Strain Effects on Amine Basicities

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Received November 11, 1988 (Revised Manuscript Received April 3, 1989)

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Roger Alder was born near Stow-on-the-Wold, England, in 1937. He was educated at Oxford University, where he obtained a D. Phil. with Mark Whiting in 1962. After postdoctoral work with James B. Hendrickson at UCLA and Brandeis University, he was a NATO fellow at Oxford before moving to the University of Bristol in 1965, where he is now a Reader in Organic Chemistry. His research interests are now centered on the preparation and study of novel molecules; in the past he has worked on strong amine bases such as 1,8-bis(dimethylamino)naphthalene, on powerful methylating agents, on the mechanism of the rearrangement of azulene to naphthalene, and on the unique chemistry of medium-ring bicyclic molecules. His main leisure interest is walking in the English countryside.

I. Introduction

This review discusses the effects of molecular strain on the Brønsted basicity of amines. The effects of strain on the interaction of amines with Lewis acids are not covered here. Gas-phase and solution data on amine basicities are accorded equal weight in the discussion. There are several reasons for this: first, the gas-phase data are fundamentally simpler to interpret; second, in some important instances only gas-phase data are available; third, in some cases strain effects may be due to altered solvation and this is only apparent if both solution and gas-phase data are available. The subject matter of this review is one aspect of the general topic of the effect of strain on proton-transfer equilibria. In practice, there are very little data on the effects of strain on the acidities and basicities of other functional groups. An obvious reason for this is that an amino nitrogen atom can be incorporated in strain-inducing ring systems and be influenced by bulky groups in ways that are impossible for hydroxylic and carboxylic acid groups.

No previous reviews cover precisely this subject area. Gas-phase basicities of amines have been reviewed several times in recent years, and strain effects are covered in these reviews.[2,3] Staab[4] has recently reviewed the aromatic "proton sponges", which derive much of their strong basicity from strain effects, while parts of earlier reviews by the present author discussing the special properties of diamines[5] and intrabridgehead chemistry[6] are also relevant. Aqueous pK_a values are taken from the compilations of Perrin,[7] unless preferable later values are available. The book *pK_a Prediction for Organic Acids and Bases* by Perrin, Dempsey, and Serjeant[8] is mostly concerned with electronic effects but does discuss some steric and strain effects.

The present review is divided into two main sections: monoamines and diamines (and polyamines). It appears that all strain effects on monoamines are base weakening, while in diamines (and polyamines), it is possible to utilize strain energy to increase base strength. This is because in diamines there are often opportunities for intramolecular hydrogen bonding in monoprotonated ions, and the strength of this bonding may be strongly influenced by geometrical effects. One general consequence of the formation of an intramolecularly hydrogen-bonded monoprotonated ion is that addition of a second proton is unusually difficult (the second pK_a is low). This will always be in part due to the necessity of breaking the hydrogen bond, but many of the dications formed will be strained.

II. A Conceptual Model Based on Molecular Mechanics

In principle, all strain effects on amine basicities can be understood in terms of molecular mechanics.[9,10] In this model, the change caused by strain in a pK_a or proton affinity (PA) (or gas-phase basicity (GB)) is a consequence of a difference in the steric energy of the amine and its protonated ion. The steric energy of each can in principle be factorized in standard molecular mechanics fasion into terms due to bond stretching,

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bond angle bending, torsional strain, and van der Waals (nonbonded) strain:

$$E_{steric} = E_{stretch} + E_{bend} + E_{torsion} + E_{van\ der\ Waals}$$

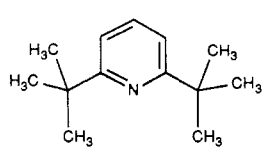
It is obviously of interest to seek examples where the strain effect can be largely ascribed to one type of strain, for example, bending of bond angles. The force constants associated with, say, bending of C–N–C angles will be different for the amine and for the ammonium ion and this can be seen as the source of the basicity effects. This approach provides a useful conceptual framework for the discussion of strain effects on amine basicities, even though hardly any actual calculations have been carried out. Force fields for amines have been developed and they seem to be reasonably successful[10] but force fields for ammonium ions are practically untried. In cases where there are no other strongly polar groups in the molecule, we have found it possible to make reasonable estimates using a hydrocarbon (H–C replacing H–N^+) as a substitute for the ammonium ion.[11,12] In amines where π electrons can overlap with the nitrogen lone pair, basicities can be strongly affected by the degree of that overlap. This requires additional terms in the equation above, but the principle of analyzing the effects through a mechanical model still holds. Much of the discussion that follows is therefore qualitative, of necessity, and it is to be hoped that more quantitative treatments will emerge in the future.

III. Monoamines

In keeping with the general approach outlined above, we divide strain effects on the basicity of monoamines into those principally caused by nonbonded interactions and those caused by angle strain. In principle, both bond stretching and torsional strain could cause basicity changes, since bond-stretching and torsional force constants for amines and their derived ammonium ions could differ. Thus the rotational barrier for methylamine differs from that of ethane (and thus probably that of the methylammonium ion). However, no actual basicity changes have been ascribed to this effect, and no examples of basicity changes caused by differential force constants for bond stretching are known.

A. The Effects of Nonbonded Interactions

Since an amine lone pair is expected to occupy less space than a proton, bulky groups near the lone pair of a nitrogen might cause a reduction in basicity. This effect was first sought in 2,6-di-*tert*-butylpyridines and related compounds. The parent 2,6-di-*tert*-butylpyridine (1) was shown to be an unusually weak base



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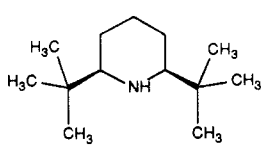

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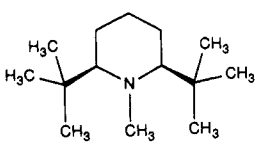

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TABLE I. Proton Affinities (PA) and pK_a Values for 2,6-Di-*tert*-butylpyridine and Related Compounds

compd	pK_a[a] of BH^+	PA[b]
pyridine	3.69[c]	220.4
2,6-di-*tert*-butylpyridine (1)	2.70 (4.65)[d]	231, 233.7[c]
2,4-di-*tert*-butylpyridine		231.4
2,6-di-*tert*-4-phenylpyridine	2.65 (4.09)[d]	
2-*tert*-butyl-4,6-diphenylpyridine	2.23 (3.81)[d]	
2,4,6-triphenylpyridine	1.84 (2.91)[d]	
piperidine	9.90	225.4, 227.3[c]
cis-2,6-di-*tert*-butylpiperidine (2)	7.09	235.8[c]
N-methylpiperidine	8.61	228.8, 231.8[c]
N-methyl-*cis*-di-*tert*-butylpiperidine (3)	7.87	240.7[c]

[a] All pK_a data are for 70% aqueous ethanol. [b] In kcal/mol; values from ref 2 and 15b unless otherwise noted. [c] From ref 19. [d] From ref 18; the numbers in parentheses are calculated values based on the additivity of substituent effects of monosubstituted derivatives. They show that the effects of strain decrease as *tert*-butyl groups are replaced by phenyl groups.

in solution by Brown and Kanner,[13] who proposed steric hindrance toward the proton as the cause. This was disputed by Wepster,[14] who analyzed the basicities of some hindered anilines and suggested that the real cause in these cases and for 1 was steric hindrance to solvation of the ammonium ion that was formed (through hydrogen bonding to the solvent). The matter was clarified when the gas-phase basicity of 2,6-di-*tert*-butylpyridine was measured;[15a] the proton affinity is normal when the usual polarizability effects of the alkyl groups are taken into account, so low pK_a is due to steric inhibition of solvation, which appears in an abnormal entropy of solution.[15b] In fact, the 2,6-di-*tert*-butylpyridinium ion seems to be solvated more like a delocalized carbonium ion than an ammonium ion.[16] The hydrogen bond strengths of the cluster ions 1-H^+·1 and 1-H^+·H_2O in the gas phase are normal but the entropies of their formation are very unfavorable.[17] A number of related compounds have now been studied[15b,18,19] (Table I). The *cis*-2,6-di-*tert*-butylpiperidines are particularly interesting. The reduction in basicity for the secondary amine 2 is 2.81 pK_a units compared with reduction of 0.74 unit for the tertiary amine 3 and 0.99 unit for 2,6-di-*tert*-butylpyridine. Day[19] suggested that *both* the acidic hydrogens of the secondary ammonium ion are inaccessible to solvent hydrogen bonding. As a consequence, the intrinsically weaker basicity of the secondary vs tertiary amine that is normally observed in the gas phase is now revealed in solution, where it is normally masked by increased solvation.

There is thus no experimental evidence for decreased basicity due simply to increased non-bonded interactions in an ammonium ion compared to a simple amine. As we shall see, there is plenty of evidence for dramatic increases in basicity in diamines when lone pair/lone pair interactions between nitrogen atoms are replaced by hydrogen bonds.

B. The Effects of Angle Strain

Unstrained amines have H–N–C and C–N–C angles that are close to tetrahedral, but they readily invert via a planar geometry with a barrier of about 6 kcal/mol. Force constants for expansion of C–N–C angles are therefore substantially less than that for the corresponding expansion of the protonated ion (these are probably roughly similar to that of the corresponding

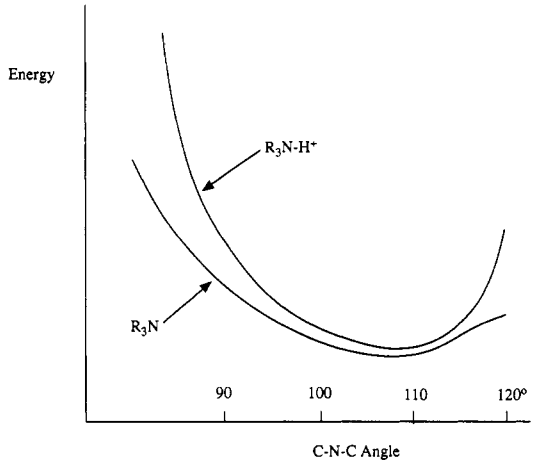


Figure 1. Schematic potential energy diagram for angle bending in an amine R_3N and its protonated ion R_3N–H^+.

TABLE II. Proton Affinities (PA) and pK_a Values for Small-Ring Amines

compd	PA[a]	GB[b]	pK_a[c] of BH^+
aziridine (4)	215.7	207.5	8.04
N-methylaziridine			7.86
azetidine (5)	222.7	214.5	11.29
1-azabicyclo[1.1.0]butane (6)	212	204	

[a] In kcal/mol; data from ref 2 and 21 relative to $PA(NH_3)$ = 205.0 kcal/mol. [b] Gas-phase basicity; from ref 2 and 21. [c] From ref 20.

hydrocarbon with H–C replacing H–N^+). Although the case is less clear, reduction in C–N–C bond angles is probably also easier in amines than in ammonium ions, so that the potential function for the two species may be schematically as shown in Figure 1 (the function for amines is of course strongly anharmonic). This implies that basicities of amines will be reduced by strain which results in both increase and decrease of C–N–C angles, and this is indeed what is found experimentally.

Aziridine (**4**) and its derivatives are substantially weaker bases than normal both in solution[20] and in the gas phase[2,21] (Table II), but azetidine (**5**) is essentially normal. The gas-phase basicity of 1-azabicyclo[1.1.0]-butane (**6**)[20] is even more strongly depressed (the pK_a

4 **5** **6**

cannot be measured in solution because of rapid ring opening). For **4** and **6** the reduction in ion gas-phase basicity seems to be approximately proportional to the strain (the strain energy of cyclopropane is 27 kcal/mol and that of bicyclo[1.1.0]butane is 67 kcal/mol). There have been ab initio calculations of the basicity of aziridine and related compounds.[22]

Another treatment of these effects emphasizes the change in hybridization at the basic nitrogen atom. Thus in small-ring amines, the C–N bonds in the ring have greater p character than normal, leading to higher s character in the lone pair. A lone pair with greater s character is more tightly bound to the nitrogen nucleus, in effect stabilizing the free base. On the other hand, N–H bonds are also strengthened by greater s character so that the effect on basicity in this treatment is again a differential effect. While the hybridization treatment emphasizes the electronic changes, the force

TABLE III. Proton Affinities (PA) and pK_a Values for Some Bridgehead Monoamines

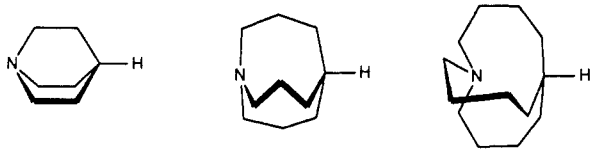
compd	PA[a]	pK_a
quinuclidine (7)	233.1	10.95
manxine (8)	232.9	9.9[b]
hiddenamine (9)	216.5	0.6[c]

[a] In kcal/mol; data from ref 2, 3, and 11, referred to $PA(NH_3)$ = 205.0 kcal/mol (see ref 2 and 3). [b] pK_a = 8.8 in 66% aqueous DMF; see ref 29. [c] In 48% (v/v) $EtOH/H_2O$ (ref 30).

field treatment treats these effects entirely in terms of geometrical (nuclear) changes. In the end, the two treatments are alternatives and are quite compatible.

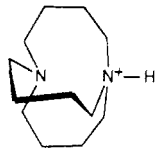
The hybridization argument has usually been applied to explaining the lower basicity of imines and nitriles. The basicity changes involved are substantial for imines (sp^2-hybridized nitrogen) and very large for nitriles (sp nitrogen). Thus the proton affinity of MeCH=NEt is 2.5 kcal/mol less than that for Et_2NH, and that for pyridine is 6 kcal/mol less than that for piperidine (in the latter comparison, there may be some additional base weakening from the inductive effects of the other two π bonds).[2] Acetonitrile has a PA 34 kcal/mol below that for ethylamine. The gas-phase data are more satisfactory here because they encompass the large differences better than the solution data, where the effects of solvent changes must be allowed for. Thus there has been some dispute[23-26] as to the pK_a values for simple nitriles, since these are only protonated in concentrated sulfuric acid, but values of −10.1 for acetonitrile and −10.4 for benzonitrile now seem accepted. Solution data on the basicity of simple imines are also very scarce due to the ease of hydrolysis of these compounds, but the pK_a of Ph_2C=NH is 7.18[27] and that of PhCH=N-Bu^t is 6.7.[28]

Amines with expanded C–N–C angles had received less attention until recently, but the bridgehead amines 1-azabicyclo[2.2.2]octane (quinuclidine) (**7**), 1-azabicyclo[3.3.3]undecane (manxine) (**8**),[29] and 1-azabicyclo-[4.4.4]tetradecane (hiddenamine) (**9**)[30] form an in-



7 **8** **9**

structive trio (1-azabicyclo[1.1.1]pentane is still unknown). Quinuclidine (**7**) has a normal pyramidal nitrogen atom, manxine (**8**) probably has an almost flat nitrogen atom (the rather indirect evidence is given below), and hiddenamine (**9**) has its bridgehead nitrogen pyramidalized inward (again the evidence is indirect). The photoelectron spectrum of manxine[31] is indicative of vertical ionization from a flat amine to a flat radical cation. The X-ray structures of two diamines with bicyclo[3.3.3]undecane skeletons[32,33] show almost flat nitrogen atoms at the bridgeheads. The X-ray structure of manxine hydrochloride shows the bridgehead atoms to be severely flattened.[34] For hiddenamine (**9**) there is unfortunately again no structural detail on the free amine, but molecular mechanics calculations indicate a pyrimidal nitrogen atom but with its lone pair inside. This is supported by the structure of the isoelectronic ion **10**[12] and the photoelectron spectrum of hid-



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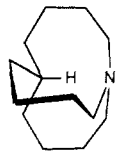

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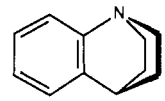
denamine, which is indicative of a pyramidal nitrogen.[11] The pK_a and PA of manxine (Table III) are slightly lower than normal but the changes are surprisingly small for such a major change in geometry. Hiddenamine is an extremely weak base. In this compound, protonation is from the outside and the nitrogen has to undergo inversion before this can occur. Calculation using the MM2 force field gives a difference in strain energy for the amine with an inside and an outside lone pair of 18.49 kcal/mol, almost equal to the observed decrease in the gas-phase proton affinity.[12] This suggests that the decreased basicity can be almost entirely accounted for in terms of the increase in strain as the nitrogen is pyramidalized outward to accept the proton. The calculations also suggest that hiddenamine would be a stronger base if it could protonate inside, but this does not occur even after prolonged heating in acidic solutions due to the kinetic difficulty of introducing the proton between the bridges. The *in*-6*H* isomer of hiddenamine (**11**) would also be a very interesting compound from the point of view of its pK_a, but is has not yet yielded to synthesis.

C. Restricted Lone Pair/π Overlap

The basic properties (and even the site of protonation) of enamines and aromatic amines are strongly influenced by lone pair/π overlap (conjugation) and also by the inductive effect of the double bond. The degree of lone pair/π overlap is subject to geometrical control and this is discussed below, but the situation for unstrained compounds must be briefly stated first.

In solution, aniline and all its simple derivatives protonate on nitrogen and are weaker bases than saturated amines. Simple enamines protonate on carbon to give iminium ions and are then stronger bases than saturated analogues.[35] The pK_a values for N-protonation of some enamines have been derived from kinetic measurements,[36] and these are about 2 pK units lower than those of saturated analogues (thus the direction of the inductive and conjugative effects is the same as for anilines). In the gas phase, N- vs C-protonation of aniline is finely balanced,[37] and electron-donating meta substituents give C-protonated ions,[38] as does 1-aminonaphthalene;[39] the solvation energies of the N-protonated ions are much higher than those for C-protonated ions. As may be expected, enamines protonate on carbon in the gas phase unless geometrical factors prevent this,[40,41] and they have PA values equal to or higher than those of their saturated counterparts (the actual values for the difference are dependent on the substitution pattern).[40]

The relative importance of the conjugative and inductive effects for aniline derivatives was first assessed by Wepster in a classic study that utilized steric inhibition of resonance.[42] 2,3-Benzoquinuclidine (**12**) has a pK_a of 7.76 and thus comes midway between *N*,*N*-diethylaniline and quinuclidine, suggesting that about half the lowered basicity of aniline could be ascribed



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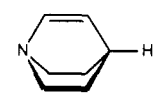

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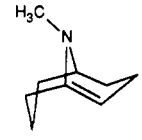
to each effect. The corresponding dissection can also be done for enamines: 2,3-dehydroquinuclidine (**13**) cannot form an iminium ion and has a pK_a of 9.82 vs 10.95 for quinuclidine itself;[43] thus again about half the lowered N-basicity for enamines that have conjugation is due to the inductive effect of the double bond. The proton affinity of 2,3-dehydroquinuclidine is 1.7 kcal/mol less than that of quinuclidine;[41] this confirms the electron-withdrawing effect of the double bond, but, since the nitrogen PA of a conjugating enamine is unknown, the relative importance of the inductive and conjugative effects in the gas phase still cannot be assessed.

In **12** and **13** the structures ensure that there is absolutely no lone pair/π overlap. Few simple enamines with partial lone pair/π overlap have been studied. Bridgehead alkenes with adjacent nitrogen atoms would be ideal, but the only compound of this type whose pK_a has been measured is 9-methyl-9-azabicyclo[3.3.1]non-1-ene (**14**), and this also has effectively zero lone pair/π overlap. Its pK_a is 9.09 in 40% aqueous ethanol, compared with 10.19 for the saturated analogue 9-methyl-9-azabicyclo[3.3.1]nonane.[44]



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IV. Diamines

As we have seen, all strain effects on the basicities of monoamines are base weakening. On the other hand, it is possible to devise diamines in which strain is relieved on protonation, and there has been much interest in making exceptionally strong bases with this strategy. Before these cases are discussed, a brief summary is given of the gas-phase and solution basicity of unstrained diamines.

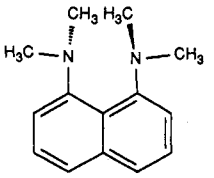
A. Unstrained Diamines

Diamines that can form intramolecularly hydrogen-bonded monoprotonated ions are much stronger bases in the gas phase than structurally comparable monoamines.[2,45,46] It is important to grasp the magnitude of this effect. The PA of 1,4-diaminobutane (238.1 kcal/mol) is 18.5 kcal/mol higher than that of *n*-pentylamine, a monoamine of comparable size and polarizability. The difference in gas-phase basicity (GB) is less (12.7 kcal/mol), because there is an entropy penalty involved in forming the intramolecularly hydrogen-bonded monocation of the 1,4-diaminobutane, but if this were to be translated into a pK_a difference, the diamine would be a stronger base by more than 9 pK_a units. In fact, the aqueous basicities of these two amines differ by less than 0.2 pK unit. The advantage of forming the intramolecularly H-bonded cation is completely swamped in solution by hydrogen bonding from the solvent. There is in fact evidence that the

monoprotonated ions formed by amines like 1,3-diaminopropane are not intramolecularly hydrogen bonded in aqueous solution.[47]

In the gas phase, the stabilization provided by the hydrogen bond reaches a maximum with 1,4-diaminobutanes, when the ring formed has seven members (counting the hydrogen). The ring can then adopt a conformation like chair cyclohexane with the N:H–N$^+$ bond replacing one C–C bond and the hydrogen bond can then be almost linear (this is illustrated by some structures discussed later). In 1,3-diaminopropane and 1,2-diaminoethane, the hydrogen bond has to be increasingly nonlinear and is therefore weaker; in effect there is strain in the protonated ion.

Is it possible to realize in solution some or all of the basicity advantage that diamines possess in the gas phase? The first diamine to be found that appeared to do this was 1,8-bis(dimethylamino)naphthalene ("Proton Sponge") (15).[48] However, the causes of the



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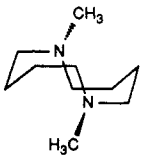
enhanced basicity of this molecule are undoubtedly complex (see below); the molecule is of interest more because it capitalizes on several effects to achieve its remarkable pK_a of 12.1 than because it offers a clear example of the operation of one strain-relieving mechanism on protonation.

B. Steric Inhibition of Solvation in Diamines

In a diamine that can form a hydrogen-bonded monocation, there is the possibility that gas-phase-like behavior can be realized by simply restricting the opportunities for solvation in the diamine and its monocation, and this should be considered before taking strain relief on protonation into account. It has recently been found that medium-ring diamines that can form transannularly hydrogen-bonded monoprotonated ions are stronger bases than normal in solution.[49] 1,6-Dimethyl-1,6-diazacyclododecane (16) was found to be the



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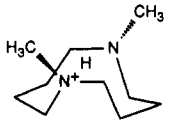

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strongest of these bases, with an apparent pK_a of 16.5 estimated from comparison with one of the strongest known proton sponges, 2,7-dimethoxy-1,8-bis(dimethylamino)naphthalene. Compound 16 forms a monoprotonated ion that has a structure like *cis*-decalin (17), with a nearly linear N:H–N$^+$ hydrogen bond taking the place of the C–C bond shared by the two rings; because of the greater length of the N:H–N$^+$ bond, this structure was quite strained, with increased bond angles in the $(CH_2)_4$ bridges. The free base adopts a [2323] (or BCB) conformation like cyclodecane, but with the nitrogen lone pairs occupying the inner positions which cause the most severe H–H interactions in cyclodecane itself, so that the diamine conformation 16 avoided much of the strain of the hydrocarbon. Although quantitative estimates could not be made, the authors suggested[49] that there was not much strain relief on protonation in this case but that normal solvation of both diamine and monocation was prevented by their structures, so that this diamine was behaving in solution as it would in the gas phase. Of course, even if this interpretation is correct, it does not follow that a diamine of this type would necessarily be a stronger base than monoamines enjoying normal solvation, although that is what is observed in this case.

The pK_a for second protonation of 16 is 0.4 ± 0.3;[49] this low value reflects not only the breaking of the intramolecular H bond but probably also some increase in strain, as the dication must adopt a strained cyclodecane conformation.

C. 1,8-Bis(dimethylamino)naphthalene

In 1,8-bis(dimethylamino)naphthalene (15) and related proton sponges, structural studies show that there is clearly strain relief when these compounds protonate, even though the energetics cannot be evaluated quantitatively. Thus the N···N distance is 2.79 Å in 15[50] but decreases to about 2.60 Å in the monoprotonated ion.[51,52] Even in the cation this distance is still larger than in an unstrained naphthalene (~2.45 Å), so that the hydrogen bond is under compression. Other geometrical changes occur during protonation. Thus the free base 15 adopts a conformation with a C_2 axis and the lone pairs make an angle of about 30° with the naphthalene π orbitals, but are then in close proximity to one of the methyl groups on the other nitrogen atom. This struture is clearly a compromise involving several factors, e.g., favorable lone pair/π overlap, lone pair/methyl nonbonded interactions, and lone pair/lone pair repulsion. The naphthalene ring system is appreciably twisted as well. In the cation, the lone pairs swing round into the molecular plane to form the (nonlinear) hydrogen bond, the nitrogen atoms can approach closer, and the naphthalene can become more planar.

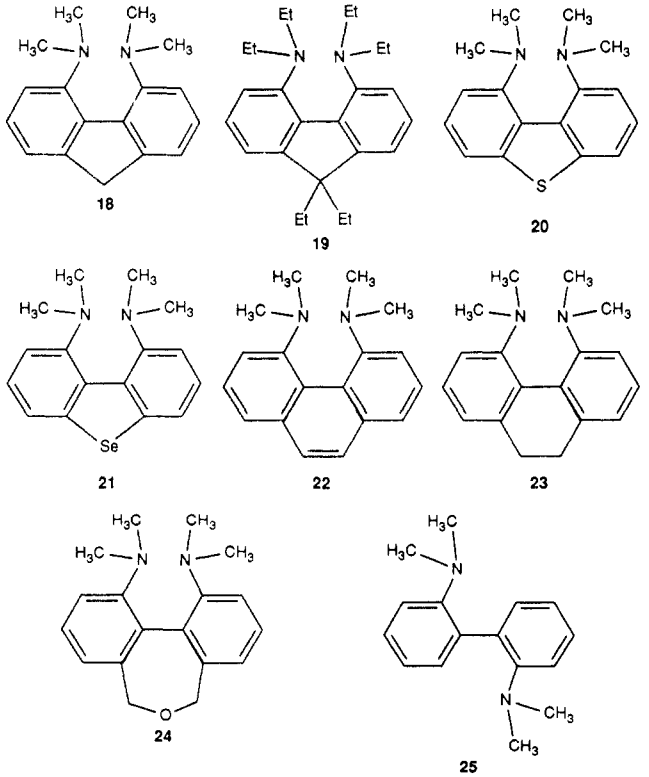
Thus the high basicity of 15 in aqueous solution relative to simple aromatic amines can be ascribed to the operation of several factors, e.g., steric inhibition of conjugation in the free base, relief of nonbonded repulsions, including a little lone pair/lone pair repulsion, stabilization of the cation by the hydrogen bond, etc. However, the solvation of both free base and monocation relative to typical aromatic amines further complicates the issue and must also be considered. It is therefore fortunate that the gas-phase basicity of 15 and a series of less highly methylated analogues has been measured.[53] In solution, less highly methylated derivatives of 1,8-diaminonaphthalene have relatively normal basicities (the trimethyl derivative has a pK_a of 6.43).[48] In the gas phase there are increases in proton affinity as methyl groups are added to 1,8-diaminonaphthalene that are consistent with expected increases arising from changing the basic site from a primary to a secondary to a tertiary amine, together with smaller changes as the other nitrogen atom becomes a better hydrogen bond acceptor in the protonated ion (it is assumed that the proton is bound to the more highly substituted nitrogen atom). However, the increase in PA as the *last* methyl group is added (6 kcal/mol) is

larger than would be expected, since the amine being protonated is already tertiary, so only an improvement in hydrogen bond acceptor character is expected. It was estimated that about 4 kcal/mol of this final increase in PA can be ascribed to relief of strain. The gas-phase data also revealed that the solvation energy of the monoprotonated ion of **15** is more like that of 2,6-di-*tert*-butylpyridine (**1**) and carbonium ions such as the cumyl cation and is less than that expected for a normal ammonium ion. It should also be remembered in trying to interpret the high pK_a values of **15** and related proton sponges that they are themselves very insoluble in aqueous solution. While **15** is a stronger base than 1,4-diazabicyclo[2.2.2]octane (DABCO) in water by 3.2 pK units, in DMSO-d_6 solution, DABCO is the stronger base by 1.5 pK units.[53,54] Benoit et al.[53] suggest that the lack of specific solvation of **15** *and* its monoprotonated ion may make it useful for measuring the heat of transfer of a proton between solvents. In conclusion, there can be little doubt that strain contributes substantially to the high basicity of 1,8-bis(dimethylamino)naphthalene (**15**) but it is very difficult to give a quantitative account of its influence.

One consequence of the strong hydrogen bond and rigid structure of the monoprotonated ion of **15** is that diprotonation is exceptionally difficult. The second protonation of **15** is only half complete in 86% sulfuric acid,[48] and it is clear that the dication must be badly strained.

D. Other Aromatic Proton Sponges

Staab and his co-workers have prepared an interesting series of aromatic molecules carrying two dialkylamino groups (**18**–**25**) in which the distance and



orientation of the two basic groups have been systematically varied.[55–57] A detailed review of these molecules has recently appeared,[4] so the discussion here will be fairly brief. All these compounds are derivatives of

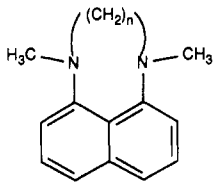
TABLE IV. pK_a Values and Geometry of Staab's Proton Sponges Based on Bridged 2,2′-Bis(dimethylamino)biphenyls[a]

compd	pK_a[b]	δ(NH)[c]	N···N,[d] Å	N···H–N⁺,[e] Å
1,8-bis(dimethylamino)-naphthalene (**15**)	12.1	18.31	2.79	2.60
4,5-bis(dimethylamino)-fluorene (**18**)	12.8	18.25		2.626
4,5-bis(diethylamino)-9,9-diethylfluorene (**19**)	13.6			
1,9-bis(dimethylamino)-dibenzothiophene (**20**)	11.9	19.06		2.587
1,9-bis(dimethylamino)-dibenzoselenophene (**21**)	11.8	19.28		2.573
4,5-bis(dimethylamino)-phenanthrene (**22**)	11.5	18.37	2.783	2.544
4,5-bis(dimethylamino)-9,10-dihydrophenanthrene (**23**)	10.9	16.50		
1,11-bis(dimethylamino)-5,7-dihydrodibenzo[*c*,*e*]oxepin (**24**)	9.4	11.76		
2,2′-bis(dimethylamino)-biphenyl (**25**)	7.9		4.738	2.650

[a] All data taken from ref 4. [b] From proton-transfer experiments in DMSO-d_6, based on a pK_a of 12.1 for **15**. [c] In DMSO-d_6. [d] N···N distance in the free base. [e] N···N distance in the protonated ion.

1,4-diaminobutane, whereas 1,8-bis(dimethylamino)-naphthalene (**15**) is a 1,3-diaminopropane derivative. The hydrogen bonds in these new proton sponges can therefore be more nearly linear, and this might in itself be expected to lead to an increase in basicity. In practice, the most basic of these molecules are the fluorene derivatives **18** and **19** (Table IV), and **18** has the most linear (but not the shortest) hydrogen bond. It is initially surprising that the phenanthrene derivative **22**, whose protonated ion has the shortest hydrogen bond, is a weaker base than **18**. Staab[4] has suggested that this may be due to the fact that the proton in **22**-H$^+$ is not so hydrophobically shielded as those in **15**-H$^+$ and **18**-H$^+$. It is not obvious to the present author that this would be expected to lead to a reduction in basicity; greater solvation of the protonated ion might be expected to lead to an increase in pK_a. Most of the discussion of the problems of interpreting the basicity of **15** applies to these compounds. Nevertheless, they undoubtedly provide very interesting examples of compounds that have enhanced basicities due to relief of strain.

Other structural variations that have been explored with 1,8-bis(dimethylamino)naphthalene (**15**) are the introduction of buttressing substituents at the 2,7-positions and the replacement of some of the methyl groups by $(CH_2)_n$ chains of various types.[48,58,59] Compounds **26**–**29** are representative; the dramatic differences in basicity for **26** as n increases are clear evidence for the need for a reasonably good alignment of the lone pairs to form a strong hydrogen bond, while all the bases with 2,7-buttressing substituents are much stronger bases than **15** (Table V). The dimethyl derivative **27** has been examined very little, due to preparative difficulties, but it is intermediate in basicity between **15** and **28**; the ethyl derivative **29** offers a modest further increase in basicity, consistent with some further increase in strain relief on protonation. The X-ray structure of **28**[5] shows the dimethylamino groups twisted more out of conjugation than in **15** and into a position causing more lone pair/lone pair repulsion. These are both factors that should increase the basicity of **28**. What is more surprising is that **28**



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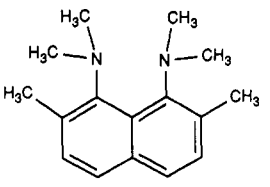

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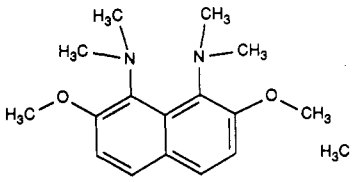

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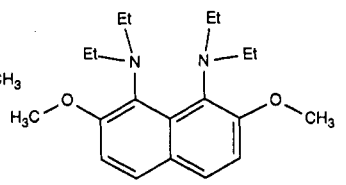

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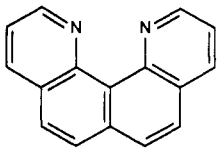
is a stronger base than **27**, since methoxy groups are normally thought to be smaller than methyl groups. It seems likely that there is some direct through-space interaction between the oxygen and nitrogen lone pairs in **28**; this could be expected to increase the electron density between the nitrogen atoms. In addition to being exceptionally strong bases, **28** and its relatives are interesting because of the extremely slow rates of proton transfer to and from them. This aspect of their chemistry has been elegantly investigated by Hibbert and his co-workers[59] and is reviewed elsewhere.[60]

E. Quino[7,8-*h*]quinoline

Staab has recently reported[61] the preparation of quino[7,8-*h*]quinoline (**30**), a compound that had been erroneously reported in the literature several times.



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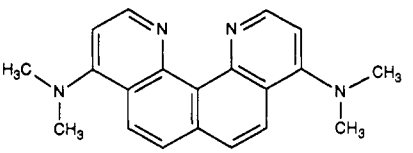

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This compound is quite different in principle from the previous proton sponges but is a comparably strong base with a pK_a of 12.8. The increase of basicity when compared with quinoline itself (pK_a = 4.91) is at least as great as that of **15** relative to 1-(dimethylamino)-naphthalene, but in this case there can be no question of steric inhibition of resonance, so the large increase in basicity is quite surprising. Another feature of **30** is of potentially greater practical importance; the rates of proton transfer to and from this base are considerably faster than for the proton sponges discussed so far. This compound could therefore be a useful base for promoting E2 and other reactions where proton transfer is part of the rate-limiting step. In view of this it would be interesting to make the 4,9-bis(dimethylamino) derivative **31**; this should be easy, since the 4,9-dichloro derivative was a synthetic intermediate on the way to **30**. Compound **31** should benefit from the vinylogous amidine residence that makes 4-(dimethylamino)-pyridine a substantially stronger base than pyridine.

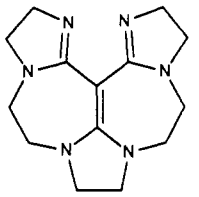
F. Vinamidine Proton Sponges

Schwesinger has recently reported[62] the preparation and properties of several pentacyclic compounds that cleverly combine the chelating properties of proton sponges with the intrinsically strongly basic vinamidine functionality. For example, compound **32** has a pK_a in

TABLE V. Basicities of Bridged and Buttressed 1,8-Diaminonaphthalenes

compd	solvent	pK_a
15	H_2O	12.1 ± 0.1
26, n = 2	H_2O	4.62 ± 0.05[a]
26, n = 3	H_2O	10.27 ± 0.07[a]
26, n = 4	30% DMSO/H_2O	13.6 ± 0.1[a]
26, n = 5	30% DMSO/H_2O	13.0 ± 0.0[a]
28	60% DMSO/H_2O	16.1[b]
29	60% DMSO/H_2O	16.3[b]

[a] From ref 59b. [b] From ref 59a.



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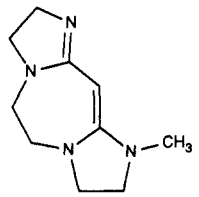

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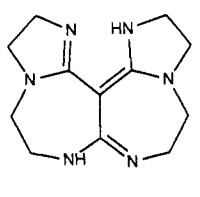

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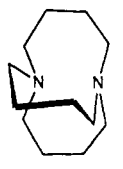
acetonitrile of 29.22 (the pK_a of **15** is 18.18 in this solvent). Comparison of **32** with **33**[63] and **34** suggests that the additional amidine unit has a base-weakening effect (comparison of **33** with **34**), while the chelate (proton sponge) effect amounts to about 4 pK units. Just how much strain comes into this 4 pK unit increase is uncertain; the structures of the monocation and dication of **32** were determined. The monocation **32**-H^+ is almost planar, while dication **32**-H_2^{2+} is strongly twisted. It was suggested that **32** itself would resemble its dication, so a certain amount of strain relief may be involved in its protonation. Compound **32** may well be near the limit of basicity attainable for a nitrogen compound, and it is interesting that it is a kinetically active base; it is also unfortunately quite easily alkylated. In other work, Schwesinger has examined the basic properties of polyaminophosphazenes; these are apparently still stronger as bases and are much less reactive toward alkylation, so they are potentially more useful as reagents.[64]

G. Bicyclic Medium-Ring Diamines

The ultimate in strain relief on protonation is probably provided by 1,6-diazabicyclo[4.4.4]tetradecane (the [4.4.4]diamine) (**35**), one of a series of bicyclic medium-ring diamines that can form inside-protonated ions.[65,66] The nitrogen atoms in **35** are 2.806 Å apart



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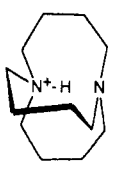

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and they move inward to 2.526 Å in the inside-protonated ion **36**.[67] At the same time, bond angles and torsion angles in the $(CH_2)_4$ bridges relax substantially toward normal values. It was estimated that strain energy in the bridges was reduced by 5.3 kcal/mol on protonation. The hydrogen bond is one of the shortest N:H–N^+ known; it is strictly linear and appears to be

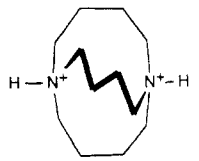
TABLE VI. Relative Basicities of 1,*k*+2-Diazabicyclo[*k.l.m*]alkanes with respect to 2,7-Dimethoxy-1,8-bis(dimethylamino)naphthalene[a,b]

[*k.l.m*] diamine	ΔpK in DMSO-d_6	ΔpK in CD_2Cl_2
[6.3.2]	−2.43 ± 0.13[c]	
[5.4.2]	−1.46 ± 0.04	
[6.4.2]	−0.80 ± 0.04	
[5.5.2]	+0.67 ± 0.04	−0.34 ± 0.05
[6.5.3]	+0.78 ± 0.04	+1.27 ± 0.05
[5.5.3]	+1.71 ± 0.08	+2.19 ± 0.09
[6.4.3]	+1.60 ± 0.08	
16 (1,6-dimethyl-1,6-diazacyclodecane)	+0.48 ± 0.03	−0.27 ± 0.04

[a] pK_a = 16.1 in 35% aqueous DMSO; see Table V. [b] Alder, R. W.; Eastment, P., unpublished results. [c] Outside protonation only. All other diamines listed give only inside-protonated ions.

of the single minimum type on the basis of spectroscopic tests and a neutron diffraction structure.[68,69] However, the pK_a of **35** cannot be measured, since the proton cannot be inserted into or removed from **35** by normal proton-transfer reactions.[65] The pK_a of **36** has been *estimated* as 25 on the basis of strain energy changes calculated by molecular mechanics.[12] Some other bicyclic medium-ring diamines behave similarly to the [4.4.4]diamine, but for others where the inside lone pairs are more accessible, proton-transfer equilibria can be established.[66] These compounds are very strong bases and relative pK_a values were measured with respect to **28**, one of the strongest proton sponges (Table VI).[70] It can be seen that compounds whose shortest bridges are $(CH_2)_3$ (1,3-diaminopropane derivatives) are stronger bases than 1,2-diaminoethane derivatives. Presumably 1,4-diaminobutane derivatives (and in particular the [4.4.4]diamine) would be even stronger bases. Once again, it is difficult to separate the effects of increasing hydrogen bond strength from those of strain relief. The structures of several of the inside-protonated ions have been determined[71,72] but unfortunately no other structural studies of free diamines except the [4.4.4]diamine are available. However, photoelectron spectra indicate substantial lone pair/lone pair interactions in all these diamines,[11,73] and it is likely that relief of this lone pair/lone pair repulsion is an important feature of these inside protonations.

The [4.4.4]diamine **35** shows reduced basicity for outside protonation to give **10** with a pK_a of about 6.5;[65] some increase in strain is clearly involved in this protonation. However, the pK_a is considerably higher than that for the corresponding monoamine **9**, because the protonated ion still has an inside lone pair and so has an *in,out* rather than a more highly strained *out,out* structure.[11,12] However, the second outside protonation to **37** requires 50% sulfuric acid (pK_a = −3.25), and this



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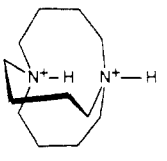

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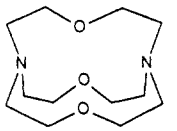
very low value is certainly largely due to the strain in the product.[65] Finally, the inside-protonated ion will add a second proton (outside) to give **38**, but only in "magic acid".[65] The extremely low pK_a (~−14?) for this process is probably more the consequence of breaking the strong hydrogen bond than strain effects, and some of the other inside-protonated ions with weaker hydrogen bonds add a second proton outside more easily (e.g., in concentrated sulfuric acid).[74] Even so, all these diprotonated ions must be severely strained.

As ring sizes increase further, the special strain effects associated with medium-ring bicyclic compounds diminish. The protonation behavior of the smallest cryptand (**39**) has been studied in detail.[75] The pK_a



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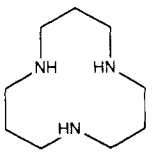
values for outside mono- and diprotonation are 7.1 and ca. 1. The first is similar to that for triethanolamine (a reasonable unstrained model), but the second may be strain affected. The pK_a for inside protonation of **39** is at least 17.8; this is based on a measured rate for insertion of the proton and an upper limit for the rate of deprotonation (which could not be detected). This pK_a is surprisingly high, since the structure of **39** and its inside mono- and diprotonated ions[76] shows that there is not a strong N:H–N^+ in the monocation, and it does not seem that there is much relief of strain during protonation. However, the ion could derive substantial electrostatic stabilization from the oxygen atoms.

V. Cyclic Triamines

1,5,9-Triaminocyclododecane (**40**) has a first pK_a of >12.5[77] and its monoprotonated ion may have a bifurcated hydrogen bond (a crystal structure of the HI salt of the *N,N'*-dimethyl derivative shows the presence of such a bond[69]). Once again, it is not clear whether the



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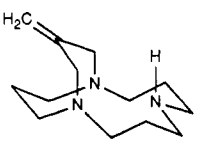

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enhanced pK_a is strain affected, since the structure of the free triamine is unknown. The bicyclic derivative **41** has pK_{a3} greater than 13.5, while pK_{a2} is only 4.4.[78] This compound is interesting because it forms an inside-protonated ion quite rapidly, and it was suggested that this was due to the nonbridgehead nitrogen atom acting as a proton-transfer relay. Unfortunately, the parent [7.3.3]diamine is not available for comparison to be made, but the [6.3.3]diamine certainly protonates much more slowly.

VI. Conclusions

Strain effects on the basicities of monoamines due to angle strain and steric inhibition of solvation are invariably base weakening. A number of types of diamines show strain-enhanced basicity where protonation can result in loss of lone pair/lone pair repulsions (or alternative steric interactions) and lead to the formation of an intramolecularly hydrogen-bonded monoprotonated ion. This review has been qualitative of necessity; it is hoped that it will stimulate interest in

the development of more quantitative treatments of strain effects on amine basicity.

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