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Review Commentary

Consequences of proton transfer in guanidine†

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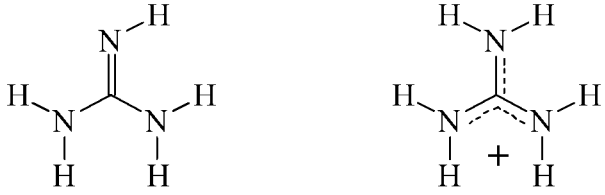
ABSTRACT: Consequences of proton-transfer reactions in guanidine in the solid state, solution and gas phase are discussed. Y-delocalization, resonance and symmetry strongly influence the basicity of guanidine in the gas phase. These effects are, however, insufficient to explain the basicity of guanidine which in aqueous solution is stronger than that of trisubstituted alkylamines and proton sponge (DMAN). The intrinsic (gas-phase) basicity of guanidine is close to that of triethylamine. The large difference between the basicities of amines and guanidine in solution is attributed to the important role played by effects such as polarizability and internal and external solvation. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: guanidine; resonance stability; Y-delocalization; proton transfer; basicity solvation

INTRODUCTION

Guanidine (Scheme 1) was first obtained by oxidative degradation of an aromatic natural product, guanine, isolated from Peruvian guano.[1] The biological activity of guanidine, its particular thermodynamic stability, exceptionally high basicity in aqueous solution and applications in synthesis have been the subject of numerous discussions in the literature during the last three decades.[2–9] Several authors tried to answer two questions: (i) why guanidine is a such strong base in aqueous solution and (ii) why the guanidinium ion is so stable. Various theories and explanations were proposed. Some of them were focused on the Y-aromaticity of the system.[2,9] Although this concept confirms the strong stability of the guanidinium ion, it does not explain different localizations of the guanidinium cation *vis-à-vis* the counter ion in salts, or the difference in the basic strength of guanidine in the gas phase (basicity close to that of triethylamine)[10] and in water (basicity comparable to that of the hydroxide ion).[11]

In this paper, we focus our attention on this peculiar compound and the structural (internal) and environmental (external) consequences of the proton-transfer reactions, which are similar in many important biomolecules containing the guanidine skeleton. The biological activity of guanidine and its derivatives is not reviewed in detail. Rather, we recall some examples of their wide applications in chemotherapy, their important interactions with other biomolecules and their particular actions in the living organisms. Next, we discuss (i) the geometry of guanidine and its cation (the latter being the biologically relevant species), (ii) the difference in the resonance stability of the neutral and ionic forms, (iii) the experimental and theoretical evidence for the sites of protonation and deprotonation in guanidine itself and (iv) its experimental basicity in various conditions. Some comments on the proton affinity predicted by quantum-chemical calculations are included. Finally, we compare



Scheme 1. Guanidine and guanidinium monocation

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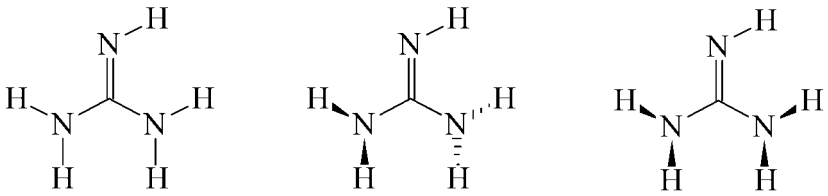
†This paper is dedicated to Professor Dr Tadeusz Marek Krygowski (University of Warsaw, Poland) on the occasion of his 65th birthday.



1a **1b** **1c**

Scheme 2. Possible structures for guanidine

the gas-phase and solution basicities of guanidine in the light of the differences between the acidity–basicity scales in these two phases to show the origin of the strong basicity of guanidine in aqueous solution.

BIOLOGICAL ACTIVITY

The guanidine moiety is incorporated in many natural products and also in synthetic systems of biological importance. Guanidine is a substructure of many important molecules, such as arginine (an amino acid), creatine (the muscular energy intermediate), guanine (the purine base of the nucleic acids DNA and RNA), streptomycin (an antibiotic), ptilomycalin A (an alkaloid) and other biomolecules.[3,12]

Although guanidine itself is fairly toxic, its derivatives find numerous applications in chemotherapy.[3,13,14] They demonstrate antibacterial, antiviral, cytotoxic and antifungal properties (sulfaguanidine, crambescidin 800, celeromycalin, fromiamycalin).[3,12] They also possess anti-inflammatory and hypotensive or hypertensive properties (clonidine, guanethidine).[3a] Some of them have been tested in oral treatment of diabetes (synthalin A, synthalin B, performin, buformin, metformin).[14] Others are antagonists (cimetidine, famotidine) or agonists of histamine receptors (SK&F 91486, impromidine, arpromidine).[15]

Other interesting properties of guanidine and its derivatives include the inhibition of DNA synthesis, the denaturation of proteins and the modification of the electrostatic surface potential of mitochondria and other membranes.[14] Hydroxyguanidine, which inhibits the synthesis of DNA, was classified as an antitumor drug.[16] By its interactions with proteins, guanidinium hydrochloride exhibits a dual function. It is a commonly used denaturant to unfold native proteins but has also been tested as a stabilizer of the folded proteins.[17] Guanidinium ion itself and its amino-substituted derivatives are capable of passing through sodium ion channels in the nerve membrane.[18] Substituted guanidinium molecules (e.g. tetradotoxin) block the passage of sodium ions thus inhibiting nerve function.[18b] They also interact with the cardiac Na^+–H^+ exchange system by blocking its activity.[18c]

Most of the biological properties of guanidine and its derivatives, such as their interaction with proteins, their influence on the function of sodium channels and their transport in different human membranes and cells, etc., are related to their strong basicity. Under physiological conditions, these strong bases exist mainly in their protonated forms. These positively charged organic ions are important elements in different mechanisms and schemes proposed in the literature to explain the biological activity of the guanidine function, particularly that of arginyl residue in the active site of various proteins and enzymes. For modeling interactions in physiological conditions, complexes between the guanidinium and carboxylate ions have been widely investigated.[19]

GEOMETRY OF GUANIDINE AND ITS CATION

Guanidine and guanidinium ion are special cases of n–π conjugated heteroallylic systems.[20] One imino and two amino nitrogens are linked to the same carbon atom, leading to a cross-conjugated or Y-delocalized hetero system containing six π-electrons.[2–9]

Unfortunately, to our knowledge, the structure of the free base has not been experimentally determined, from either x-ray diffraction,[21] electron diffraction or microwave spectra. Information on its structure has only been obtained from the infrared spectrum of guanidine in the solid state[22] and quantum-chemical calculations.[5,6,23,24] From the analysis of the IR spectrum, it was concluded that guanidine prefers to adopt a planar form (probably point group C_s, but for the purpose of describing the skeletal modes, the C_{2v} symmetry was assumed).[22] On this basis, early calculations were based on the assumption that guanidine was planar (**1a** in Scheme 2), and therefore its geometry was optimized with the constraint of planarity.[23] In the last decade, non-planar structures have also been considered (**1b** and **1c**), and calculations performed without any symmetry constraint.[5,6,24] Two conformations with the guanidine group (CN_3) planar and the amino groups pyramidal at the nitrogen atoms (**1b** and **1c**, both C_1 symmetry) are evidently favored with respect to the planar one (by 4–7 kcal mol^{-1}; 1 cal = 4.184 J), and **1b** corresponds to the energy minimum at the HF

Table 1. Bond lengths and bond angles of a few guanidine derivatives (for definition of geometric parameters, see Fig. 1)[a]

Derivative		Bond length (Å)			Bond angle (°)			
R_1, R'_1	R_2, R'_2	CN^1	CN^2	CN^3	α_1	α_2	α_3	Ref.
H, Ph	H, H	1.386	1.357	1.287	121.1	127.4	111.3	25a
H, Ph	H, H	1.374	1.358	1.278	122.4	125.3	112.3	25a
H, Ph	H, H	1.366	1.357	1.278	122.4	124.7	112.9	25b
H, Ph	H, H	1.368	1.335	1.292	121.6	125.2	113.2	25b
Me, Ph	H, H	1.393	1.345	1.284	119.8	125.0	115.2	25a
H, Ph	H, Me	1.380	1.379	1.270	127.8	120.8	111.4	25a
Me, Ph	Me, Me	1.409	1.344	1.298	125.1	119.3	115.5	25a

[a] For one or two independent molecules present in the unit cell of the crystal derivative.

(Hartree–Fock), MPn (*n*th order of the Møller–Plesset) and CISD (configuration interaction method with single and double excitations) levels with the use of the 6–31G* basis set.[24] Independently of the assumption accepted and structures considered, all theoretical results indicate that the CN bond of the imino NH group is shorter (by ca 0.1 Å) than the two CN bonds of the amino NH_2 groups.

A similar conclusion concerning the bond lengths is also achieved from the analysis of experimental x-ray geometries of the guanidine derivatives. Table 1 presents selected geometric parameters of *N*,*N*′-diphenylguanidine, *N*-methyl-*N*,*N*′-diphenylguanidine, *N*″-methyl-*N*,*N*′-diphenylguanidine and *N*,*N*,*N*′-trimethyl-*N*′,*N*″-diphenylguanidine.[25] In fact, not only may the imino and amino CN bonds differ significantly (by about 0.08 Å) but also substantial differences due to substitution are observed in the bond lengths of the two amino groups (up to 0.065 Å in the case of *N*,*N*,*N*′-trimethyl-*N*′,*N*″-diphenylguanidine). This indicates that the guanidine moiety is sensitive to structural effects. This in turn implies that the electronic structure of the fragment may be highly labile. Indeed, possible intra- and intermolecular interactions such as substituent effects[26] and hydrogen bonds in the crystal lattice may drastically reduce the alternation between the lengths of formally different types of CN bonds [e.g. in cyanoguanidine, 2-nitroguanidine, glyoxal bis(amidinohydrazone) or sulfaguanidine].[27] As expected, all guanidine fragments are planar within the experimental error [the mean deviation from the least-square plane usually does not exceed 0.007 Å (based on derivatives from Table 1)].

In the case of guanidinium ion, assumptions similar to those for the free base have been used in quantum-chemical calculations, and different structures considered (**2a–e** in Scheme 3).[5,6,23c,28,29] Currently, there is no common theoretical conclusion about the geometry corresponding to the total energy minimum of the cation [D_{3h}, completely planar (**2a**); C_3 and C_1, with planar NH_2 groups rotated out of plane by about 12–18° (**2b** and **2c**); C_s and C_{3v}, with pyramidal NH_2 group (**2d** and **2e**)][5,6,29] The differences between total energies of stable structures are small, and the point group symmetry of the global minimum depends on the level of calculations.[5] Independently of this lack of definite conclusion, the CN_3 moiety of the monocation is planar and the CN bond lengths are identical. The only differences are in the positions of the hydrogen atoms. Their positions depend strongly on the level of calculations, and are also exceptionally difficult to determine experimentally, either by x-ray diffraction or by IR, Raman and NMR spectrometry. Different symmetries for the guanidinium ion have also been proposed based on spectroscopic measurements for various salts: D_{3h},[30] C_{3h}[31] and C_{3v}.[32]

A statistical analysis of 112 molecular geometries of guanidium ion in 80 salts and complexes retrieved from the Cambridge Structural Database[21] [only the highest precision molecular geometries (*R*-factor smaller than 5% and the mean standard deviation for bond lengths does not exceed 0.005 Å) were analyzed] fully confirms that the CN_3 moiety is planar within experimental error. The mean deviation of carbon and nitrogen atoms from the least-square plane is only 0.004 Å. Unfortunately, the x-ray analysis does not give further, reliable information on the position of hydrogen atoms,[33] and neutron diffraction data are available for only a few derivatives of the guanidinium ion.[34] These, however, reveal that only in the case of creatine[34b] is one of the amino groups slightly non-planar. Further statistical analysis of the molecular geometries of guanidinium ions confirms also that the CN bond lengths are nearly equal (the mean C—N bond length is 1.321 ± 0.009 Å), indicating that the electrons can be regarded as essentially delocalized in the moiety. The highly symmetric and planar guanidinium ion, with its six equivalent protons, is a hydrogen bond

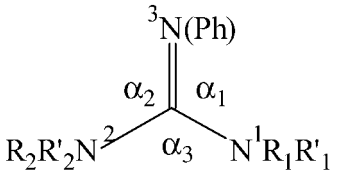
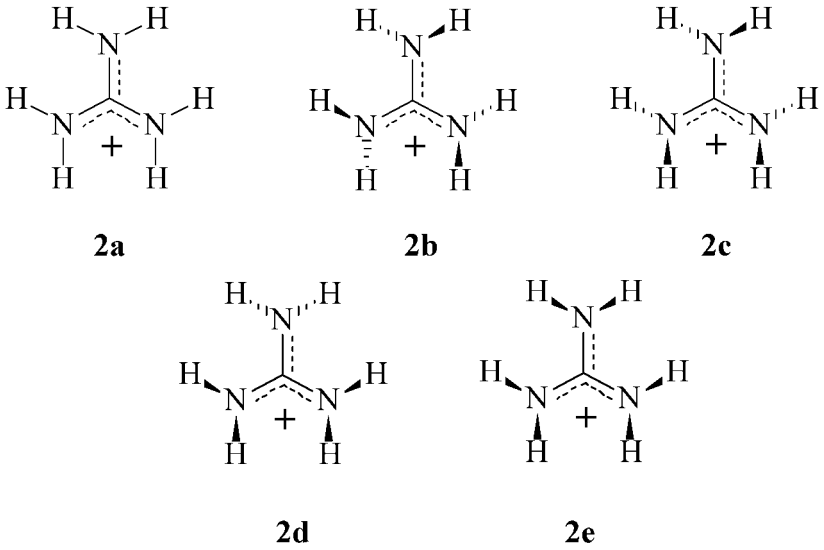


Figure 1. Selected geometric parameters of guanidine fragment

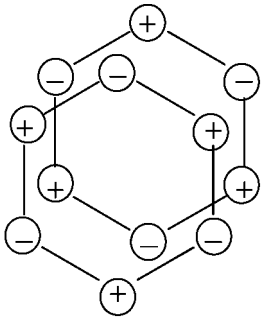


Scheme 3. Possible structures for guanidinium ion

donor. Hence, hydrogen bonding provides the major driving force for crystal packing. Since the H-bond donor and acceptor are charged species, the electrostatic interactions in the crystal lattice may additionally modify the hydrogen bond network. The richness of possible interactions (hydrogen bonds, electrostatic interactions, van der Waals contacts) has stimulated great interest in experimental x-ray studies of many, if not most, of guanidinium derivatives. The most common three-dimensional motifs of hydrogen bonds are observed, for instance, in salts of guanidinium: nitrite semihydrate, chloride, hydrogen squarate, phthalate, hydrogen l-aspartate, carbonate or diguanidinium: tetrachlorozincate and tetrabromozincate, hexafluorosilicate, hydrogen phosphate, sulfate and zinc guanidinium sulfate.[35] In these structures, the hydrogen bonding patterns are different, whereas their topology allows one to classify most of them as of medium strength. The two-dimensional type of arrangement is observed in the structures of, e.g., guanidinium nitrate, perchlorate and alkane- and arenesulfonates.[36] In contrast to the three-dimensional networks, where the crystal lattice is strongly stabilized by hydrogen bonds, the low-dimensional bonded aggregates are susceptible to thermodynamic conditions and easily undergo transformations.[36b,c] Moreover, it has been demonstrated[36b,d] that the electrostatic interactions may play a very significant role in further enhancing the network formation. For instance, depending on the steric constraints of penetrating groups, the sheets of guanidinium alkane- and arenesulfonates[36d] assemble in a third direction as either single layers or bilayers. Clearly, in the case of bilayers, the positively charged guanidinium ions are situated in proximity to negatively charged sulfonate ions in adjacent sheets, as shown at Scheme 4. The interlayer spacing between the sheets of adjacent bilayers ranges from 3.33 to 4.06 Å, depending on the kind of substituent.

Similarly, the antiparallel structure of guanidinium nitrate (Fig. 2) is strongly stabilized by electrostatic interactions between the sheets as compared with the parallel arrangement.[36b] Additionally, it has been shown that the electrostatic forces between the ions within one sheet also favor the antiparallel motif.[36b] Clearly, also in the case of guanidinium perchlorate the Coulomb interactions play a prominent role in the stabilization of the crystal structure.[36c]

There are also a few examples in which the guanidinium ion forms a crystal structure with weak (or does not reveal any) hydrogen bonds, as it is observed, e.g., in the structures of guanidinium iodoplumbates.[37] Recently, is has been shown that some guanidinium salts may be useful compounds to obtain materials of required properties and/or predictable structures,[36d,38] e.g. crystalline clathrates[39] or nanoporous molecular sandwiches.[40]



Scheme 4. The adjacent layers form pseudo-hexagonal nets of hydrogen-bonded $C(NH_2)_3^+$ (denoted by positive sign) and RSO_3^- (denoted by negative sign). In the crystal lattices the nets are shifted

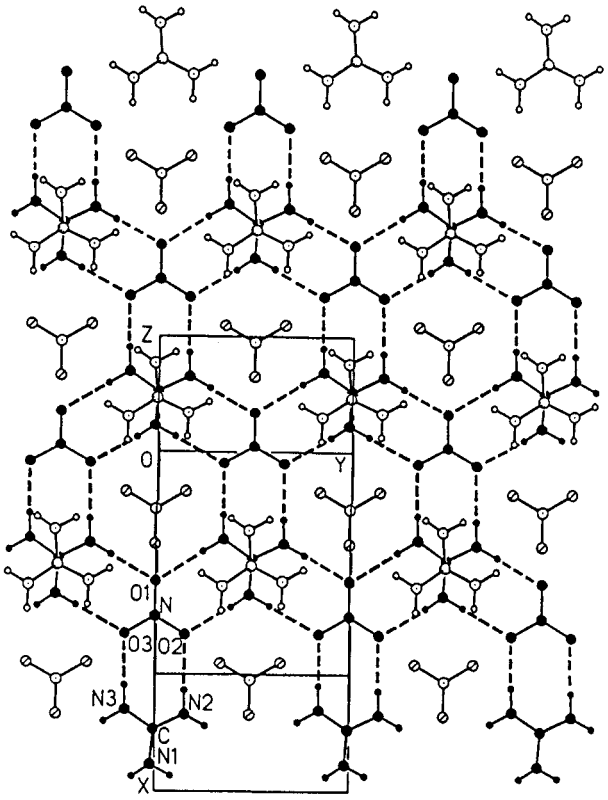


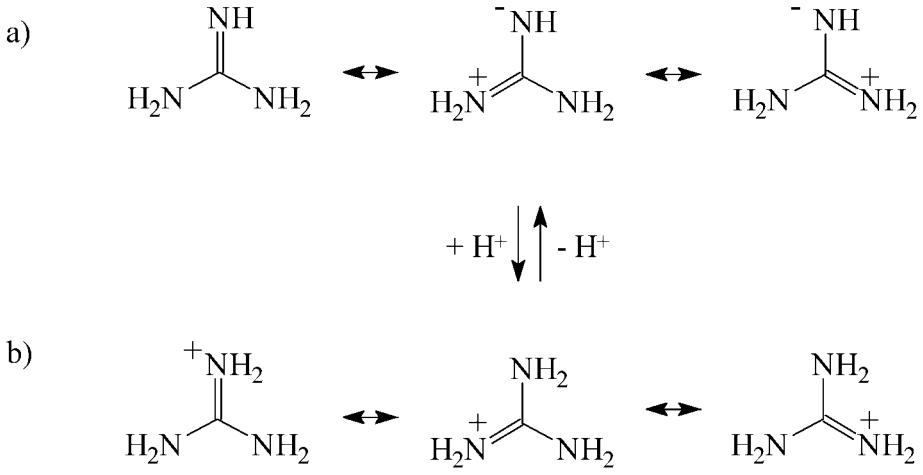
Figure 2. Two sheets of the hydrogen-bonded ions in the antipararell arrangement. For clarity the hydrogen bonds of only one sheet are indicated by dashed lines. Reprinted from the Journal of Molecular Structure, Vol. 378, Kartusiak A, Szafrański M. "Structural phase transitions in guanidium nitrate", 205–233, Copyright 1996 with permission from Elsevier Science

RESONANCE STABILIZATION

Guanidine and guanidinium ion exhibit unusual (for acyclic systems) thermodynamic stability, delocalization of six π-electrons and energetic barriers to rotation. More than 60 years ago, the enhanced stability of the neutral and of the ionic species was considered in terms of resonance theory.[41] According to this theory, the free base may be written using three non-equivalent resonance structures, in two of which the charges are separated (Scheme 5). Protonation of guanidine leads to a highly symmetric ion, for which three equivalent resonance structures are possible. Pauling,[41b] using valence bond theory, estimated the difference in the stabilization energy (being a result of resonance) between the free base and its monocation and found that the guanidinium ion is more stable than guanidine by 6–8 kcal mol^{-1}. This phenomenon has been observed in various IR, Raman and NMR spectroscopic experiments[22,30c,31,32,42] and has been examined by quantum-chemical calculations.[23a,c]

The remarkable stability of guanidinium ion (similar to that observed for other Y-delocalized systems containing six π-electrons) has led to the proposition of a new type of aromaticity, the so-called 'Y-aromaticity.'[2] The concept of Y-aromaticity of guanidinium ion and its consequences on physicochemical properties, particularly on the basicity of guanidine in aqueous solution, have been the subject of numerous discussions both for[7,9] and against.[4,5,43]

Gund,[2] utilizing the HMO (Hückel molecular orbital) theory, observed that orbitals occupied by the six π-electrons in the guanidinium cation resemble those in benzene. The delocalization energy calculated for the cation, equal to 1.60β (about 26.4 kcal mol^{-1}), is similar to that of 2.00β for benzene (about 33 kcal mol^{-1}). The loss of a proton by the cation appears to perturb relatively weakly the six π-electron system. The free base retains most of the Y-delocalization, with the energy of delocalization equal to 1.20β (19.8 kcal mol^{-1}). The difference in the delocalization energy between the free base and its cation, equal to



Scheme 5. Resonance stabilization of (a) guanidine and (b) guanidinium ion

0.4β (6.6 kcal mol^{-1}), is close to an earlier estimate by Pauling.[41b]

Opponents of the Y-aromaticity concept have indicated many other reasons for the exceptional stability of Y-conjugated systems. Among them, the favorable positive charge distribution[44] and the favorable Coulombic interactions[43b] were claimed to be more important than Y-aromaticity. However, Wiberg[4] concluded, using high-level *ab initio* calculations (MP3/6–311 ++ G**// 6–31G*), that neither resonance stabilization nor favorable charge interactions stabilize the guanidinium ion vs the free base. The charge distributions on the nitrogens do not vary much on proceeding from the neutral to the ionic form. Both species have about the same π-electron populations. The protonation of guanidine is only 10 kcal mol^{-1} more exothermic than that of propanimine (imine of acetone), indicating that six π-electrons do not necessarily lead to strong stabilization. Wiberg suggested that the rotational barrier around one single bond found on the basis of both experiment ($\Delta G^{\#} \leq 13$ kcal mol^{-1} derived from the NMR spectrum of guanidinium ion in anisotropic liquid crystalline nematic solution)[45] and theory (10–20 kcal mol^{-1})[4–6,23a,28,45–47] may be an indication of the low resonance stability of the guanidinium ion. In the light of these observations, it was suggested that the high stability of the guanidinium ion, and thus the strong basicity of guanidine in aqueous solution, originate from a strong hydrogen bonding between the cation and water molecules.[4–6,8,48]

Contrary to these hypotheses, Ohwada *et al.*[7] concluded, using the constrained HF method (which gives a direct measure of the π-conjugation energy), that a special stability in Y-shaped systems exists. For a single constraint in the guanidinium ion, the intrinsic π-conjugation effect is about 28 kcal mol^{-1}, significantly larger than that for the free base (7 kcal mol^{-1}). Guanidine is also a Y-delocalized system, but the delocalization is not as large as in its ion.

Krygowski *et al.*[9] applied the geometry-based HOMA (harmonic oscillator measure of aromaticity) index of aromaticity[49] (HOMA is defined in such a way to give 0 for a model non-aromatic system and 1 for a system where full π-electron delocalization occurs) to quantify the extent of π-electron delocalization and the resistance of guanidinium ion to perturbations. The HOMA is the geometry-based index of aromaticity defined as follows:

$$\mathrm{HOMA} = 1 - \frac{\alpha}{n}\sum\left(d_{\mathrm{opt}} - d_i\right)^2$$

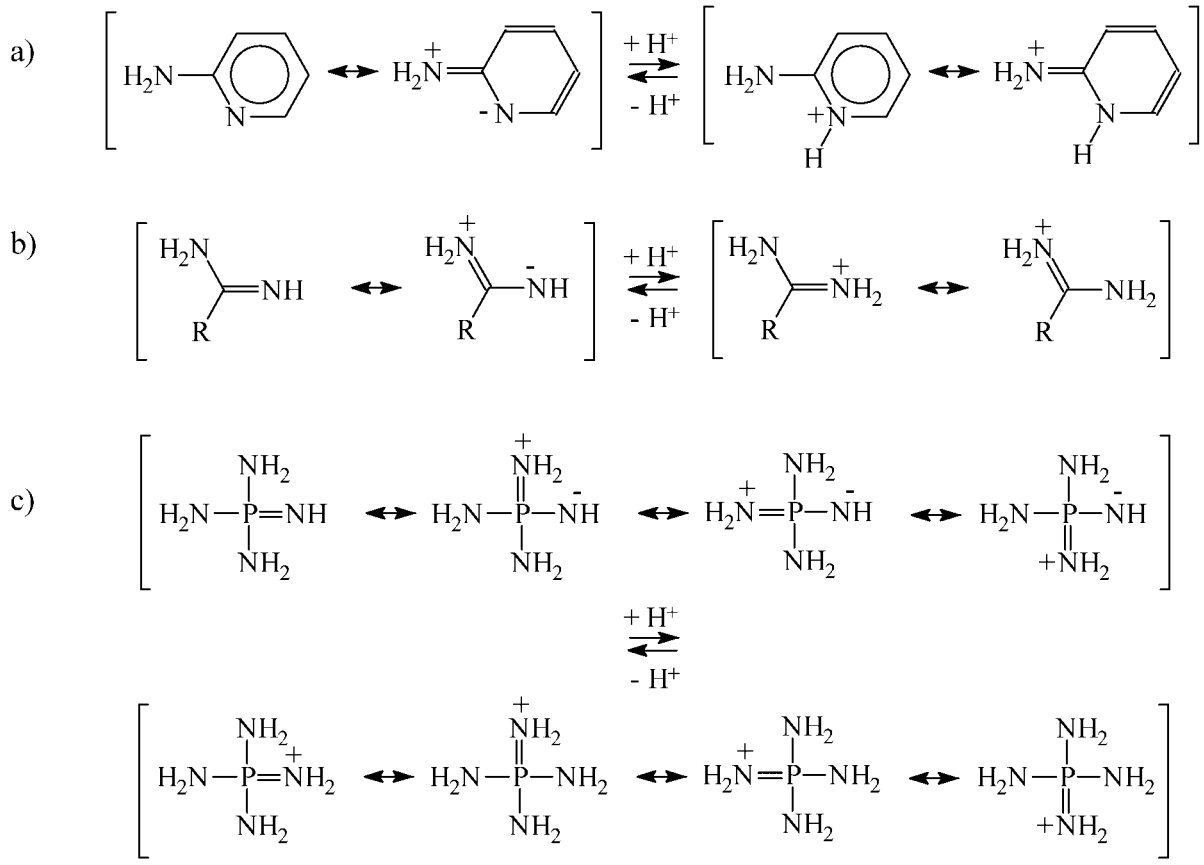
where n is the number of bonds taken into account; α (equal to 93.52 for CN bonds) is a normalization constant (to give HOMA = 0 for a model non-aromatic system and HOMA = 1 for the system with all bonds equal to the optimal value); d_{opt} is the optimum bond length which is assumed to be realized when full delocalization of π-electrons occurs (1.334 for CN bonds); and d_i are the running bond lengths. The statistical analysis based on the most precise molecular geometries of guanidinium salts retrieved from the Cambridge Structural Database[21] revealed that the delocalization of π-electrons in the moiety was very high with HOMA = 1.011 (for benzene HOMA = 0.979). Moreover, they have also shown that the variation of the HOMA index was characterized by a smaller dispersion than it is in the case of benzene derivatives.[50] This indicates that the intermolecular interactions present in the crystal lattice do not affect much the Y-delocalization and suggests that the moiety is more resistant to perturbations than benzene itself. For these reasons, it was suggested to call the guanidinium ion an acyclic analogue of benzene.[9]

Obtaining guanidine as a free base according to the procedure described by Bordwell and Ji[51] in 1991 allowed gas-phase measurements,[6] and gave the possibility to explain the difference between the basicities of guanidine in the gas phase and in solution. Comparison with other organic bases, exhibiting smaller or higher basicity than that of guanidine, indicates that all the factors, Y-delocalization, resonance and symmetry, play an important role in the stability of protonated forms of the exceptionally strong bases both in the gas phase and in solution. In condensed phases, the difference in solvation of the basic and acidic forms is decisive.[6,23b,52]

THEORETICAL AND EXPERIMENTAL ARGUMENTS FOR THE ATTRIBUTION OF THE SITE OF PROTONATION OR DEPROTONATION

Guanidine possesses three nitrogen atoms, susceptible to be protonated. The n–π conjugation possible between the amino and imino nitrogens (Scheme 5) increases the basicity of the *N*-imino and decreases the basicity of the *N*-amino atom, similarly to 2-aminopyridines, amidines and phosphazenes (Scheme 6). As a consequence of this conjugation effect, the *N*-imino atom is first protonated.[3,6,20,29,34–36,52c,53,54] The basicity of the *N*-amino atom is relatively weak. Several quantum-chemical calculations performed at the MP2 and MP4 levels with the use of 6–31G* or 6–31G** basis sets for isolated molecules indicated that in guanidine the *N*-amino is less basic than the *N*-imino atom by ca 30 kcal mol^{-1}.[6,19f,29] A similar behavior was observed in amidines.[55] In the neutral amidine molecule, the *N*-imino atom is much more susceptible to proton attachment than the *N*-amino atom.

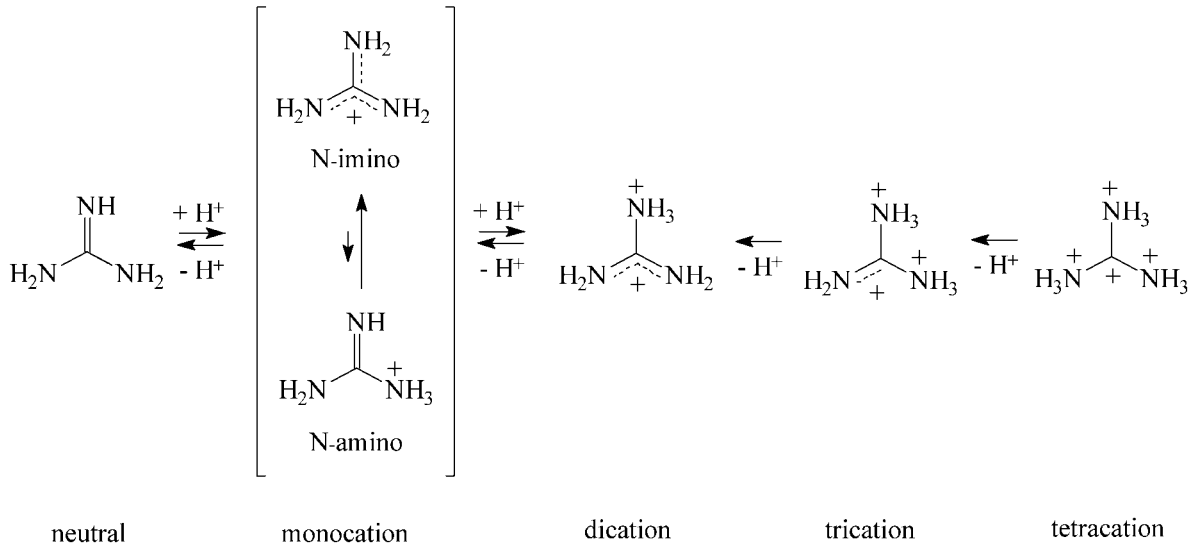
Even in strong acids, such as H_2SO_4, CF_3SO_3H and FSO_3H in SO_2ClF, only monoprotonated guanidinium ion was observed.[29,53,56] A second protonation of guanidine (at the *N*-amino atom in the monocation) is possible in the so-called 'magic acid'[57] (the 1:1 molar FSO_3H–SbF_5 acid system) diluted in SO_2 or SO_2ClF.[29,53] The same kind of protonation has been observed in another superacidic medium (FSO_3H:2SbF_5 in



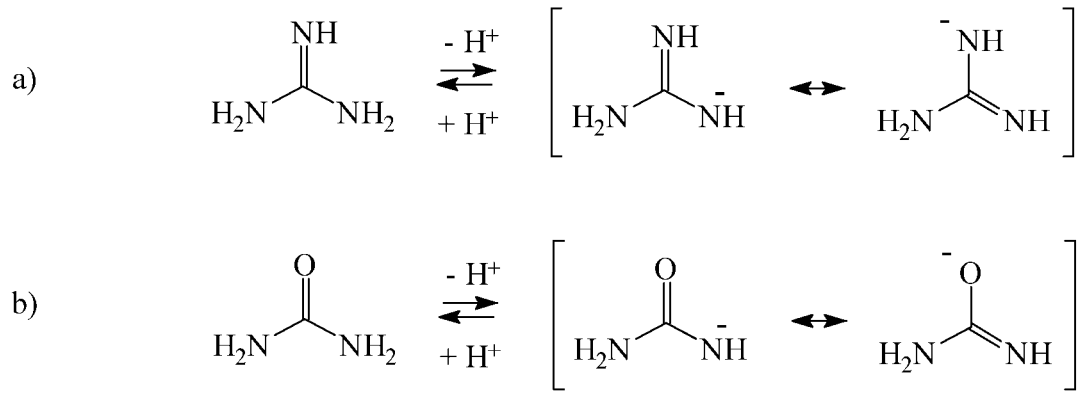
Scheme 6. Resonance stabilization of the neutral and protonated forms in (a) 2-aminopyridine, (b) amidine and (c) phosphazene

SO_2ClF).[29] Tri- and tetraprotonated guanidines (Scheme 7) have not been identified. They have only been investigated theoretically using *ab initio* methods.[29]

The monoprotonation of guanidine in water is a very exothermic process, it is more exothermic (by ca 20 kcal mol^{-1}) than that of OH^-, the strongest base in aqueous solution.[58] The quantum-chemical calculations performed by Olah *et al.*[29] for successive protonations of the monocation to form a dication, a trication and a tetracation (Scheme 7) explained why the dication can be



Scheme 7. Protonated forms of guanidine



Scheme 8. Comparison of deprotonation reaction in (a) guanidine and (b) urea

formed in acidic solution, but both the tri- and the tetracations have never been identified in the strongest superacidic media. Only the formation of the dication is an exothermic process (by 60–70 kcal mol^{-1}). The protonation of the dication leading to the trication is endothermic (by 70 kcal mol^{-1}), and the tetracation is thermodynamically and kinetically unstable.

Considering neutral guanidine as a Brønsted acid, two types of acidic sites can be distinguished, the amino and imino groups. Bordwell and Ji[51] showed that in dimethyl sulfoxide (DMSO) solution the acidity of guanidine ($pK_{HA} = 28.5$) is close to that of 2-aminopyridine ($pK_{HA} = 27.7$). Comparison of the pK_{HA} of various imines and amidines led to the conclusion that the amino (NH_2) group is more acidic than the imino (NH) group in the amino–imino conjugated systems, and that the NH_2 group is preferentially deprotonated. The pK_{HA} of the imino group is larger than that of the amino group by ca 4 pK_{HA} units {e.g. $pK_{HA}(R_2C{=}N\underline{H}) = 31.0$, $pK_{HA}[Et_2N{-}C(R){=}N\underline{H}] = 30.7$, $pK_{HA}[\underline{H}_2N{-}C(R){=}NH] = 26.7$, where R = Ph and all p*K*s are in DMSO}.

The acidity of guanidine is also close to that of urea ($pK_{HA} = 26.95$).[59] This indicates that the Y-conjugation between one C=NH and two NH_2 groups in guanidine has an effect on acidity similar to that between one C=O and two NH_2 groups in urea (Scheme 8). A slight decrease in the acidity of guanidine with respect to urea (by 1.55 pK_{HA} units) may result from the smaller electronegativity of the nitrogen atom in the C=NH group than that of the oxygen atom in the C=O group. A similar decrease (by 1.6 pK_{HA} units) was observed for acetamidine {$pK_{HA}[\underline{H}_2N{-}C(Me){=}NH] = 27.1$} compared with acetamide {$pK_{HA}[\underline{H}_2N{-}C(Me){=}O] = 25.5$}.[51]

SOLUTION BASICITY

The particular acid–base properties of guanidine, its ability to attach a proton on a basic site or to loose a proton from an acidic site are well described by the Brønsted–Lowry theory.[3,6,20,29,51,60] In solution, the free species (guanidine, its conjugate acid and the proton) do not exist; they are always solvated by one or more solvent molecules. Therefore, measurements of intrinsic (absolute) Brønsted acidity and basicity are impossible. Only the relative acid–base parameters (e.g. pK_a) can be measured.[11,52c,61] They always refer to a given solvent, which participates in the following proton transfer reaction:[62]

$$B_{sol} + SolH^+ \rightleftharpoons BH^+{}_{sol} + Sol \qquad (1)$$

Guanidine is an exceptionally strong base. It reacts with water and CO_2 from air giving the corresponding guanidinium salts. In neutral aqueous solution, it exists mainly in the monoprotonated form. The basicity of guanidine is close to that of hydroxide ion ($pK_a = 13.6$).[60c] Since guanidinium ion bears six equivalent acidic protons, the measured pK_a has to be corrected by a statistical factor of log 6. This correction gives a microscopic pK_a value of 14.4.[23b]

Substitution of the nitrogen atoms in guanidine by electron-donating groups (e.g. alkyls) slightly increases its basicity, and substitution by electron-accepting groups (e.g. Ph, NH_2, OH, OMe, COMe, CN, NO_2) causes a reverse effect.[63] Several linear relationships between the pK_a and the Hammett σ constants (or other structural parameters) describe this behavior.[63,64] Exceptionally high basicities have also been observed for polyguanides[20,65] and guanidine derivative of 1,8-diaminonaphthalene.[66]

Guanidine is a stronger base than nitrogen compounds containing one potentially basic site (*N*-imino or *N*-amino) linked to a carbon atom, e.g. pyridines, amines and amidines. It is also stronger than compounds with two basic nitrogens, e.g. diamines (Table 2).[11,20,67] Other bidentate nitrogen ligands with a rigid structure, such as proton sponges[67] and vinamidines,[68] have an even higher basicity than guanidine. More basic also are phosphazenes[69] (Scheme 6) containing a potentially basic *N*-imino atom bonded to a phosphorus(V) atom. In phophazenes, the difference in electronegativity between

the P and N atoms is higher than that between the C and N atoms in guanidine. The effect of three amino groups enhances the resonance stability of the phosphazenium ion in comparison with the guanidinium ion, bearing only two amino groups. A similar behavior (except for aromatic derivatives) has been observed for the gas phase; the absence of a solvent allowing one to obtain absolute acid–base parameters.[54e,f]

EXPERIMENTAL GAS-PHASE BASICITY (GB)

For the gas-phase protonation reaction (2) of the neutral base B, the thermodynamic basicity parameters, such as gas-phase basicity (*GB*) and proton affinity (*PA*), are defined.[10] The absolute *GB* corresponds to the negative of the Gibbs free energy change [Eqn. (3)]. The absolute *PA* is the negative of the enthalpy change [Eqn. (4)]. These basicity parameters are linked together by the entropy term $T\Delta S°$(2).

$$B + H^+ \rightleftharpoons BH^+ \quad (2)$$

$$GB(B) = -\Delta G°(2) \quad (3)$$

$$PA(B) = -\Delta H°(2) = GB(B) - T\Delta S°(2) \quad (4)$$

The protonation reaction in the gas phase is a very exergonic ($\Delta G° \ll 0$) and exothermic ($\Delta H° \ll 0$) process.[10,73] Therefore, determinations of the absolute parameters are very difficult, and limited to a small number of simple species. Only for a few molecules could the absolute parameters be calculated from other thermodynamic quantities.[10] Fortunately, the relative parameters can be measured by various mass spectrometric methods.[10,74] In one of them, the relative parameters correspond to a proton exchange between the conjugate acid BH^+ of a base and a reference base Ref, and between the base B and the conjugate of Ref, $RefH^+$. The relative GB for a neutral base B can be obtained from the equilibrium constant of a gas-phase proton-transfer reaction [Eqn. (5)] between conjugate ionic acid of the reference base ($RefH^+$) and base (B). The equilibrium constant can be obtained from mass spectrometric observation of the relative intensities of two ions $RefH^+$ and BH^+ in a mixture of two bases B and Ref of a known composition.

$$RefH^+ + B \rightleftharpoons Ref + BH^+ \quad (5)$$

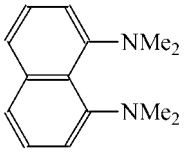
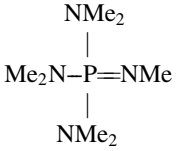
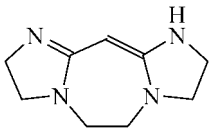
$$\Delta GB = GB(B) - GB(Ref) = RT \ln K(5) \quad (6)$$

Many neutral bases have been studied by indirect methods and a gas-phase basicity scale constructed.[10] This scale, however, is strongly dependent on the values of absolute parameters obtained by direct methods for the reference standards.

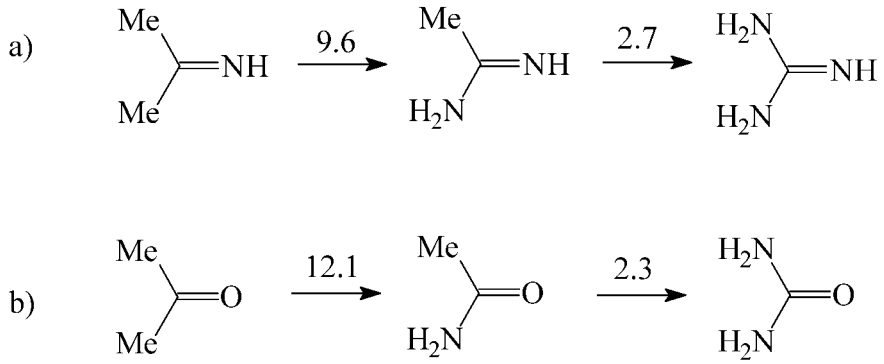
The *GB* of guanidine was obtained by an indirect method, i.e. from gas-phase measurements of the equilibrium constant for the proton-transfer reaction (5).[6] Two reference bases, *N*,*N*-dimethylcyclohexylamine and quinuclidine, were chosen. In both cases, guanidine was found to be a weaker base by 0.72 ± 0.07 and 1.17 ± 0.09 kcal mol^{-1}, respectively (at 338 K). According to these results, and to the re-evaluated *GB* values for the reference bases given in a recent compilation by Hunter and Lias,[10] the measured *GB* of guanidine was found to be 226.9 kcal mol^{-1}. Since this value was obtained in indirect measurement, the absolute *GB* of guanidine may change slightly in the future, depending on re-evaluations of the absolute gas-phase basicity scale. The most recent re-evaluated *GB* of guanidine[10] differs by 2.5 kcal mol^{-1} from the published value (224.4 kcal mol^{-1}).[6] It should be noted that the stated uncertainties on absolute *GB*s are estimated to be 2–2.5 kcal mol^{-1} in general. The relative values are nevertheless much more precise.

The gas-phase basicity of guanidine[6,10] is not as large as could be expected from its solution basicity (Table 2). In the gas phase, the charges localized on protonated centers are stabilized by the so-called[75] polarizability effect, *P*. The *P* effect of the six π-electrons of the pyridine ring (with a HOMA close to 1)[49c,76] contributes

Table 2. Experimental basicities determined in water (pK_a) and in the gas phase (*GB*, kcal mol^{-1}, 1 cal = 4.184 J) for selected nitrogen bases (data taken from Refs 10, 11, 20, 67a and 70)

Compound	pK_a	*GB*
	5.2	214.7
Me_2NH	10.7	214.3
Et_3N	10.9	227.3
H_2N— C(Me)=NH	12.4	224.2
$Me_2NCH_2CH_2NMe_2$	9.0	239.0
	12.1 (18.2)[a,b]	238.0
$(H_2N)_2C$=NH	13.6	226.9
	(27.6)[a,c]	253.3
	(26.2)[a,d]	254.9

[a] In acetonitrile.
[b] Ref. 71.
[c] Schwesinger, unpublished data cited in Ref. 72.
[d] Ref. 68.



Scheme 9. Effect of the amino group on the *GB* of the (a) C=NH and (b) C=O bases (in kcal mol^{-1})

to its relatively high basicity, which is close to that of Et_3N. This effect apparently does not contribute to the gas-phase basicity of guanidine. The guanidine also contains six delocalized π-electrons (HOMA = 1.011),[9] but its *GB* is larger than that of acetamidine[10] (four delocalized π-electrons) by only 2.7 kcal mol^{-1}. Some bidentate ligands (diamines) are stronger bases than guanidine in the gas phase by more than 10 kcal mol^{-1}. As mentioned by several researchers;[4–6,23b] guanidine appears to be a strong base only in solution.

On the other hand, comparison of the *GB* values of acetonimine, acetamidine and guanidine with those of acetone, acetamide and urea[10,77] indicates that the electron-donating effects of the two amino groups in guanidine and urea and their Y-conjugation are similar (Scheme 9). The substitution of one Me group in acetone and its imino derivative by an NH_2 group increases the value of *GB* by 10–12 kcal mol^{-1}, the site of protonation being the *O*-carbonyl in acetamide and the *N*-imino in acetamidine. Successive replacement of Me by NH_2 in acetamide and acetamidine increases the *GB* of the *O*-carbonyl in urea and the *N*-imino in guanidine by only 2–3 kcal mol^{-1}. There are no remarkable differences in the substituent effects in the two series. The reduced effect of the second replacement may be attributed to a resonance saturation. This kind of non-additivity of substituent effects has also been observed in the gas phase acidities.[78]

The replacement of the hydrogen atoms of the NH_2 and NH groups in guanidine by alkyl and heteroalkyl groups augments the *GB* of the *N*-imino atom by more than 25 kcal mol^{-1}.[54e,72] This is due to the significant polarizability of the alkyl groups and internal solvation (chelation of the attached proton by a second heteroatom on a flexible alkyl chain) observed in alkoxy and aminoalkyl derivatives (bidentate ligands). Guanidine ethers and guanidine amines belong to the class of the strongest bases in the current gas-phase basicity scale. Only vinamidines and phosphazenes are stronger bases than these guanidines.

In a hydrogen bond acceptor solvent, the charge of the protonated center is dispersed in the solvent by hydrogen bonding, and cannot polarize efficiently the distant electrons within the cation. The *P* effect of alkyl groups and internal solvation in acyclic systems are reduced to almost zero in aqueous solution.[54c,e,73a,b,75,79] Therefore, alkylguanidines have only slightly higher pK_a values than unsubstituted guanidine.[20,60c] Acyclic diamines have even smaller aqueous basicity than the corresponding monoamines.[11] The aza-aromatic bases (e.g. pyridines), which are as strong as aliphatic amines in the gas phase, lose their polarizability effect in aqueous solution and become bases of medium strength.[11,73a,75] Noteworthy exceptions are proton sponges [e.g. 1,8-dimethylamino-naphthalene (DMAN)], in which the rigid structure makes impossible the interruption of the N···H–N$^+$ bridge in the cation.[80] Proton sponges are strong bases in both the gas phase and solution.[10,67a]

As a consequence of solvation, the basicity order is not the same in the gas phase and in solution. A particular example is urea (discussed above), which is a stronger base than ammonia in the gas phase, whereas it is weaker than aromatic amines in water. The explanation of this fact is not easy because solvation effects are very complex. Part of the solvation effects may result from changes in hydrogen bonding between the solute and solvent molecules during protonation/deprotonation reaction. Small cations are always favored in polar solvents.[52a] For example, NH_4^+ is very well solvated by water molecules, whereas the solvation of neutral NH_3 is relatively weak.[52b] In the case of urea, there is probably less difference in solvation between the neutral and protonated species. Both groups, the C=O in neutral molecule and the C=OH$^+$ in the cation, form strong hydrogen bonds with water molecules. On the other hand, a strong reduction of the *P* effect of the C=O group in solution decreases the basicity.

The absolute *PA* for guanidine was obtained from the measured *GB* and the corresponding $T\Delta S$ term according to Eqn. (4), where $\Delta S(1) = S(BH^+) - S(B) - S(H^+)$, $S(H^+) = 26.039 \pm 0.002$ cal mol^{-1} K^{-1},[81] $S(BH^+) - S(B) = R\ln[\sigma(B)/\sigma(BH^+)] = R\ln 1/6$, $\sigma(B)$ and $\sigma(BH^+)$ being the rotational symmetry numbers of B and BH^+.[6] Using the revised *GB* of guanidine (226.9 kcal mol^{-1}) and the calculated $T\Delta S$

(8.8 kcal mol^{-1}), *PA* is equal to 235.7 kcal mol^{-1} at 298.15 K.

To our knowledge, the gas-phase acidity of guanidine has not yet been investigated, either by experiment or by computations. Modeling interactions between the guanidine moiety and other molecules, under physiological conditions, involve essentially a protonated guanidine. The biological activity of the guanidine skeleton, in particular the role of arginyl residues in the active site of various enzymes,[19] is therefore dependent on the basic properties of guanidine. This may explain the lack of interest in guanidine deprotonation.

CALCULATED PROTON AFFINITY (PA)

The absolute *PA* derived from the gas-phase protonation reaction (2) for a neutral base B can be calculated from the enthalpy of formation ($\Delta_f H°$) of the free base (B), its conjugate ionic acid (BH^+) and of the proton (H^+) using the equation

$$PA(B) = \Delta_f H°(B) + \Delta_f H°(H^+) - \Delta_f H°(BH^+) \quad (7)$$

It should be noted that there are two different conventions for the treatment of an electron when dealing with ion formation.[10,74,82] The electron may be treated as a species at rest without any heat capacity (the 'ion convention') or as a moving particle (the 'electron convention'). The difference in $\Delta_f H°$ between these two conventions is equal to the integrated heat capacity $H_T - H_0 = 5/2RT$, i.e. to 1.5 kcal mol^{-1} at 298.15 K. According to these two conventions, the experimental $\Delta_f H°(H^+)$ is equal to 365.7 or 367.2 kcal mol^{-1}, respectively. If the thermodynamic parameters of the ion formation originate from different conventions, the difference between $\Delta_f H°(H^+)$ and $\Delta_f H°(BH^+)$ may introduce a significant error in the calculated *PA* value. On the other hand, if the parameters are from the same convention, the quantities related to the electron cancel out, and the correct *PA* is obtained.

In semi-empirical methods (MINDO/3, MNDO, AM1), Dewar and co-workers[83] used the 'electron convention.' These methods are parameterized on experimental values of $\Delta_f H°$(ion). The data were taken from Ref. 84, and were corrected by +1.5 kcal mol^{-1} because the 'ion convention' was used in this compilation. When calculating *PA*s by semi-empirical methods, the value of 367.2 kcal mol^{-1} should be used for $\Delta_f H°(H^+)$. The same convention was applied in PM3, a version of AM1 reparameterized by Stewart.[85]

In *ab initio* calculations,[10,86] *PA*, as the negative of the direct enthalpy of the protonation reaction (2), can be obtained from Eqn. (7) or (8). Equation (8) includes the changes in total energy, in zero-point energy (*ZPE*), in vibrational energy on going from 0 to 298.15 K, and in rotational and translational energy, and a work term [$\Delta(pV) = -RT = -0.592$ kcal mol^{-1} at 298.15 K]. For H^+, only the translational energy term is not equal to zero ($3/2RT = 0.889$ kcal mol^{-1} at 298.15 K). Many researchers, however, took the negative of the protonation energy (E_{prot}) at 0 or 298.15 K as *PA* and compared it with the experimental *PA* value. This is an approximation, which neglects differences in vibrational, rotational and translational characteristics of B and BH^+, translational characteristics of H^+, and the work term.

$$PA = -\Delta_r H_{298}(2) = H_{298}(B) + H_{298}(H^+) - H_{298}(BH^+) \quad (8)$$

$$E_{prot} = E(BH^+) - E(B) - E(H^+) \quad (9)$$

Table 3 summarizes the *PA* and E_{prot} values calculated at different semi-empirical and *ab initio* levels. Most of the data were taken from the literature.[4–6,8,19b,c,f,23b,c,28a,44a,47,87–89] For a more complete picture of the theoretical data, calculations were also performed at the MNDO, AM1 and PM3 levels. These semi-empirical calculations were performed using HyperChem (Hypercube, Waterloo, ON, Canada). *Ab initio* calculations (HF, MP2, DFT) were carried out using Gaussian 94.[90] Planar and non-planar structures were considered for both the neutral and protonated forms (Schemes 2 and 3). All semi-empirical results led to the non-planar structure **1b** for the neutral form, in agreement with the results of *ab initio* calculation predictions.[24] The monocation structure depends strongly on the level of calculations: the planar structure **2a** is favored at the AM1 level, whereas the non-planar structure **2d** is preferred at the PM3 level. The *PA* obtained for the preferred reaction **1b** → **2a** at the AM1 level is closest to the experimental value, and differs from it by only 1 kcal mol^{-1}. Other semi-empirical results are lower (PM3) or larger (MINDO/3) than *PA*(exp) by more than 5 kcal mol^{-1}.

In *ab initio* calculations, various structures (planar and non-planar, constrained and optimized) were considered for both the neutral and protonated forms. Hence it is difficult to compare directly the early *ab initio* results, frequently obtained for planar, and/or constrained geometries, with the recent ones for fully optimized geometric structures. Moreover, the point symmetry group of the most stable conformation depends on the level of calculation. For the neutral form, it is evident that the structure **1b** is favoured at each *ab initio* level,[24] whereas for the monocation, the situation is not clear (see section on geometry).[5,6,29] Taking into account these discrepancies, only some general conclusions can be drawn. HF results strongly overestimate *PA*(exp) even when the calculations were performed for unconstrained geometries. The MPn and DFT (density functional theory) results do not differ from *PA*(exp) by more than 10 kcal mol^{-1}. The G2 (Gaussian-2) method gives the theoretical *PA* closest to the experimental value. An

Table 3. Calculated *PA* (at 298.15 K and 1 atm) and/or E_{prot} (at 0 K) for guanidine (in kcal mol^{-1})

Method	Eqn. used	Protonation reaction	$-E_{prot}$	*PA*	Ref.
FT-ICR (exp.)	6	**1** → **2**		235.7	6
MINDO/3	7	**1a** → **2a**		240.7	47, a
MNDO	7	**1b** → **2a**		218.0	a
AM1	7	**1b** → **2a**		234.7	a
PM3	7	**1b** → **2d**		221.5	a
PCILO/3	9	**1a** → **2a**[b]	264.0		19b
HF/STO-3G//HF/STO-3G	9	**1a** → **2a**[b]	312.1		87
			307.3		23c
			308.6		19c
HF/3–21G//HF/STO-3G	9	**1a** → **2a**[b]	267.3		23c
HF/3–21G//HF/3–21G	9	**1a** → **2a**[b]	267.1		23c
HF/4–31G//HF/4–31G	9	**1a** → **2a**[b]	263.5		28a
			263.4		44a
			262.9		47
			265.1		87
			260.0		19c
HF/6–31G//HF/6–31G	9	**1a** → **2a**[b]	264.3		23b
HF/6–31G*//HF/6–31G*	8/9	**1a** → **2a**	256.0	247.3	a
		1b → **2a**	252.0		4
			252.0	245.3	5, a
			252.0	245.3	88
HF/6–311++G**//HF/6–31G*	9	**1b** → **2a**	250.3		4
MP2/6–31G*//MP2/6–31G*	8/9	**1b** → **2a**	244.4	238.7	a
			244.7	238.5	5
		1b → **2b**	244.8	238.3	a
			245.0	238.2	5
	8			238.3	8
MP2/6–31G**//MP2/6–31G**	8	**1b** → **2b**		242.6	8
MP2(full)/6–31G**//MP2/6–31G**	7	—[c]		231.7	19f
	8/9	—[c]	249.5	240.4	19f
MP2/6–311G**//MP2/6–31G*	8/9	**1b** → **2b**	245.5	238.7	5
MP2(fc)/6–311 + G**//HF/6–31G*	8/9	**1b** → **2a**	240.4	233.7	88, 89
MP2/6–311 ++ G**//HF/6–31G*	9	**1b** → **2a**	240.0		4
MP3/6–311 ++ G**//HF/6–31G*	9	**1b** → **2a**	243.6		4
MP3/6–311G**//MP2/6–31G*	8/9	**1b** → **2b**	248.4	241.6	5
MP4/6–311G**//MP2/6–31G*	8/9	**1b** → **2b**	245.7	238.9	5
DFT(B3LYP)/6–31G*//DFT(B3LYP)/6–31G*	8/9	**1b** → **2a**	248.7	242.7	a
		1b → **2b**	249.0	242.3	a
	8			246.2	8
DFT(B3LYP)/6–31G**//DFT(B3LYP)/6–31G**	8	**1b** → **2b**		244.8	8
DFT(BLYP)/6–311 + G(3df,2p)//DFT/6–31G*	8/9	**1b** → **2b**	232.4	234.4	6
DFT(SVWM)/6–311 + G(3df,2p)//DFT/6–31G*	8/9	**1b** → **2b**	234.2	232.5	6
G1	8/9	**1b** → **2a**	233.9	234.7	a
		1b → **2b**	234.2	234.9	a
G2	8/9	**1b** → **2b**	235.0	235.8	a
			234.8	234.4	6
G2(MP2)	8/9	**1b** → **2b**	234.9	235.7	a
			234.7	234.4	6
G2(MP2/BLYP)	8/9	**1b** → **2b**	233.3	233.5	6
G2(MP2/SVWM)	8/9	**1b** → **2b**	236.2	233.5	6

[a] This work.
[b] Constrained geometry.
[c] Not given.

extension of these studies to the G3 (Gaussian-3) level of theory[91] is highly recommended.

Calculations of accurate *PA*s are even more demanding for systems containing the guanidine group because this group can be involved in a variety of intramolecular hydrogen bonds. Arginine, which has the largest proton affinity among common naturally occurring amino acids, serves as a good example. The guanidine group becomes hydrogen bonded to the carboxylic group in the neutral form, and in the protonated form the guanidinium group is hydrogen bonded to the C_α-amino group. In a recent study, the lowest energy structures of the neutral and protonated forms were searched for using a simple genetic algorithm at the semi-empirical PM3 level and

also subsequent higher level theory.[92] The final structures were optimized at the MP2 level using the 6–31 ++ G** basis set and electronic energies were determined at the CCSD/6–31++G** level. The thermal contributions to thermodynamic functions were determined at the B3LYP/6–31++G** level ($T = 298$ K, $p = 1$ atm). If we use a window of 5 kcal mol^{-1} in the Gibbs free energy scale, then eight structures were identified for the neutral form with qualitatively different networks of hydrogen bonds and five structures were identified for the protonated form. The calculated value of *PA* was found to be 256.3 kcal mol^{-1}. The corresponding experimental finding depends on the evaluation of the absolute gas-phase superbasicity scale. The most recent revision of the experimental *PA* values for superbases[54e] (particularly for reference bases TMG, DBN and DBU used for *PA* measurements of arginine[93]) changes the *PA* value (251.2 kcal mol^{-1}) reported in the Hunter and Lias compilation[10] by − 2.5 kcal mol^{-1}. The re-evaluated experimental *PA* value of arginine (248.7 ± 0.5 kcal mol^{-1}) is by 0.1 kcal mol^{-1} lower than that of DBN. Two points should be made regarding these results. First, the *PA* of arginine is larger by ca 15 kcal mol^{-1} than that of guanidine, which may by at least partly ascribed to intramolecular hydrogen bonds being operative in arginine, similar to other aminoguanidines.[54e,72] Second, the overestimation of the calculated value of *PA* relative to the experimental data (more than 5 kcal mol^{-1}) may be due to several factors. First, there are deficiencies in the theoretical model such as incomplete one-electron basis sets and insufficient treatment of electron correlation effects. Also, the harmonic approximation to molecular vibrations is probably a source of error. On the other hand, the observed disagreement can also be ascribed to experimental problems such as clustering reactions for protonated molecules with polar neutral molecules at low temperatures, pyrolysis and isomerization reactions of molecules and ions at high temperatures, and difficulties in attaining thermodynamic equilibrium. In fact, the propensity of arginine to form unusually stable charged aggregates is well established.[94] The discrepancy between the calculated and measured proton affinity of arginine remains to be addressed in futures studies.

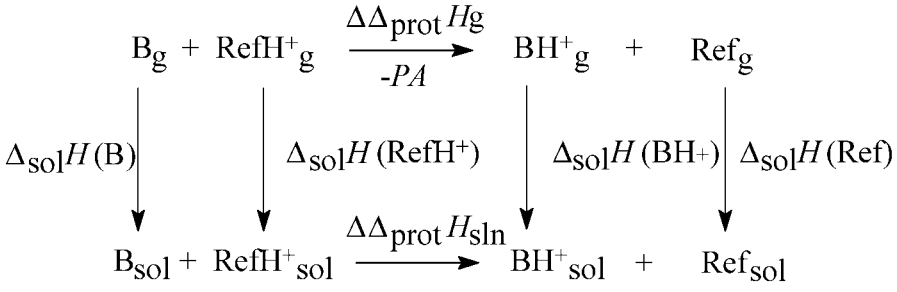
FROM THE GAS PHASE TO SOLUTION

The high basicity of guanidine in aqueous solution has been the subject of many debates. Apart from internal effects, e.g. resonance stabilization, the Y-delocalization of six π-electrons, the symmetry of the guanidinium ion, the ability to disperse the positive charge to the peripheral hydrogens, etc., which without any doubt influence the gas-phase basicity of guanidine, the solvation is of utmost importance in determining the difference between the gas-phase and solution basicities.

According to the classical electrostatic theory of Born,[52a] the interactions with solvent molecules and the influence of this effect on the acid–base properties of the neutral and ionic forms can be quantitatively analyzed. On the basis of a thermodynamic cycle (Scheme 10) applied to nitrogen bases, Aue *et al.*[52b] showed that the difference between the *PA* and the enthalpy of protonation in solution depends on the enthalpy of solvation of the neutral base, its ionic form and the proton. Similar relations can be derived for the difference between the *GB* and Gibbs free energy of protonation (or pK_a), which take into account both the enthalpy and entropy terms of the protonation reaction and the corresponding enthalpy and entropy terms of solvation.

$$\Delta\Delta_{\text{prot}}H_{\text{sln}} = -\Delta PA + \Delta\Delta_{\text{sol}}H(\text{BH}^+/\text{RefH}^+) - \Delta\Delta_{\text{sol}}H(\text{B/Ref})) \quad (10)$$

Comparing two bases, the difference between their basicities (in terms of enthalpy) in aqueous solution and in the gas phase arises only from differences in the enthalpy of hydration of the neutral and ionic forms [Eqn. (10)]. For nitrogen bases, the enthalpy of hydration depends strongly on the number of hydrogens linked to the nitrogen atom(s), the size of the neutral and ionic species and the charge dispersion in the ionic form. The number of positively charged peripheral hydrogens in guanidinium ion, capable of forming hydrogen bonds with water molecules, and the relatively small size of cation capable of interacting electrostatically with water dipoles may be the reason for the high enthalpy of hydration of the guanidinium ion. This may account, at least in part, for the higher basicity of guanidine as



Scheme 10. Thermodynamic cycle for the proton-transfer reaction between base (B) and reference base (Ref) from the gas phase to solution[52b]

compared with trimethylamine, which contains the same number of heavy atoms.

CONCLUSION

Most of the biological properties of guanidine and its derivatives, such as their interactions with proteins, influence on the function of sodium channels, transport in different human membranes and cells, etc., are related to their strong basicity. Under physiological conditions, these strong bases exist mainly in their protonated forms. These positively charged organic ions are important elements in different mechanisms and schemes proposed in the literature to explain the biological activity of guanidine function, particularly that of arginyl residues in the active site of various enzymes. Moreover, the richness of intermolecular interactions in guanidinium salts (hydrogen bonds, Coulomb and van der Waals interactions) has recently been used in crystal engineering to design materials with required properties and predictable structure.

Theoretical calculations indicate that neutral guanidine is non-planar with the CN bond of the imino NH group shorter (by ca 0.1 Å) than the two CN bonds of the amino NH_2 groups. The discrimination of the CN bond lengths has been confirmed from the analysis of experimental x-ray geometries of the guanidine derivatives.

The protonation of guanidine occurs at the imino nitrogen, as the *N*-amino is less basic than the *N*-imino atom by ca 30 kcal mol^{-1}. A second protonation of guanidine is possible in 'magic acid' (the 1:1 molar FSO_3H–SbF_5 acid system) diluted in SO_2 or SO_2ClF. Tri- and tetraprotonated guanidines have not been experimentally identified and theoretical results suggest that the formation of the trication and the tetracation is endothermic.

The minimum-energy structure of monoprotonated guanidine has been extensively studied using calculation methods. The optimum structure depends strongly on the level of theory and the quality of one-electron basis sets. All calculations indicate, however, that the CN_3 moiety of the protonated form is planar and the CN bond lengths are the same. These properties of the CN_3 moiety are consistent with the experimental x-ray geometries of guanidinium cations.

The unusual thermodynamic stability of acyclic guanidine and its monoprotonated form has been discussed in terms of (i) resonance stabilization, (ii) Y-aromaticity, (iii) favorable distribution of positive charge that leads to a favorable Coulomb interaction and (iv) the geometry-based HOMA index of aromaticity. In addition, the effect of solvation on the stability of the protonated form has been identified.

The gas-phase basicity of guanidine was found to be 226.9 kcal mol^{-1}, as deduced from an indirect method consisting in gas-phase measurements of the equilibrium constant for the proton-transfer reaction between guanidine and two reference bases: *N,N*-dimethylcyclohexylamine and quinuclidine. The proton affinity of 235.7 kcal mol^{-1} was proposed on the basis of the experimental gas-phase basicity and an estimation of the entropy term. The most advanced *ab initio* calculations performed at the G2 level of theory provide a proton affinity of guanidine of 235–236 kcal mol^{-1}. *Ab initio* methods can also provide a value for the gas-phase basicity, which is experimentally measured, although indirectly. A state-of-the-art calculation of the gas-phase basicity and proton affinity of guanidine, e.g. at the G3 level of theory, would provide an invaluable insight into (i) accuracy of the *GB* scale and (ii) accuracy of the common treatment of the entropy term.

The solution basicity of guanidine (pK_a = 13.6) is close to that of hydroxide ion and is larger than could be expected from its gas-phase basicity. Guanidine is a stronger base than other nitrogen compounds containing one potentially basic site (*N*-imino or *N*-amino) linked to a carbon atom, e.g. pyridines, amines and amidines, and also those with two basic nitrogens, e.g. diamines. Other bidentate nitrogen ligands with a rigid structure, such as proton sponges and vinamidines, have even a higher basicity than guanidine. More basic also are phosphazenes containing a potentially basic *N*-imino atom bonded to a five-valent phosphorus atom.

Solvation effects are of the utmost importance in determining the difference between the gas-phase and solution basicities of guanidine. The enthalpy of hydration depends strongly on the number of hydrogens linked to the nitrogen atom(s), the size of the neutral and ionic species and the charge dispersion in the ionic form. The number of positively charged peripheral hydrogens in the guanidinium ion, capable of forming hydrogen bonds with water molecules, and the relatively small size of the cation capable of interacting electrostatically with water dipoles may be the reason for the high enthalpy of hydration of the guanidinium ion. This may account, at least in part, for the higher basicity of guanidine compared with trimethylamine, which contains the same number of heavy atoms. We expect future theoretical studies to concentrate on solvation effects for guanidine and its protonated form using solvation models developed to approximate the effect of polar environments on the electronic structure of molecules and clusters.

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