quad (3)$$

For the *GB* measurements based on the proton-transfer reaction (2), we used the Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer constructed at the University of Nice–Sophia Antipolis.[20] The conditions for measurements were the same for all bases investigated: temperature of the cell 65 °C (338 K), maximum practical temperature of the inlet system 140 °C (413 K) and maximum pressures of bases B and B_0 10^{-6} mbar (10^{-4} Pa).

We started the *GB* measurements with series of



Scheme 1. Strong organic nitrogen bases

N^1,N^1-dimethylformamidines (FDMs) (Scheme 1) which generally are weaker bases than 1,1,3,3-tetramethylguanidine (TMG*H). Some exceptions were found for the FDM*1-adamantyl and FDM*$(CH_2)_3NMe_2$. At that time (about 8–10 years ago), TMG*H was the strongest monofunctional organic base (in the gas-phase basicity scale) for which the *GB* value was known.[21,22] The *GB* values for pyridines, amines and diamines (weaker bases than TMG*H in the gas phase) were also well known, and these nitrogen derivatives could therefore be used as reference bases for the *GB* measurements of FDMs.

The same reference bases (pyridines, amines and diamines) were used for amidines weaker than TMG*H.[4] For amidines of comparable or slightly stronger basicity than TMG*H we used FDMs and TMG*H as reference bases.[4] For other derivatives stronger than TMG*H we could determine only their relative basicities (ΔGB <12 kJ mol^{-1}).[4–6] In this way (step by step), we extended upwards the gas-phase basicity scale reported by Lias *et al.*[22] in 1988 by $\approx$60 kJ mol^{-1}, and we could try to perform measurements for vinamidines, biguanides and phosphazenes which have the highest strength among organic neutral bases. We found that their gas-phase basicities were higher than the corresponding primary amines by $\approx$200 kJ mol^{-1}.[12]

All revised *GB* values obtained for amidines, guanidines, vinamidines, biguanides and phosphazenes are listed in Table 1. These values differ from those reported previously[2–9,12,15] because we used the re-evaluated[15] *GB* values for all reference bases in our *GB* determination. Previously reported data were based only on the re-evaluated *GB* values of three reference bases: n-Pr_3N, n-Bu_3N and TMG*H.[12,15] In Table 1, our experimental data obtained for the imine PhCH=NMe are also given. The *GB* revised for FDM*aryl and FDM*heteroaryl have been discussed in a separate paper.[23] The averaged *GB* values are given in kcal mol^{-1} and next recalculated in kJ mol^{-1} (1 cal = 4.184 J). This kind of data presentation is thought to be useful for structural effect analyses, which have often been reported in kcal mol^{-1} for other derivatives.[24,25]

First comparison of the *GB* values indicates that for simple alkyl derivatives, the basicity in series increases with the polarizability of alkyl groups. We can distinguish the following orders of gas-phase basicities: *GB*(PDMs) $>$ *GB*(ADMs) $>$ *GB*(FDMs), *GB*(DBU) $>$ *GB*(DBD) $>$ *GB*(DBN), *GB*(TEGs) $>$ *GB*(TMGs), *GB*(ITBD) $>$ *GB*(ETBD) $>$ *GB*(MTBD) $>$ *GB*(TBD), *GB*(MTTT) $>$ *GB*(TTT), *GB*(P_1*Me) $>$ *GB*(P_1*H) and *GB*(P_p*t-Bu) $>$ *GB*(P_p*H). Effects of the aryl groups depend on their position in the molecule. Higher basicity is observed for derivatives bearing the aryl group (Ar) at the functional carbon than for derivatives with Ar on the imino nitrogen, e.g. *GB*(H*BTM) $>$ *GB*(ADM*Me) $>$ *GB*(FDM*Me) whereas *GB*(FDM*Me) $>$ *GB*(FDM*Ph), *GB*(TMG*Me) $>$ *GB*(TMG*Ph) and *GB*(TEG*Me) $>$ *GB*(TEG*Ph). Acyclic derivatives containing the heteroalkyl groups [$(CH_2)_nX$, $n = 2$ or 3, X = OMe or NMe_2] at the imino nitrogen deserve comment. Although these groups have an electron-accepting power due to the presence of a heteroatom, they induce the strongest increase in basicity. The order of this increase is the same in each series, i.e. *GB*[$(CH_2)_2OMe$] $>$ *GB*[$(CH_2)_2NMe_2$] $>$ *GB*[$(CH_2)_3OMe$] $>$ *GB*[$(CH_2)_3NMe_2$]. An increase in the number of amino groups in the molecule has an

Table 1. *GB*s of superbases revised according to the re-evaluated scale of Hunter and Lias[15]

Base	$GB(B)_{av}$ kcal mol^{-1}	$GB(B)_{av}$ kJ mol^{-1}	Base	$GB(B)_{av}$ kcal mol^{-1}	$GB(B)_{av}$ kJ mol^{-1}
FDM*CH_2CN	218.85	915.7	TMG*Ph	240.7	1007.0
FDM*OMe	218.9	915.9	PDM*i-Pr	240.7	1007.2
PhCH=NMe	220.8	924.0	ADE*n-Pr	240.75	1007.3
FDM*CH_2CF_3	223.15	933.7	4-Me*BTM	240.8	1007.5
FDM*$(CH_2)_2CN$	226.5	947.7	PDM*n-C_5H_{11}	240.9	1007.8
BNH_2	228.2	954.8	ADM*t-Bu	240.95	1008.1
IDM	228.3	955.1	DBN	241.0	1008.4
HA	229.5	960.3	PMDBD	241.15	1009.0
FDM*$CH_2C{\equiv}CH$	229.6	960.8	FDM*$(CH_2)_3NMe_2$	241.7	1011.2
FDM*NMe_2	230.1	962.9	TMG*4-C_6H_4Me	242.0	1012.6
HP	231.0	966.6	PDM*t-Bu	242.15	1013.2
FDM*Me	232.0	970.5	TEG*Ph	242.3	1013.9
FDM*$CH_2CH{=}CH_2$	232.3	971.9	DBD	242.5	1014.6
4-NO_2*BTM	232.7	973.5	TMG*Me	242.8	1015.9
FDM*c-C_3H_5	232.8	974.0	TMG*4-C_6H_4OMe	243.0	1016.6
FDM*Et	233.3	976.1	DBU	243.4	1018.2
IP	233.65	977.6	ADM*$(CH_2)_2NMe_2$	243.4	1018.4
FDM*n-Pr	234.1	979.5	TMG*Et	243.75	1019.9
FDM*n-Bu	234.5	981.1	ADM*1-Adam	244.0	1020.9
FDM*i-Pr	234.8	982.4	TBD	244.7	1023.8
FDM*CH_2Ph	234.8	982.5	TMG*i-Pr	244.8	1024.2
FDM*i-Bu	235.05	983.4	TEG*Me	246.1	1029.7
BMP	235.5	985.2	ADM*$(CH_2)_3NMe_2$	246.1	1029.8
FDM*n-C_6H_{13}	235.6	985.8	TMG*t-Bu	246.4	1030.9
FDM*n-C_5H_{11}	235.85	986.8	TMG*$(CH_2)_2OMe$	246.6	1031.7
FDM*s-Bu	235.85	986.8	MTBD	246.95	1033.2
FDM*$(CH_2)_2OMe$	236.1	987.9	TEG*Et	247.25	1034.5
FDM*c-C_6H_{13}	236.35	988.9	ETBD	247.5	1035.4
FDM*t-Bu	236.6	989.8	TEG*i-Pr	248.0	1037.6
FDM*t-C_5H_{11}	236.8	990.9	ITBD	248.3	1038.9
ADM*Me	237.4	993.2	TMG*$(CH_2)_2NMe_2$	248.4	1039.2
ADM*c-C_3H_5	237.55	993.9	TMG*$(CH_2)_3OMe$	248.75	1040.8
TMG*4-C_6H_4Cl	238.1	996.3	TEG*$(CH_2)_2OMe$	248.8	1041.0
FDM*$(CH_2)_2NM_2$	238.3	997.0	P_1*H	249.2	1042.8
ADM*n-Bu	238.4	997.6	TMG*$(CH_2)_3NMe_2$	250.65	1048.7
ADM*Et	238.75	998.9	TEG*$(CH_2)_2NMe_2$	250.7	1048.8
TMG*4-C_6H_4F	238.8	999.0	TEG*$(CH_2)_3OMe$	251.25	1051.2
ADM*n-Pr	239.1	1000.3	TEG*$(CH_2)_3NMe_2$	252.55	1056.7
ADM*i-Pr	239.4	1001.5	P_1*Me	253.25	1059.6
FDM*1-Adam	239.6	1002.6	P_p*H	254.35	1064.2
H*BTM	239.7	1002.9	TTT	254.85	1066.3
ADM*n-C_6H_{13}	239.8	1003.2	MTTT	>258	>1080
ADM*n-C_5H_{11}	240.1	1004.5	BG*i-Pr	>259.5	>1086
ADM*$(CH_2)_2OMe$	240.55	1006.5	P_p*t-Bu	>261	>1092

exceptionally strong influence on the gas-phase basicity. Generally, vinamidines, biguanides and phosphazenes which contain three amino groups are stronger bases than guanidines which have two amino groups. Guanidines are stronger bases than amidines which contain only one amino group, and amidines are stronger bases than imines which have no amino group. The same behaviour was found in solution. The pK_a values in acetonitrile (AN) for vinamidines (26–27), biguanides (27–32) and phosphazenes (26–46) were larger than for the corresponding guanidines (23–26)[13] (G. Gelbard and F. Vielfaure-Joly, unpublished results). Good correlation between the pK_a(AN) and *GB* values (reported as Fig. 1 in Ref. 5) predict the *GB*s for MTTT (1060 kJ mol^{-1}), BEMP (1070 kJ mol^{-1}) and BG*i-Pr (1170 kJ mol^{-1}) which are outside our superbasicity scale (>1050 kJ mol^{-1}). The *E–Z* isomerism present in acyclic and cyclic amidines has only a weak effect on the *GB* values. All these structural (internal) effects which increase the basicity of the *N*-imino bases need particular attention and are discussed separately below.

Site of protonation in alkyl derivatives

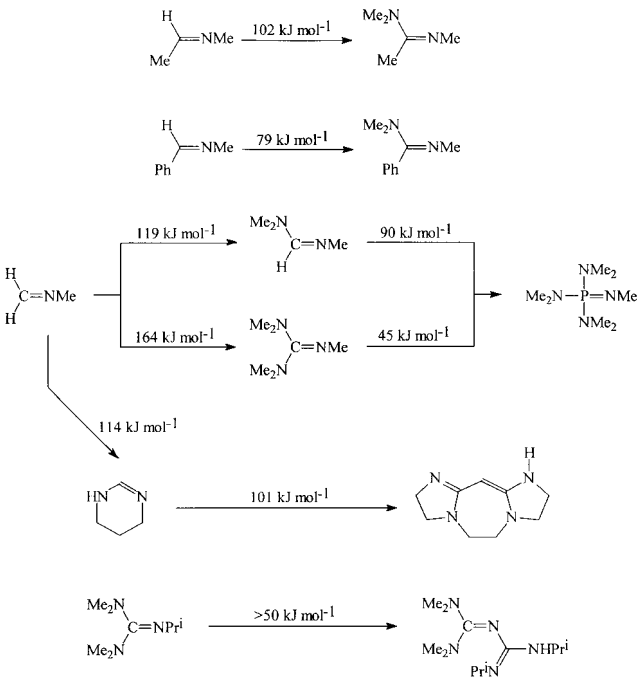
Amidines, guanidines, vinamidines, biguanides and

phosphazenes (Scheme 1) contain the imino group conjugated with one or more amino groups by the n–π resonance effect (the so-called 'push–pull' effect).[14] This conjugation strongly increases the basicity of the imino group in comparison with the corresponding imines, and strongly decreases the basicity of the amino group(s) in comparison with the corresponding amines. *Ab initio* calculations performed for unsubstituted acetamidine (ANH_2) and guanidine (GNH_2) for protonation at the *N*-imino atom are in good agreement with experimental results.[10,11] Semiempirical calculations carried out recently for amidines[7–9,26,27] and guanidines[27] together with the experimental results[1–9] compared with the corresponding imines confirm without any doubt that the imino nitrogen is the preferred site of protonation in the gas phase. For example, the proton affinity (*PA*) calculated[26] for FDM*Me is higher by >100 kJ mol^{-1} when protonation occurs on the imino group than on the amino group. On this basis, one can assume that the imino nitrogen is the preferred site of protonation in the gas phase for vinamidines and phosphazenes. Biguanides contain two imino nitrogens. If the mechanism of n–π conjugation is the same in biguanides as in other 'push–pull' molecules, the second imino nitrogen (linked with the alkyl group R) is more basic than the first.

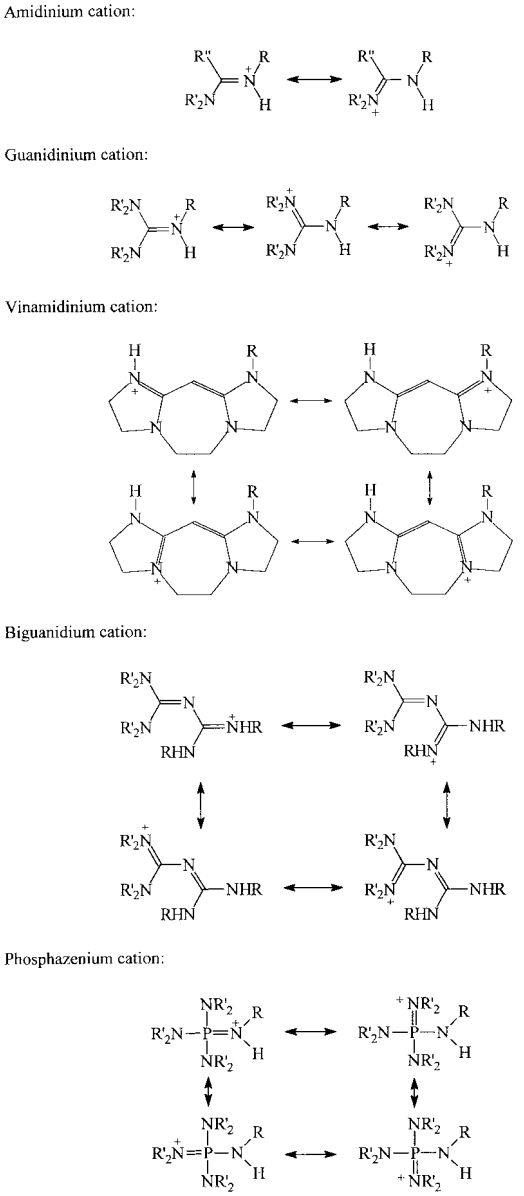
The n–π conjugation of the imino group with one amino group in amidines, two amino groups in guanidines and three amino groups in vinamidines augments the gas-phase basicity by ca 100, 150 and 200 kJ mol^{-1}, respectively, in comparisons with the model imines (Scheme 2). The *GB* values for imines were taken from Table 1 and Ref. 15. It is interesting that the effect of the amino group in imines is not additive. In 1,1,2,3,3-pentamethyl guanidine, the second dimethylamino group increases the basicity of the *N*-imino atom by 45 kJ mol^{-1} in comparison with N^1,N^1,N^2-trimethylformamidine, whereas the first dimethylamino group in formamidine augments the basicity of the *N*-imino atom by 119 kJ mol^{-1} as compared with *N*-methylimine. The effect of the amino group in imines depends also on the substituent at the functional carbon atom. The following increases in basicity have been found for N^1,N^1,N^2-trimethylformamidine (R″ = H), acetamidine (R″ = Me) and benzamidine (R″ = Ph): 119, 102 and 79 kJ mol^{-1}, respectively. This indicates that a kind of resonance saturation operates between the imino function and the R″ group, although some steric interaction between the introduced groups may induce a decrease in the donor effect of NMe_2 by a geometry constraint. A detailed analysis of the effect of the R″ group on the basicity of amidines has been reported in a previous paper.[27]

The n–π conjugation effect of the imino group with three amino groups in phosphazenes is difficult to estimate owing to the lack of the *GB* (or *PA*) for the respective phosphoimine (e.g. $H_3P{=}NH$ or $H_3P{=}NMe$). However, comparison of the *GB* of P_1*Me with that of FDM*Me and TMG*Me indicates that phosphazenes are stronger bases than formamidines and guanidines by ca 100 and 50 kJ mol^{-1}, respectively. Basicities of biguanides may be compared with those of the respective guanidines. Comparison of the *GB* values of the *iso*-propyl derivatives shows that biguanides are stronger bases than guanidines by ca 50 kJ mol^{-1}. The same order of magnitude has been found recently by Maksić and Kovačević between the proton affinities of unsubstituted guanidine and biguanide by *ab initio* calculations.[28]

The strong basicity of amidines, guanidines, vinamidines, biguanides and phosphazenes studied here originates from the high stability of the corresponding cations, resulting from protonation of the imino nitrogen atom (Scheme 3). The number of resonance structures, and thus the resonance stabilization of the cation, depend on the number of the amino nitrogens conjugated with the imino nitrogen. In amidines there are two representative resonance structures (in which the resonance effect of R″ can be neglected) contributing to the basicity enhancement, in guanidines three and in vinamidines and phosphazenes four. Within the families of bases studied here, the basicity order follows roughly the possibilities of charge delocalization: vinamidines, phosphazenes > guanidines > amidines. In biguanides there are two imino nitrogen atoms (guanidine and amidine functions). The larger number of possible resonance structures indicates the preferred site of protonation. For the first (guanidine) imino-protonated form only three resonance structures are possible, similarly as in guanidines, whereas for the other (amidine) four resonance structures are possible, similarly as in vinamidines and phospha-



Scheme 2. Structural effects on gas-phase basicity of nitrogen bases



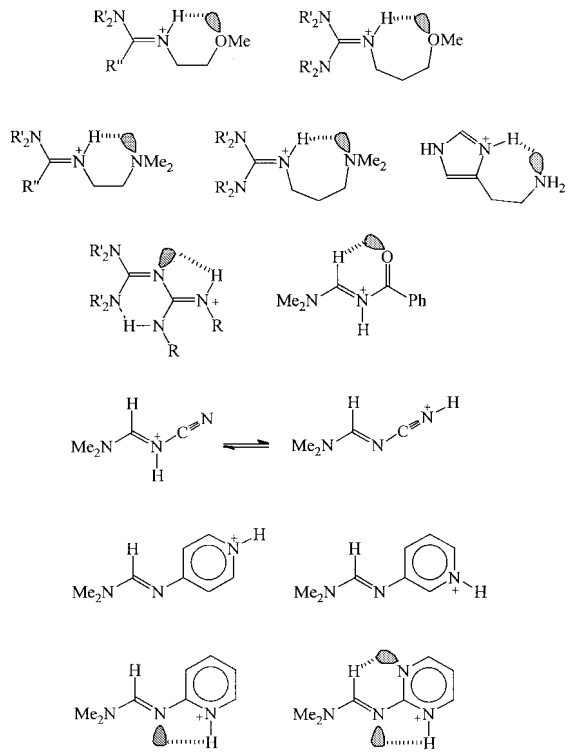
Scheme 3. Resonance structures for monoprotonated forms of amidines, guanidines, vinamidines, biguanides and phosphazenes

zenes. The high basicity of biguanides is similar to that of vinamidines and phosphazenes (Table 1). This is a good indication that the second imino nitrogen (with the R group) is the preferred site of protonation. The other imino nitrogen may be engaged in an intramolecular hydrogen bonding with the NHR group. Representative resonance structures for the respective amidinium, guanidinium, vinamidinium, biguanidium and phosphazenium cations are shown in Scheme 3.

Site of protonation in heteroalkyl and 'push–pull' derivatives

Heteroalkyl derivatives in series of FDMs, ADMs, TMGs and TEGs may be considered as bifunctional bases, containing two potential basic sites, the imino nitrogen in the amidine group and the heteroatom in the heteroalkyl group. Separation of these sites by methylene groups eliminates any additional resonance conjugation effect. Analysis of experimental gas-phase basicities of the corresponding monofunctional model series together with theoretical calculations indicated that the imino nitrogen in amidines and guanidines have stronger basicity than the oxygen atom in ethers and than the nitrogen atom in amines or nitriles.[1–5,15,26,29] For derivatives containing heteroalkyl groups bearing the cyano, methoxy or dimethylamino group at the end of the chain [$(CH_2)_nX$, n = 2 or 3, X = CN, OMe, or NMe_2], the imino nitrogen in the amidine and guanidine group is the preferred site of protonation. Owing to the flexible conformation of the side-chains, an intramolecular ionic hydrogen bond may be formed in the monoprotonated form between the protonated iminium group and the unprotonated heteroatom X ($NH^+\cdots X$) in the methoxy and dimethylamino derivatives Scheme 4). This kind of chelation of the proton explains the exceptionally high gas-phase basicity of the heteroalkyl derivatives of amidines and guanidines with the OMe and NMe_2 groups. The same type of intramolecular interaction effect (which strongly influences the gas-phase basicity) has been reported in the literature for diamines, diols, diethers, amino alcohols and amino ethers.[15,17,30]

Formation of an intramolecular hydrogen bond is also possible for the monoprotonated histamine (Scheme 4),



Scheme 4. Site of protonation in polyfunctional bases

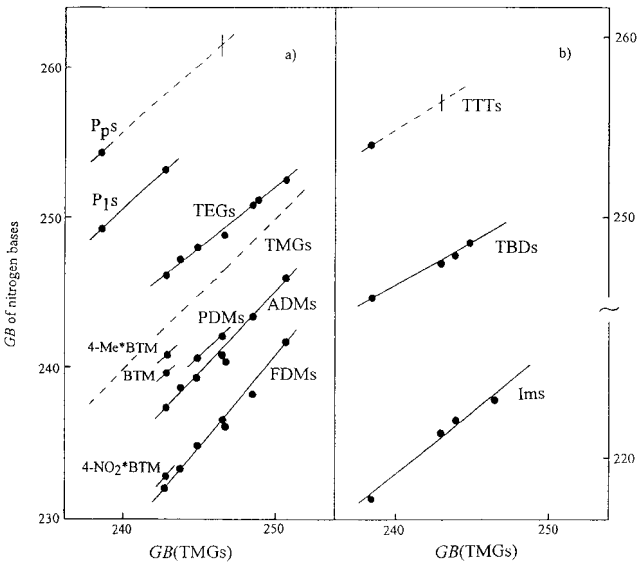


Figure 1. Correlation of the *GB* of nitrogen bases substituted by alkyl group(s) at (a) the *N*-imino and (b) *N*-amino with the *GB* of 1,1,3,3-tetramethylguanidines (TMGs)

for which an exceptionally high basicity has been observed.[4,31] In histamine, the ring imino nitrogen seems to be more basic than the side-chain amino nitrogen.[5] The same conclusion is possible for its *N*,*N*-dimethyl derivative although the *ab initio* calculations indicate the side-chain amino nitrogen as slightly more basic than the ring imino nitrogen.[32]

Biguanides (BG) discussed in the previous section may be considered as an example of 'push–pull' molecules. Biguanides contain two groups (guanidine and amidine) linked in such a way that they display complementary electronic character (pushing and pulling). The guanidine group $(R'_2N)_2C{=}N$ linked by its imino nitrogen to the amidine group presents a strong electron-donating character, and the amidine group C(NHR)=NR linked by its functional carbon to the guanidine group presents a strong electron-accepting character. Therefore, the n–π conjugation possible in the guanidine group may be transmitted to the imino nitrogen in the amidine group. In biguanides, this 'push–pull' effect may explain the stronger basicity exhibited by the amidine imino nitrogen than the guanidine imino nitrogen. The exceptionally high basicity of biguanides may additionally result from the formation of intramolecular hydrogen bonds (Scheme 4).

Amidines containing a strong electron-accepting group (e.g. COPh, CN, 4-, 3- and 2-azinyl, 1,3-diazin-2-yl) directly linked to the imino nitrogen atom in FDMs (Scheme 4) belong also to the family of 'push–pull' molecules. For these bifunctional amidines, the imino nitrogen in the amidine group is the preferred site of protonation only for the benzoyl derivative.[33] For the cyano derivative, analysis of the experimental and theoretical results indicates that both nitrogens (imino and cyano) have comparable gas-phase basicity, and it is difficult to indicate the preferred site of protonation.[15,26,34] For the azinyl derivatives, the experimental results indicate, without any doubt, that the aza nitrogen is more basic than the imino nitrogen in the amidine group, independently on the position of the aza-nitrogen in the ring, and thus it is the preferred site of protonation.[23] For the *ortho* position, an enhancement of basicity was observed due to formation of an intramolecular hydrogen bond in the monoprotonated form. All these effects have been discussed in previous papers.[23,26,33]

Substituent electronic effects

First perusal of the gas-phase basicity of strong nitrogen bases indicates that the total gas-phase substituent electronic effects are similar in all investigated series. The *GB* values of alkyl and heteroalkyl derivatives substituted at the imino nitrogen (FDMs, ADMs, PDMs, TEGs, P_1s) correlate well with those of TMGs taken as model series [Fig 1(a)]. Similarly, the *GB* values of derivatives substituted at the amino nitrogen (TBDs) correlate well with the *GB* of TMGs (Fig. 1b). In Fig. 1b, the *GB* of *N*-substituted imidazoles (Ims) studied previously by Taft and co-workers[35] is also plotted against the *GB* of TMGs. For unsubstituted and *N*-methylimidazoles, the *GB* values were taken from Ref. 15. For other derivatives (Et and t-Bu), the *GB* values were estimated on the basis of substituent effects given in Ref. 35

Generally, the slopes of regression lines in Fig. 1(a) are close to unity (Table 2). Even for phosphazenes (P_1s), which contain three amino groups and the phosphorus atom (instead of the functional carbon atom), the total substituent effects seem to be almost the same as those in TMGs. This permits us to esimate quickly the *GB* values for other derivatives in series of P_1s. For example, the *GB* values for the Et, i-Pr, and t-Bu derivatives should be close to 254, 255 and 256.5 kcal mol^{-1}, respectively. Assuming that the total substituent effects in series of P_ps are close to those in TEGs (owing to similarities of the bulk amino groups), the following *GB* values proposed for the Me, Et, i-Pr and t-Bu derivatives are 258, 259, 260 and 261 kcal mol^{-1}, respectively. Errors of these estimations should not be higher than 1 kcal mol^{-1}.

Table 2. Slopes of regression lines given in Fig. 1 for correlations between the *GB* of nitrogen bases and TMGs

Series	Slope	*r*(*s*)	*n*
FDMs	1.19 ± 0.06	0.994 (0.39)	7
ADMs	1.07 ± 0.07	0.990 (0.45)	7
PDMs	0.91	1.0	2
TEGs	0.80 ± 0.04	0.994 (0.28)	7
P_1s	0.92	1.0	2
Ims	0.85 ± 0.10	0.986 (0.58)	4
TBDs	0.55 ± 0.03	0.997 (0.15)	4

The slope of the regression line for TBDs (cyclic guanidines) in Fig 1(b) is considerably smaller than that found for imidazoles (cyclic amidines). This is in good agreement with the previously observed attenuation of the n–π conjugation effect in guanidines ('Y-conjugation') in comparison with amidines (Scheme 2).[5,27] As shown in a previous section, one NMe_2 group in TMG*Me has a smaller effect on the *GB* of *N*-methylimine than one NMe_2 group in FDM*Me (Scheme 2). The attenuation factor of this effect is about 0.7. A slightly smaller value (0.65) is found for the ratio of regression line slopes calculated for TBDs and imidazoles.

Series of TTTs containing different substituents at the amino nitrogen cannot be considered either as amidines or as guanidines. They belong to vinylogues of amidines (vinamidines). Therefore, it is difficult to estimate the *GB* values for other alkyl derivatives, because there is no information on the transmission of substituent effects in such types of molecules.

Substituent electronic effects at the functional carbon atom have been studied in previous work[27]. It has been shown that the *GB* values of differently substituted series of acyclic derivatives can be correlated with the *GB* values of FDMs. However, separate regression lines have been distinguished for aryl, alkyl and heteroalkyl derivatives. For this reason, in search of some general relations for the *GB* prediction in amidines and guanidines, subfamilies of aryl, alkyl and heteroalkyl derivatives should be considered separately. This is in good agreement with our observations based on the comparison with imines (Scheme 2) that some kind of 'Y-conjugation' can take place between the substituents at the functional carbon atom and the imino group.

The good correlations found for N^1- and N^2-alkyl substituted derivatives which display stronger basicity than aryl derivatives entitle us to perform correlations for acyclic amidines and separately for acyclic guanidines studied here according to Eqn. (4):

$$GB = GB^\circ - \rho_\alpha(\mathrm{Im})\sigma_\alpha(\mathrm{Im}) - \rho_\alpha(\mathrm{Am})\Sigma\sigma_\alpha(\mathrm{Am}) - \rho_\alpha(\mathrm{F})\sigma_\alpha(\mathrm{F}) \quad (4)$$

GB° is the gas-phase basicity of unsubstituted derivative, formamidine $H_2NCH,{=}NH$ for amidines and guanidine $(H_2N)_2C{=}NH$ for guanidines; ρ_α(i) and σ_α(i) are the reaction constants for polarizability effects and the directional polarizability parameters of Taft and coworkers,[25,36] respectively, for substituents at the *N*-imino (Im), *N*-amino (Am) and *C*-functional atom (F). The sumation Σ is made on all alkyl groups at the amino nitrogen atom(s).

For the calculation of the parameters in Eqn. (4), only derivatives with hydrogen and simple alkyl groups (Me, Et, n-Pr, i-Pr, t-Bu and l-Adam) at the atoms of the functional group were considered. Their *GB* values were taken from Table 1. For unsubstituted acetamidine [$H_2NC(Me){=}NH$], a component equal to *RT*ln4 was added to the measured *GB* value given in Ref. 15 (224.2 kcal mol^{-1}) to obtain the microscopic (statistically corrected) *GB* value (225.0 kcal mol^{-1}). Similarly, for unsubstituted guanidine [$(H_2N)_2C{=}NH$], a component equal to *RT*ln6 was added to the measured *GB* value given in Ref. 15 (226.9 kcal mol^{-1}) to obtain the microscopic *GB* value (228.0 kcal mol^{-1}). We added *RT*ln2 for TMG*H. The microscopic basicity parameters result from the consideration of deprotonation reaction (1). The formamidinium cation may lose one of four hydrogens to give free base, and the guanidinium cation one of six hydrogens. In the case of TMG*H, the guanidinium cation may lose one of two hydrogens. The microscopic *GB* values were taken into account in calculations of the parameters of Eqn. (4).

Parameters of Eqn. (4) calculated for acyclic alkylamidines and guanidines are given in Table 3. The single substituent at the *N*-amino has a slightly smaller effect on the basicity of both amidines and guanidines than that at the *N*-imino. It has also a smaller effect than that at the functional carbon. The order of the ρ_α values is $\rho_\alpha(\mathrm{F}) > \rho_\alpha(\mathrm{Im}) > \rho_\alpha(\mathrm{Am})$. The ρ_α values represent the sensitivity to the polarizability effect, which decreases rapidly with increasing distance between the charge and the substituent in non-conjugated systems.[25] In the system described here, it can be seen that the sensitivity is not directly linked to the distance substituent-function, because of the charge delocalization on three atoms or more (Scheme 3).

The ρ_α(Im) values are considerably smaller that those found for primary amines (18.65) and nitriles (19.03).[2] The values obtained for the ρ_α(Am) parameter in acyclic amidines (9.98) and guanidines (7.24) are of the same order of magnitude as those found in imidazoles[35] (11.69) and TBDs (5.77) considered as cyclic amidines and guanidines, respectively. The ρ_α(F) parameter in acyclic amidines (12.46) is close to that found for *N*,*N*-dimethylamides differently substituted at the functional carbon (12.3)[25]

The good correlations ($r > 0.99$) obtained in both cases

Table 3. Parameters of Eqn. (4)) for alkyl derivatives of acyclic amidines and guanidines (*GB*° and ρ_α are in kcal mol^{-1})

Eqn. (4)	Series	Formula	*GB*°	ρ_α(Im)	ρ_α(Am)	ρ_α(F)	*r*	*s*	*n*
(4a)	Amidines	$R'_2NC(R'){=}NR$	220.8 ± 0.6	11.89 ± 0.77	9.98 ± 1.88	12.46 ± 0.76	0.994	0.57	16
(4b)	Guanidines	$(R'_2N)_2C{=}NR$	228.5 ± 0.5	9.98 ± 0.86	7.24 ± 1.15	—	0.997	0.53	9

indicate that Eqns (4a) and (4b) (see Table 3) can be used for general *GB* prediction for other simple alkyl derivatives. The most interesting are derivatives with a basicity comparable to that of the strongest bases in the current scale (Table 1). However, application of Eqns (4a) and (4b) to derivatives containing the i-Pr or t-Bu groups at each atom of the functional group (derivatives not yet studied in the gas phase) shows that neither amidines nor guanidines have a predicted *GB* value larger than 255 kcal mol^{-1}, and therefore they could not be used as reference bases for the *GB* measurements of vinamidines, phosphazenes and biguanides with *GB* >258 kcal mol^{-1}. Only for the 1-adamantyl derivatives (if they could be synthesized) are the predicted *GB* values higher than 260 kcal mol^{-1}. This indicates that for the stronger bases in our scale and proposed in the literature[28,37–40] (*GB* > 258 kcal mol^{-1}), series of simple vinylogues and iminologues of amidines and guanidines should be tested.

Cyclization effects

It is well known that for acyclic amidines two configurations at the C═N double bond are possible, one *E* with the amino group and the substituent at the imino nitrogen in the *trans* position and the other *Z* with both groups in *cis* positions. Generally, acyclic amidines prefer the *E* form.[14,41] In the cyclic amidines studied here, each atom of the amidine group belongs to the ring, and thus the configuration *Z* on the C═N bond is well determined. To see the effect of cyclization on the basicity of the *N*-imino, the *GB* values measured for cyclic amidines were compared with those predicted from Eqn. (4a) for acyclic amidines (Table 4). For estimation of the *GB* value of *N*-ethylbenzamidine, the ρ_α(Im) and ρ_α(Am) values were taken from Eqn. (4a). For the unsubstituted benzamidine (BNH_2, Scheme 1), the statistically corrected (*RT*ln4) *GB* was used.

The comparison given in Table 4 shows that five-membered cyclic amidines (IDM and IP, Scheme 1) are weaker bases than the corresponding acyclic models, whereas six-membered cyclic amidines (HP, DBN, DBD and DBU) are stronger bases. The differences are not very large, but they indicate that the number of atoms in the ring determine some kind of strain effects, e.g. strain angle effects which slightly change the electronic properties of ring atoms. Bouchoux and co-workers attributed a part of the cyclization effects observed in ketones and esters to hybridization changes.[42,43] An increase in basicity in lactones (in comparison with acyclic esters) has also been explained by an extra stabilizing interaction between the protonated carbonyl group and the ether-like oxygen. Exceptions have been observed for β-propiolactone[44] and 2-azetidinone,[45] for which cyclization effects were negative. All these explanations, however cannot be transferred to amidines and guanidines, because the imino nitrogen atoms are intracyclic, whereas the carbonyl oxygens are exocyclic in ketones and lactones.

In the case of guanidines, similar comparison of cyclic and acyclic derivatives gives possibilities for estimation of the cyclization effect. For the cyclic guanidines studied here (TBDs), the four atoms of the guanidine group belong to two six-membered rings. This cyclization increases the basicity of the *N*-imino by ca 2–2.5 kcal mol^{-1}, relative to the *GB* of the corresponding acyclic guanidines predicted from Eqn. (4b). The cyclization effect in guanidines is of the same order of magnitude as that for six-membered cyclic amidines.

Table 4. Effects of cyclization (δGB in kcal mol^{-1}) estimated for amidines and guanidines (see text)

Cyclic compound	*GB*	Acyclic model	*GB*	δGB
IDM	228.3	$H_2NCH{=}NBu^t$	229.7	−1.4
IP	233.6	$H_2NC(Ph){=}NEt$	234.8	−1.2
HP	231.0	$H_2NCH{=}NPr^n$	227.2	3.8
DBN	241.0	$Et_2NC(Me){=}NMe$	239.1	1.9
		$Me_2NC(Et){=}NEt$	239.7	1.3
DBD	242.5	$Et_2NC(Et){=}NMe$	240.8	1.7
		$Me_2NC(Pr^n){=}NEt$	240.3	2.2
DBU	243.3	$Et_2NC(Pr^n){=}NMe$	241.5	1.8
MTBD	246.7	$Et_2NC(NMe_2){=}NMe$	244.15	2.55
ETBD	247.35	$Et_2NC(NMe_2){=}NEt$	245.5	1.85

Intramolecular H-bonding

Intramolecular H-bonding in monocations of bifunctional derivatives (Scheme 4) induces strong enhancement of the gas-phase basicity.[5,12,30–32] Comparison of the *GB* values found for such derivatives with those of the corresponding monofunctional model derivatives permits us to estimate this effect.

For bifunctional derivatives of the general formula $X(CH_2)_nY$, where X is the OMe or NMe_2 group and Y is the amidine (N═CR—NR'_2) or guanidine group [N═$C(NR'_2)_2$], the monofunctional derivatives $H(CH_2)_nY$ can be taken as reference models. The difference between the *GB* values of bifunctional and model derivatives ($\delta_{tot}GB$) is the sum of two effects: the substituent electronic effect of the X group ($\delta_X GB$) and the intramolecular H-bonding effect ($\delta_{IHB}GB$). Assuming that (i) the $\delta_X GB$ values for the OMe and NMe_2 group in each type of acyclic amidines are the same as those found for FDMs using Eqn. (4a) from Ref. 3, and (ii) the $\delta_X GB$ effects are smaller in guanidines than amidines by the same factor as the ρ_α(Im) values in Table 3 (1.2), we can easily estimate the $\delta_{IHB}GB$. The $\delta_{tot}GB$, $\delta_X GB$ and $\delta_{IHB}GB$ estimated in this way are listed in Table 5. The *GB* values for bifunctional and model compounds were taken from Table 1. The *GB* values for model TMG*n-Pr and TEG*n-Pr were calculated from Eqn. (4b). For histamine, such a kind of estimation is difficult to

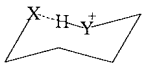
Table 5. Intramolecular H-bonding effects ($\delta_{IHB}GB$ in kcal mol^{-1}) estimated for bifunctional derivatives of acyclic amidines and guanidines (see text)

Bidentate ligand	Model compound	*n*	$\delta_{tot}GB$	$\delta_{X}GB$	$\delta_{IHB}GB$
FDM*$(CH_2)_2$OMe	FDM*Et	2	2.8	−2.3	5.1
ADM*$(CH_2)_2$OMe	ADM*Et	2	1.8	−2.3	4.1
TMG*$(CH_2)_2$OMe	TMG*Et	2	2.85	−1.9	4.75
TEG*$(CH_2)_2$OMe	TEG*Et	2	1.4	−1.9	3.3
TMG*$(CH_2)_3$OMe	TMG*n-Pr	3	4.7	−1.1	5.8
TEG*$(CH_2)_3$OMe	TEG*n-Pr	3	3.15	−1.1	4.25
FDM*$(CH_2)_2NMe_2$	FDM*Et	2	5.0	−0.2	5.2
ADM*$(CH_2)_2NMe_2$	ADM*Et	2	4.65	−0.2	4.85
TMG*$(CH_2)_2NMe_2$	TMG*Et	2	4.65	−0.2	4.85
TEG*$(CH_2)_2NMe_2$	TEG*Et	2	3.45	−0.2	3.65
FDM*$(CH_2)_3NMe_2$	FDM*n-Pr	3	7.8	0.2	8.0
ADM*$(CH_2)_3NMe_2$	ADM*n-Pr	3	6.9	0.2	6.7
TMG*$(CH_2)_3NMe_2$	TMG*n-Pr	3	6.65	0.2	6.45
TEG*$(CH_2)_3NMe_2$	TEG*n-Pr	3	4.45	0.2	4.25

perform owing to lack of the *GB* value for model 4(5)-ethylimidazole, and even the possibility of predicting its *GB*.

The calculated $\delta_X GB$ values for the NMe_2 derivative are very small and can be neglected in estimations of the $\delta_{IHB}GB$ for other derivatives. However, for the OMe derivatives the $\delta_X GB$ are considerably larger than the error of this estimation (<0.4 kcal mol^{-1}), and should always be taken into account.

Generally, in amidines and guanidines, larger IHB effects are found for the NMe_2 than OMe derivatives, and for three ($n = 3$) than two ($n = 2$) methylene groups in the chain. This may be explained by the fact that amines are stronger bases than ethers, and that the six-membered ring with intramolecular H-bonding is more stable than the five-membered ring. The same behaviour has also been observed for diamines and amino ethers.[15,17,30] IHB effects have been found to be (i) larger for diamines than for amino ethers and (ii) larger for compounds with 3-methylene than 2-methylene side-chains. The largest IHB effects have been observed when a 4-methylene side-chain links the basic sites, and this was attributed to a chair-like conformation[46] In this geometry, the hydrogen bond is almost linear, reducing the strain to a minimum.



All these observations indicate that the IHB effects are mainly due to two contributions: the strength of the basic sites which can chelate the proton and the geometry of monocations which favours formation of an intramolecular H-bond.

EXPERIMENTAL

The origin of acyclic (BMP, FDMs, ADMs, ADEs, PDMs, BTMs, TMGs, TEGs, P_1s) and cyclic (DBD, MTBD, ETBD, ITBD, TTT, MITT, P_ps, BEMP) derivatives was the same as described previously[2–5,9,13] Biguanides were synthesized as described[47] by addition of guanidines to carbodiimides. Other derivatives (imine, BNH_2, IDM, IP, HA, HP, DBN, DBU, PMDBD, TBD) and reference bases were commercial products (Aldrich, Merck or Fluka). The procedure for the gas-phase basicity measurements was the same as described previously.[2–5]

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