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Using the Pyridine and Quinuclidine Scaffolds for Superbases: A DFT Study

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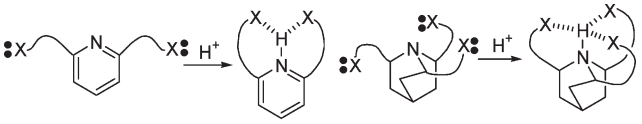

2,6-Disubstituted pyridines and 2,6,7-trisubstituted quinuclidines are screened as potential strong bases. The relative proton affinities of the bases are computed at PBE1PBE/6-311G(d,p) in the gas phase and in the solution phase (THF) at the same level with the IEFPCM treatment. Basicities are enhanced by the lone-pair possessing atoms on the substituents' arms stabilizing the conjugate acid through hydrogen bonding. The strongest bases are 2,6-bis(3-methoxy-2-furyl)-4-dimethylaminopyridine and 2,6-di(2-dimethylaminoethyl)pyridine.

Introduction

The discovery of the strong basicity of 1,8-bis(dimethylamino)naphthalene **1** (DMAN) by Alder[1] in 1968, later christened "proton sponge", inspired the search for even stronger organic bases. Superbases with a variety of interesting scaffolds have been proposed. Schwesinger prepared the vinamidine proton sponge[2] **2** and a series of phosphazenes,[3,4] of which **3** represents a very potent base. Both **2** and **3** express better kinetic acidity than DMAN. However, **2** is also a strong nucleophile, a complication that **1** does not exhibit. Zirnstein prepared quino[7,8-*h*]quinoline **4**, which has similar basicity as **1** but is kinetically faster at deprotonation.[5] Raab combined the concept of phosphazenes with the naphthalene backbone of DMAN to create **5**, which is 11 orders of magnitude more basic than **1**.[6] A number of superbases have been proposed based on computation: these include the chiral diamine **6**,[7] the tetraazatricyclooctane **7**,[8] the tripyridine **8**[9] and tetrapyridine **9**,[10] the diamine **10**,[11] and the tetraamine **11**.[12]

The computed gas-phase proton affinities of **1**−**11** are collected in Table 1. These were computed with density functional theory (DFT) and a variety of different basis sets. Superbases might be defined as those bases stronger than **1**. Compounds **2**−**11** fit that designation as all are either more basic or predicted to be more basic in the gas phase than **1**; some are predicted to be substantially more basic than **1**. Of the compounds listed here, **3** is likely to be the most basic, with a proton affinity about 55 kcal mol^{-1} larger than that of **1**!

The majority of these proposed superbases are designed with a consistent theme. **1** is thought to be so basic because of two effects: (1) the strain in the parent molecule due to having

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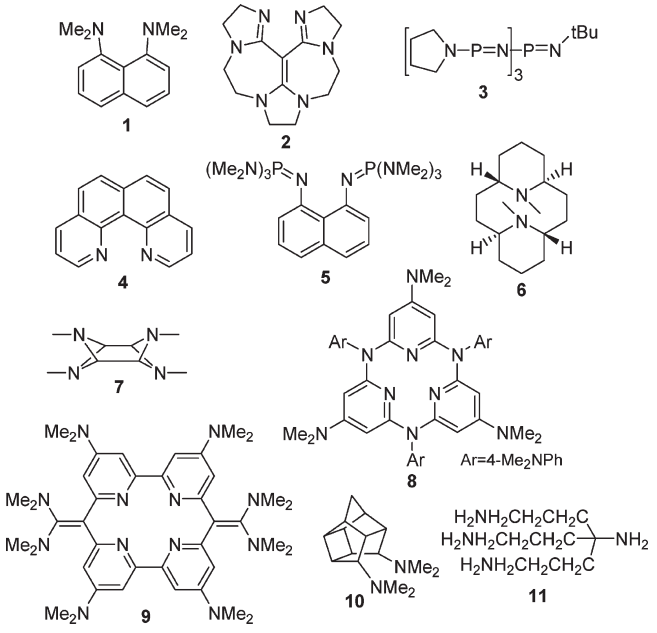
TABLE 1. Computed Gas-Phase Proton Affinity (PA) of 1-11

compd	PA, kcal mol^{-1}	method
1	245.0	B3LYP/6-311+G**/B3LYP/6-31G*[11]
	245.8	expt[13]
2	270	scaled HF/6-31G*[14]
3	301.0	unspecified[15]
4	253.7	B3LYP/6-311+G(d,p)//B3LYP/6-31G(d)[16]
5	274.1	B3LYP/6-311+G(2df,p)//B3LYP/6-31G*[6]
6	264.1	B3LYP/6-311+G**/B3LYP/6-31G*[7]
7	263.6	B3PW91/6-311++G(d,p)[8]
8	296.6	B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d)[9]
9	291.4	B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d)[17]
10	265.3	B3LYP/6-311+G**/B3LYP/6-31G*[11]
11	261.3	B3LYP/aug-cc-pVDZ[12]

SCHEME 1



the two nitrogen lone pairs near each other and (2) the relief of the strain upon protonation with the formation of a strong intramolecular hydrogen bond. The different architectures of the superbases in Scheme 1 represent clever schemes to force two nitrogen lone pairs near each other, inducing a strong strain that can be relieved when protonated. The resulting conjugate acid is stabilized by a strong internal hydrogen bond to the neighboring nitrogen. Repulsion of three nitrogen lone pairs destabilizes **8**, but in its conjugate acid the proton is bound to one of the nitrogens and is stabilized by hydrogen bonds to the two other pyridine nitrogens. Though it appears that four nitrogens might be involved in the stabilization of the conjugate acid of **9**, in fact the proton interacts with just two of the pyridinyl nitrogen lone pairs.

Our design criteria are somewhat different. Instead of forcing lone pairs near each other, we are interested in finding molecules that can bring in remote atoms with lone pairs to stabilize the added hydrogen upon protonation. Thus, the major mechanism for producing a superbase will be stabilization of the conjugate acid. This concept is demonstrated in the top part of Scheme 2. We envisage a molecule with a basic nitrogen that has two arms each bearing a lone-pair donor atom (Scheme 2a). Upon protonation, the arms wrap up to bring these atoms into contact with the proton, forming a bifurcated intramolecular hydrogen bond. Scheme 2b presents the same idea but where there are three arms with lone-pair-donor atoms, potentially forming a trifurcated hydrogen bond to the proton. This design criterion was recently implemented by Kass in the computational and experimental determination of the proton affinity of **11**.[12] Sequential addition of a propylamine arm to methylamine increased the PA; i.e. the PAs for $(H_2NCH_2CH_2CH_2)_nH_{n-2}CNH_2$ are 239, 253, and 261 (**11**) kcal mol^{-1} for n = 1−3, respectively. Kass has also used an analogous concept for the design of polyols that express enhanced acidity through stabilization of the oxyanion by arms with hydrogen donors.[18] We will explore one representative scaffold for each type: for the two-armed model we will examine 2,6-disubstituted pyridines and for the three-armed model we will use 2,6,7-trisubstituted quinuclidines. These two scaffolds are considerably simpler than many of the examples shown in Scheme 1 and may therefore present easier synthetic targets.

Computational Methods

All bases and their conjugate acids were fully optimized at PBE1PBE/6-311G(d,p).[19,20] Justification for this computational method is presented below. All structures were confirmed to be local energy minima by computing their analytical vibrational frequencies. The pyridine bases were first optimized under C_2 symmetry (where possible) and then broken symmetry structures were sought. Similarly, optimization of the quinuclidine bases was first constrained to C_3 symmetry and broken symmetry structures were located if the C_3 structures possessed one or more imaginary frequencies. All energies were corrected for zero-point vibrational energy (ZPVE), used without any correction. This is equivalent to an enthalpy at 0 K, and results in proton affinities that are slightly smaller than the PA at 298 K, the temperature of most experiments. The conjugate acids will be noted with "**H**" following the number of the corresponding base. Optimized coordinates and energies of all structures are included in the Supporting Information.

Solution-phase computations were performed by reoptimizing the structures of the bases and their conjugate acids by using PBE1PBE/6-311G(d,p) with the polarized continuum method (the IEFPCM[21,22] formulation) with solvent parameters for tetrahydrofuran (THF). The energies include the nonelectrostatic terms and ZPVE, computed with the IEFPCM treatment.

All computations were performed with the Gaussian-03[23] suite.

Results and Discussion

Benchmarking the Methodology. We have successfully employed PBE1PBE for predicting the structures of clusters formed between some amino acids and water, where evaluation of

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SCHEME 2

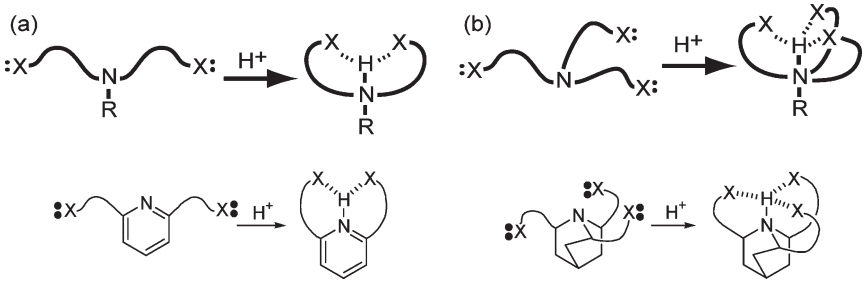
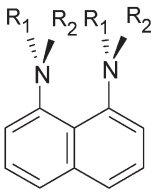
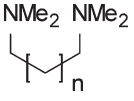


TABLE 2. Comparison of Experimental and Computed (PBE1PBE/6-311G(d,p) Proton Affinities for Some Nitrogen Bases



12: $R_1 = R_2 = H$
13: $R_1 = Me$, $R_2 = H$
1: $R_1 = R_2 = Me$

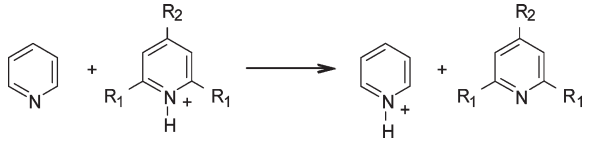


14: n = 1
15: n = 2

	PA, kcal mol^{-1}	
compd	expt	computed
ammonia	204.0	207.5
4-nitropyridine	209.0	209.7
aniline	210.9	211.1
methylamine	214.9	217.1
4-formylpyridine	216.2	217.4
N-methylaniline	219.1	217.4
pyridine **16**	222.0	223.7
dimethylamine	222.2	222.8
12	225.7	227.2
2-aminopyridine	226.4	229.4
4-methylpyridine	226.4	228.4
trimethylamine	226.8	226.1
piperidine	228.0	228.7
13	229.5	232.2
4-aminopyridine	234.2	237.8
1,2-bis(dimethylamino)benzene	234.8	235.6
quinuclidine	235.0	234.6
4-dimethylaminopyridine	238.4	242.1
14	242.1	240.5
1	245.8	246.4
15	247.4	246.2

hydrogen bonding is critical.[24,25] Other benchmark studies have also identified the PBE1PBE functional as appropriate for treating hydrogen-bonded systems.[26−29] Since our proposed superbases make use of hydrogen bonding to stabilize the conjugate acid, we believe this method will be effective for our purposes here.

SCHEME 3



Kebarle has measured the gas phase proton affinities of a variety of bases related to proton sponge **1**.[30] This series provides an excellent opportunity for benchmarking the performance of computational methods in predicting proton affinities. In Table 2 we report the experimental values (at 298 K) of the proton affinity (PA) of a series of nitrogen bases, using the values in the latest NIST database.[31] These PAs are compared with the values predicted from computation (at 0 K) with the PBE1PBE/6-311G(d,p) method.

In general, the agreement between the experimental and computed PA is quite acceptable. The average error is 1.1 kcal mol^{-1} and the mean unsigned error is 1.6 kcal mol^{-1}. A plot of the experimental vs computed PA (shown in Figure S1, Supporting Information) shows a linear relationship with an r^2 value of 0.980. We therefore expect the PBE1PBE/6-311G(d,p) method to be suitable for estimating the proton affinity of the bases examined herein.

Pyridine Superbases (Gas Phase). The pyridine scaffold we will use is displayed in Scheme 3. Pyridine was suggested as a building block of strong bases by Maksic.[32] The R_1 groups will possess an atom with a lone pair that can donate to the pyridinyl proton in the conjugate acid, thereby stabilizing the acid. The R_2 group, as we will demonstrate next, is an electron-donating group that can stabilize the conjugate acid through the standard resonance effect.

We report proton affinities of the bases relative to pyridine using the reaction shown in Scheme 3. This measure takes advantage of the cancellation of errors inherent in the methodology, especially with the solution phase computations, where we can avoid the problem of computing the solvated proton.[33,34] With this reaction, a positive value

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TABLE 3. Computed Relative Gas and Solution Proton Affinities of Pyridine Bases 16−24

			relative PA, kcal mol^{-1}	
compd	R_1	R_2	gas	THF
16	H	H	0.0	0.0
17	H	NH_2	14.1	8.9
18	H	NMe_2	18.4	8.2
19	NH_2	H	8.7	5.1
20	NH_2	NH_2	18.0	10.1
21	NH_2	NMe_2	20.6	9.5
22	NMe_2	H	15.9	−1.8
23	NMe_2	NH_2	23.9	4.5
24	NMe_2	NMe_2	26.0	4.4

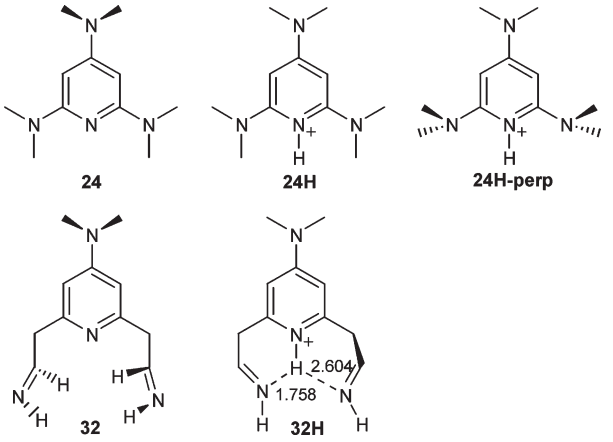

FIGURE 1. Structures of **24**, **24H**, **24H-perp**, **32**, and **32H**.

means the substituted pyridine is a stronger base than pyridine and has a larger proton affinity than pyridine.

The first group of pyridine bases we examined have amine or dimethylamine substitutents. The computed gas phase and solution phase (THF) proton affinities for bases **17**−**24** are listed in Table 3. In all cases except where noted, we report protonation of the pyridine nitrogen. This is expected to be the most basic site. For example, the PA of aniline is computed to be 12.6 kcal mol^{-1} smaller than that of pyridine (the experimental difference is 11.1 kcal mol^{-1}) and the PA of the amine in **17** and **18** is 37.2 and 29.1 kcal mol^{-1}, respectively, smaller than that for protonation of its pyridinyl nitrogen.

Amine substitution at the 4-position of pyridine dramatically increases the basicity of the pyridine nitrogen through resonance stabilization. Comparison of **16** with **17**, **19** with **20**, and **22** with **23** indicates that the *p*-amino group provides an increase of the PA of about 8−9 kcal mol^{-1}. The effect is greater still with para substitution with a dimethylamino group: the PA is increased by another 2 kcal mol^{-1} over the amine group. We will therefore include a 4-amino or 4-dimethylamino substituent to enhance the basicity over the anticipated affect of the ortho substituents as per Scheme 2a.

The amino groups in the 2 or 4 position are only slightly pyramidal in the neutral bases **17**−**24**. They are all nearly planar and coplanar with the pyridine ring in the conjugate acids; see, for example, the structures of **24** and **24H** shown in Figure 1. This suggests that all of these amino substituents are acting as electron donors, and stabilize the conjugate acid by delocalizing the positive charge onto the amino groups.

TABLE 4. Computed Relative Gas and Solution Proton Affinities of Pyridine Bases 25−36

			relative PA, kcal mol^{-1}	
compd	R_1	R_2	gas	THF
25	CHO	H	−10.9	−16.0
26	CHO	NH_2	1.8	−5.8
27	CH_2CHO	H	10.9	−2.2
28	CH_2CHO	NH_2	19.4	4.7
29	CHNH	H	6.4	−4.5
30	CHNH	NH_2	17.6	4.5
31	CH_2CHNH	H	21.8	4.4
31a	CH_2CHNH^a	H	15.5	3.8
32	CH_2CHNH	NH_2	30.3	11.8
32a	CH_2CHNH^a	NH_2	25.4	
33	CH_2CONH_2	H	16.2	2.1
34	CH_2CONH_2	NH_2	23.4	7.6
35	NHCHO	H	4.4	−5.2
36	NHCHO	NH_2	12.8	1.4

[a]Only one R_1 substituent, i.e., **31a** is 2-(2-iminoethyl)pyridine and **32a** is 4-amino-2-(2-iminoethyl)pyridine.

Natural population analysis (NPA)[35] confirms this notion. The amino group of **17** loses 0.16 e$^-$ upon protonation while the dimethylamino group of **18** loses 0.18 e$^-$. The added methyl groups in **18** make the nitrogen slightly better at carrying positive charge, and this accounts for its slightly greater PA than **17**. The amino groups of **19** lose 0.12 e$^-$ each, indicating that these ortho groups are slightly weaker in their ability to stabilize positive charge by resonance than are *p*-amino groups. This is also seen in the changes in NPA charges on the amino groups upon protonation of **20** and **24**; each *o*-amino group of **20** loses 0.095 e$^-$ while the para group loses 0.13 e$^-$, and similarly each ortho group of **21** loses 0.08 e$^-$ while the para group loses 0.13 e$^-$. The greater donation of charge from the *p*-amino groups to the pyridinium than from the ortho group leads to a C−N distance that is about 0.01 Å shorter for the para group.

The amino groups in the ortho positions are not stabilizing the pyridinium proton in the mechanism proposed in Scheme 1; their lone pairs are conjugated into the ring and not directed toward the proton. We have optimized the structures of **19** and **24** with the *o*-amine groups constrained to have their lone pairs lying in the pyridine plane, perpendicular to their preferred orientation. The structure of **24H-perp** is shown in Figure 1. Both **19H-perp** and **24H-perp** have two imaginary frequencies corresponding to rotation of the amino groups back into the plane. The ortho amines in both of these compounds are highly pyramidal, with the lone pairs directed toward the pyridinyl proton. Nonethless, these structures are noncompetitive with the planar conformers: **19H-perp** lies 16.7 kcal mol^{-1} above **19H** and **24H-perp** is 15.6 kcal mol^{-1} above **24H**.

The second set of pyridine bases have ortho substituents with a carbonyl or imine group. This provides a formal sp^2 oxygen or nitrogen lone pair to donate to the proton of the conjugate acid. The computed gas-phase and THF-solution-phase proton affinities are listed in Table 4.

The formyl group is an electron-withdrawing group and that alone would suggest that formyl-substituted pyridines would be poor bases. 4-Formylpyridine is in fact a weaker base than pyridine: its experimental PA is 5.8 kcal mol^{-1}

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TABLE 5. Computed Relative Gas and Solution Proton Affinities of Pyridine Bases 37−54

			relative PA, kcal mol^{-1}	
compd	R_1	R_2	gas	THF
37	CH_2OH	H	12.0	3.8
38	CH_2OH	NH_2	20.8	10.2
39	CH_2CH_2OH	H	17.1	6.7
40	CH_2CH_2OH	NH_2	25.6	12.4
41	$CH_2CH_2OCH_3$	H	23.6	5.5
42	$CH_2CH_2OCH_3$	NH_2	33.0	13.2
43	$CH_2CH_2OCH_3$	NMe_2	35.6	12.3
44	2-OHPh	H	9.8	−1.1
45	2-OHPh	NH_2	16.2	2.6
46	2-OMePh	H	24.8	3.8
47	2-OMePh	NH_2	33.1	10.8
48	2-OMePh	NMe_2	35.3	8.4
49	2-furyl	H	12.6	−3.7
50	2-furyl	NH_2	21.0	3.1
51	2-furyl	NMe_2	23.5	1.6
52	3-MeO-2-furyl	H	30.4	4.9
53	3-MeO-2-furyl	NH_2	38.6	13.9
54	3-MeO-2-furyl	NMe_2	40.7	12.5

smaller than that of pyridine (the difference is computed to be 6.3 kcal mol^{-1}). The computed PA of 3,5-diformylpyridine is 12.6 kcal mol^{-1} less than that of pyridine. The PA of 2,6-diformylpyridine (**25**) is 10.9 kcal mol^{-1} smaller than that of pyridine; the slightly greater basicity of **25** over the 3,5-isomer is suggestive of some stabilization of the conjugate acid from the neighboring oxygen atoms. Adding the amino substituent to **25** makes **26** only slightly more basic than pyridine.

The PA of 4-pyridylmethanimine (225.0 kcal mol^{-1}) is larger than that of pyridine and 4-formylpyridine (223.7 and 217.4 kcal mol^{-1}, respectively). This suggests that **29** will be more basic than pyridine, and it is—its PA is 6.4 kcal mol^{-1} greater than that of pyridine.

To increase the basicity, however, both the C=O and C=N groups need to be out of resonance with the pyridine ring yet close enough to interact via hydrogen bonding with the pyridinyl proton. This suggests compounds **27** and **31**. The former is significantly more basic than the formyl analogue, but remains too weak a base for our purposes. The latter, particularly with the 4-amino substituent (**32**), is quite basic: the PA of **32** is 30.3 kcal mol^{-1} greater than that of pyridine. The structure of **31H** and **32H** has no symmetry and one imine group is closer (1.758 Å) to the pyridinyl proton than the other (2.604 Å). (The structures of **32** and **32H** are shown in Figure 1.) Though the second imine is farther away, it does still provide some significant enhancement of the basicity. The PAs of **31a** and **32a**, each has only one CH_2CHNH group, are 6.3 and 5.9 kcal mol^{-1} smaller than that of **31** and **32**, respectively.

The amide substituents of **33** and **34** should provide more stabilization of their conjugate acids than the simple carbonyl groups of **27** and **28** since their oxygens should bear more negative charge. This is in fact true, but **33** and **34** are less basic than **32**.

Members of the third group of pyridine bases possess alcohol substituents on the 2 and 6 positions. The compounds examined are listed in Table 5 along with their computed gas-phase and THF-solution-phase proton affinities.

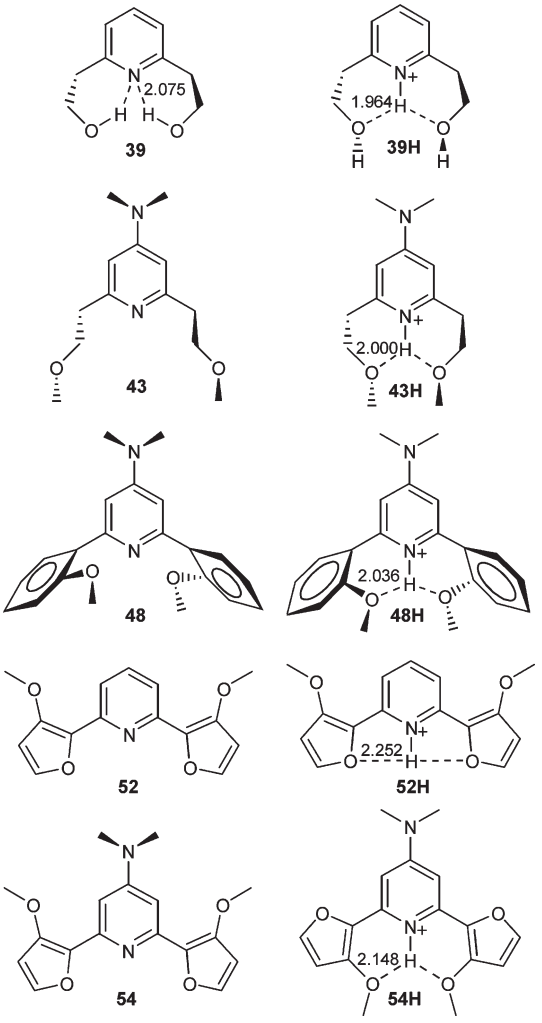


FIGURE 2. Structures of **39**, **43**, **48**, **52**, and **54** and their conjugate acids.

The hydroxymethyl substituent (**37** and **38**) only moderately increases the basicity of pyridine. This is likely due to the long NH···O distance (2.03 Å) in the conjugate acid along with its very nonlinear N−H···O angle (105.9°), which does not facilitate a strong hydrogen bond. The hydroxyethyl substituent (**39** and **40**) does allow for better hydrogen bonding in the conjugate acid: r(NH···O) = 1.964 Å and θ(N−H···O) = 127.6°. However, the PA of **39** and **40** remain only 17 and 26 kcal mol^{-1} greater than that of pyridine. The problem is not that the hydroxyl groups are poorly stabilizing the positive charge on the pyridinyl proton in the conjugate acid **39H**, but rather that the hydroxyl groups are donating their protons to the nitrogen lone pair of **39**, stabilizing the reactant. This is clearly evident in the structure of **39**, shown in Figure 2, where each N···HO distance is 2.075 Å.

To reduce this stabilization of the base, we looked at the methoxyethyl substituent, which has no proton to donate to the pyridinyl nitrogen, yet remains a potential proton acceptor in the conjugate acid. This substitution does lead to a stronger base (the PA of **41** is 23.6 kcal mol^{-1} greater than that of pyridine), and with a 4-dimethylamino substituent as well, a very potent base is produced: the PA of **43** is 35.6 kcal mol^{-1} greater than that of pyridine. The structures of **43**

TABLE 6. Computed Relative Gas and Solution Proton Affinities of Pyridine Bases 55−72

			relative PA, kcal mol^{-1}	
compd	R_1	R_2	gas	THF
55	CH_2NH_2	H	25.5	10.9
56	CH_2NH_2	NH_2	−34.3	17.9
57	$CH_2CH_2NH_2$	H	26.9 (24.0)[b]	12.9
57a	$CH_2CH_2NH_2$[a]	H	19.1 (16.7)[b]	
58	$CH_2CH_2NH_2$	NH_2	35.4	18.2
59	$CH_2CH_2NMe_2$	H	27.0 (26.9)[b]	9.7
59a	$CH_2CH_2NMe_2$[a]	H	21.1 (22.9)[b]	
60	$CH_2CH_2NMe_2$	NH_2	35.9	19.8
60a	$CH_2CH_2NMe_2$[a]	NH_2	30.7	
61	$CH_2CH_2NMe_2$	NMe_2	38.2	17.0
62	2-NH_2Ph	H	14.7	−1.8
62a	2-NH_2Ph[a]	H	10.9	−1.7
63	2-NH_2Ph	NH_2	22.9	4.7
64	2-NH_2Ph	NMe_2	25.1	4.3
65	2-NMe_2Ph	H	25.6	4.9
65a	2-NMe_2Ph[a]	H	20.1	
66	2-NMe_2Ph	NH_2	34.0	13.3
67	2-NMe_2Ph	NMe_2	36.3	11.2
68	3-NH_2-2-furyl	H	19.1	0.8
69	3-NH_2-2-furyl	NH_2	25.4	5.8
70	3-NH_2-2-furyl	NMe_2	27.3	4.6
71	3-NMe_2-2-furyl	H	26.1	1.4
72	3-NMe_2-2-furyl	NH_2	32.9	6.6
73	3-NMe_2-2-furyl	NMe_2	34.9	7.9
74	4-NH_2-2-furyl	H	18.3	−1.3
75	4-NH_2-2-furyl	NH_2	26.0	4.8
76	4-NH_2-2-furyl	NMe_2	28.2	3.8
77	4-NMe_2-2-furyl	H	19.7	−2.0
78	4-NMe_2-2-furyl	NH_2	27.1	4.5
79	4-NMe_2-2-furyl	NMe_2	29.0	2.2
80		H	34.3	17.1
81		NH_2	43.5	24.9

[a]Only one R_1 substituent, i.e., **57a** is 2-(2-aminoethyl)pyridine. [b]Protonation at the amine nitrogen rather than at the pyridinyl nitrogen.

(lacking the proton donation evident in **39**) and **43H** are shown in Figure 2.

We next surmised that the basicity of ether-substituted pyridines might become even stronger if we could position the ether oxygen even closer to the proton of the conjugate acid. The NH···O distance in **41H** and **43H** is 1.964 and 2.000 Å, respectively. Constraining rotation about the C−C bond of the ethyl group might force the oxygen closer to the pyridine plane. The 2-hydroxyphenyl substituent prevents any rotation about the C−C bond, and the NH···O distance is slightly shorter in **44H** (1.972 Å). Unfortunately **44** is a relatively weaker base because of proton donation from the hydroxyl groups to the pyridine nitrogen. This problem is cured by using the 2-methoxyphenyl substituent. The structure of **48**, possessing this substituent and a dimethylamino group, and its conjugate acid are displayed in Figure 2. However, **48** is no more basic that the methoxyethyl derivative **43**.

A possible limitation in the effectiveness in the phenolic oxygen to stabilize the conjugate acid is the inability of the phenol and pyridine rings to become coplanar, thanks to ortho,ortho′ hydrogen interaction. To minimize this unfavorable interaction, we tested the furanyl ring as a substituent. The 2,6-bis(2-furyl)pyridines **49**−**51** show moderate enhancement of the basicity of pyridine, with **51** having a PA some 23 kcal mol^{-1} larger than that of pyridine.

Adding an electron-donating group to the furan ring should make the oxygen more negatively charged and better able to stabilize the added proton. Placing a methoxy group on the 3-position of furan not only should increase the stabilizing effect of the furanyl oxygen, but the methoxy oxygen might be a suitable electron donor to the pyridinyl proton. The effect of the methoxy substituent is profound: the PA of **52** is 30.4 kcal mol^{-1} greater than for pyridine. The stabilization of the proton in **52H** is by the furanyl oxygens (see Figure 2). For the amino and dimethylamino analogues **53** and **54**, the methoxy groups stabilize the proton (Figure 2), though the energy difference between it and the conformer with the furanyl oxygens near the proton is less than 1 kcal mol^{-1}. **54** is the most basic of the compounds described so far, with a PA 40.7 kcal mol^{-1} greater than that of pyridine.

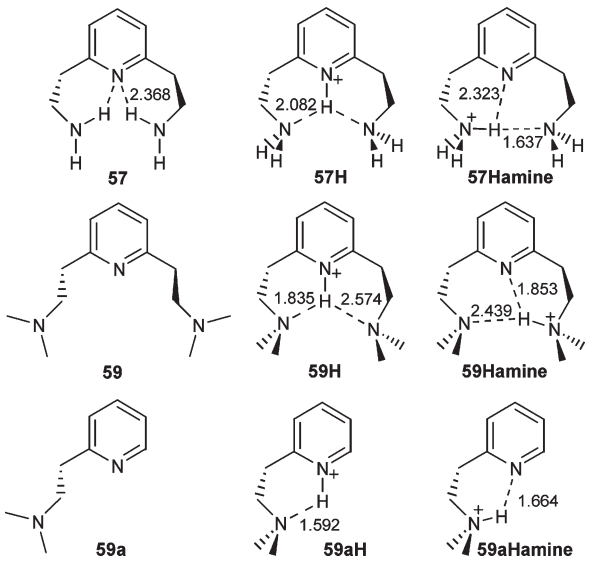


FIGURE 3. Structures of **57**, **59**, and **59a** and their conjugate acids.

The last group of pyridine bases possess amino substituents on the 2 and 6 positions. The compounds examined are listed in Table 6 along with their computed gas-phase and THF-solution-phase proton affinities.

The aminomethyl group (**55** and **56**) increases the basicity of pyridine by 25 and 34 kcal mol^{-1}, respectively. This is significantly more than the effect of the hydroxymethyl substitutent (**37** and **38**). The hydroxymethyl stabilizes the free base through intramolecular hydrogen bonding to the pyridinyl nitrogen, which is largely absent with the aminomethyl group: the OH···N distance is 2.068 Å in **37** while the NH···H distance in **49** is 2.338 Å.

Lengthening the chain by one carbon by using the aminoethyl group (**57** or **58**) only slightly improves the basicity. The two amino groups symmetrically bridge to the proton in the conjugate acid (**57H** and **58H**). Protonation of the pyridine nitrogen is favored over protonation of one of the amines by almost 3 kcal mol^{-1}. The structures of **57**, **57H** and its protonated amine analogue **57Hamine** are shown in Figure 3. The assistance of both substituents in enhancing the basicity is seen in the difference in PA between **57** and **57a** (which has a single aminoethyl substituent) of 7.8 kcal mol^{-1}.

Addition of methyl groups to the amine results in only slight increases in basicity. So, the PA of **59** is only 0.1 kcal mol^{-1} greater than that of **57**. These methyl groups increase the steric bulk about the nitrogens, which does not allow the two amines to symmetrically bridge the pyridinyl proton; the shorter NH···H distance is 1.835 Å, while the other amine is

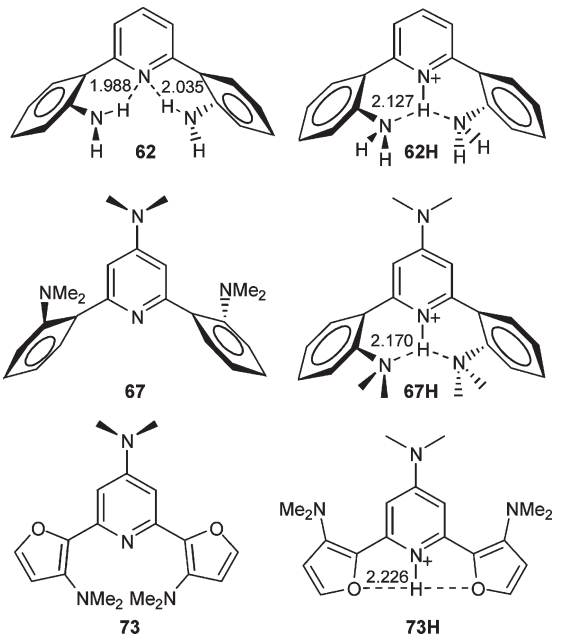


FIGURE 4. Structures of **62**, **67**, and **73** and their conjugate acids.

a rather remote distance of 2.574 Å away from the proton (see Figure 3). Nonetheless, the pyridinyl nitrogen is more basic than the amine nitrogens (by 0.1 kcal mol^{-1}) and the second amine does enhance the basicity: the PA of the disubstituted **59** is 5.9 kcal mol^{-1} greater than that of the monosubstituted **59a**. In **59aH** (see Figure 3), the NH···H distance is much shorter than that in **59H** (1.592 Å vs 1.835 Å), and though this hydrogen bond must be stronger in **59aH**, the bifurcated hydrogen bonds in **59H** lead to greater stabilization of the conjugate acid. Interestingly protonation of the amine of **59a** is more favorable than at the pyridinyl nitrogen. This is likely attributable to the quaternary nature of the resulting protonated amine.

The strongest base of the alkyl-amino-substituted pyridines is **61**, which possesses a dimethylamino group on the 4-position. Its PA is 38.2 kcal mol^{-1} greater than that of pyridine.

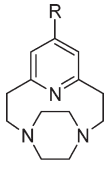
Restricting the rotational freedom about the C−C bonds might afford the amine a closer approach to the pyridinyl proton, and so we next examined aniline substituents. A drawback to aromatic amines is that their preferred planar structure reduces the availability of the lone pair for use in stabilizing a neighboring positive charge. In fact, the bis-(anilinyl)-substituted pyridines **62**−**63** are weaker bases that the ethylamine analogues **57**−**58**. This weakness as a base is evident in structural elements of both **62** and its conjugate acid **62H** (Figure 4). The amino groups of **62** are slightly distorted from planarity (the sum of the angles about N is 350.6° and 348.7°), indicating the preference of the lone pair to conjugate with the phenyl ring, and the amino hydrogens closely approach the pyridine nitrogen, indicating some intramolecular hydrogen bonding. This latter effect weakens the basicity of the pyridinyl nitrogen. In **62H**, while the pyridinyl proton is stabilized by both amine groups, the amines are quite pyramidal (the angle sum at N is 335.9°), reflecting loss of the energy afforded by delocalization of the lone pair into the phenyl ring upon protonation of the pyridine.

Substitution of the amine of **62** with methyl groups mitigates these problems. The permethylated analogue **67** and its conjugate acid are shown in Figure 4 and demonstrate the base-enhancing properties of the methyl groups. The methyl groups force the phenyl groups to rotate so that no internal stabilizing interactions to the pyridinyl nitrogen are present. Steric interactions of these methyl groups with the pyridine ring lead to a pyramidal amine. Upon protonation (forming **67H**) the phenyl groups rotate to bring the amines close to the added proton. Since the amines are already pyramidal, there is little energy loss to position the lone pairs toward the proton. The net result is that **67** is a strong base, with a PA 36.3 kcal mol^{-1} greater than that of pyridine.

Following on the results of the furanyl-substituted pyridines, we supposed that an aminofuranyl substituent might allow for the nitrogen lone pair to coordinate well with a protonated pyridine. However, the 3-amino-2-furylpyridines **68**−**70** are only moderately basic. Once again, the amine protons stabilize the lone pair of the pyridine nitrogen (making it less basic). If the amine is to stabilize the proton, it must pyramidalize in order to direct its lone pair toward the proton, reducing its conjugation with the furanyl ring. In fact, this is too energetically costly, and it is the furanyl oxygen that acts as the hydrogen acceptor in the conjugate acid. This can be seen in **73H**, shown in Figure 4. Just as with the methoxy-substituted furans, the amino substituent acts as an electron donor, increasing the negative charge on the furanyl oxygen, making it a stronger hydrogen bond acceptor. The strongest of the 3-amino-2-furylpyridines bases (**68**−**73**) is **73**, with a PA 34.9 kcal mol^{-1} greater than that of pyridine.

Since the 3-amine group enhances the basicity solely by donating charge to the furanyl oxygen, placing it on the 4-position should also serve this purpose, while diminishing the steric conflict with the pyridine ring. However, the 4-amino-2-furylpyridines **74**−**79** are slightly weaker bases than their corresponding 3-amino analogues.

Though it violates the spirit of the design of our bases as depicted in Scheme 2, the strong basicity of the aminoethyl-pyridines inspired the design of a compound where the two amino groups are permanently aligned near the lone pair of the pyridinyl nitrogen. This can be accomplished by tying the two amines together with an ethyl linker, as in **80**. Though the amines are linked together, **80** is flexible and the two amines lie above the pyridine plane, but upon protonation, the amines move so that they symmetrically bridge the proton. This compound is quite basic, with a PA 34.3 kcal mol^{-1} greater than that of pyridine. Addition of an amino group at the 4-position of pyridine increases the PA and **81** is the most basic compound we describe, with a PA that is 43.5 kcal mol^{-1} greater than that of pyridine.



80: R=H
81: R=NH_2

Quinuclidine Superbases (Gas Phase). The quinuclidine scaffold, shown in Scheme 4, places groups on the three

SCHEME 4

TABLE 7. Computed Relative Gas and Solution Proton Affinities of Quinuclidine Bases 82−91

		relative PA, kcal mol^{-1}	
compd	R	gas	THF
82	H	10.8	6.9
83	CH_2OH	20.4	12.2
84	CH_2CH_2OH	24.4	12.6
85	CH_2OCH_3	32.9	9.7
86	$CH_2CH_2OCH_3$	30.2	12.6
87	2-OHPh	22.7	
88	CH_2CHO	23.7	9.8
89	CH_2NH_2	29.2	15.6
90	$CH_2CH_2NH_2$	35.9	19.4
91	CH_2CHNH	33.5	14.7

carbons adjacent to the nitrogen. Each of these groups will include an atom with a lone pair that can be brought into the interior to stabilize the protonated amine. The reaction shown in Scheme 4 will be used to evaluate the basicity of the substituted quinuclidine relative to pyridine, enabling us to compare these compounds with the substituted pyridine bases described above. The reaction will be used for both gas-phase and solution-phase (THF) computations. Again, a positive value indicates a quinuclidine base with a PA greater than that of pyridine.

The proton affinity of unsubstituted quinuclidine **82** has been measured experimentally, with a value of 235.0 kcal mol^{-1}. The PBE1PBE/6-311G(d,p) computed PA is 234.6 kcal mol^{-1}, in excellent agreement with the experimental value. Experimentally, the PA of quinuclidine is 13 kcal mol^{-1} greater than that of pyridine, while the computational difference is 10.9 kcal mol^{-1}. Given the errors associated with the experiments and our computations, this difference is certainly acceptable.

Given the results for the substituted pyridine scaffold, we examined a much smaller range of substituted quinuclidines, featuring alkyl amines and alcohols, along with a single example involving an sp^2-nitrogen- and sp^2-oxygen-containing group. All of these examples are listed in Table 7 with their gas- and solution-phase (THF) relative PAs.

The three hydroxymethyl groups of **83** enhance the PA of quinuclidine by almost 10 kcal mol^{-1}. Lengthening the chain by one carbon further increases the PA: the PA of **84** is 4 kcal mol^{-1} greater than that of **85**. As with **39**, the PA of **84** is somewhat diminished by the intramolecular hydrogen bond between one of the hydroxyl groups and nitrogen, along with the hydrogen bonds from each of the other two hydroxyl groups to the third oxygen (see Figure 5). All of these hydrogen bonds are broken upon formation of the conjugate acid, replaced by the three interactions of the oxygen lone pair with the added proton. The PA of **83** is similarly reduced by the cyclic array of hydrogen bonds between the three hydroxyl groups.

Replacing the hydroxyl group with a methoxy group in **83** or **84** removes the hydrogen bonding that stabilized these bases. The three ether oxygens are able to associate with the

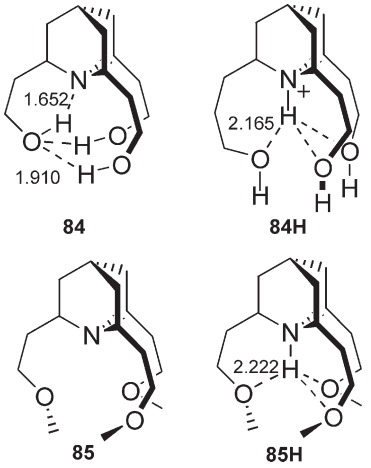


FIGURE 5. Structures of **84** and **85** and their conjugate acids.

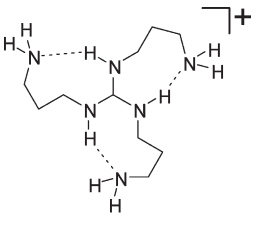
quinuclidine proton in the conjugate acids (see the structure of **85H** in Figure 5), resulting in dramatic increases in basicity. The PA of **85** is 12.5 kcal mol^{-1} larger than that of **83**, but the PA of **86** is only 5.8 kcal mol^{-1} larger than that of **84**. While the NH···O distances in **85H** and **86H** are similar (2.222 and 2.226 Å, respectively), the terminal methyl groups are much closer to each other in the latter (5.25 Å in **85H** vs 4.05 Å in **86H**), leading to some steric destabilization.

The triphenoxyquinuclidine **87** is a slightly weaker base than **84**. We supposed that the phenyl ring would allow close approach of the oxygen to the quinuclidine proton. The oxygen stabilizes the proton by donation of its lone pair, but if the phenyl ring were to be coplanar with the N−H bond, the phenoxy hydrogen would have to rotate out-of-plane to orient the oxygen lone pair toward the hydrogen. However, there is strong conformational preference for the O−H bond and phenyl ring to be coplanar. This results in the phenyl rings rotating more than 60° from the C−N−H plane to properly orient the lone pair, increasing the NH···O distance and providing only weak stabilization of the conjugate acid.

Lastly, we examined amine substituents on quinuclidine. Methylamine groups increase the proton affinity by 18 kcal mol^{-1}, and ethylamine substituents are even better: the PA of **90** is 35.9 kcal mol^{-1} greater that the PA of pyridine. With the pyridine bases, we observed that dimethylamino groups enhanced the basicity even more than amino groups. However, the interior space about the proton of **90** is quite congested and cannot accommodate even the relatively small methyl chain. If methyl groups were placed on the nitrogens of **90**, at least one, if not two, of the aminoethyl chains would have to move away from the interior, allowing likely only one of the arms to associate with the quinuclidine proton.

The congestion about the protonated nitrogen accounts for in general poorer performance of the quinuclidine bases compared to the pyridine bases. It is simply too crowded to get three substituents to closely approach the proton. It is therefore unlikely that the trifurcated hydrogen-bonding model of Scheme 2b will produce a base much stronger than **90**. But as we discuss next, **90** is predicted to be the strongest base in solution. It is worth noting that the trifurcated hydrogen bonding in **90** creates a base with a PA of 270 kcal mol^{-1}, or an increase in the PA of quinuclidine by about

25 kcal mol^{-1}. The three separate hydrogen bonds in the guanidine conjugate acid **92** create a base that is somewhat stronger (its PA is 268 kcal mol^{-1}) and the hydrogen bonds collectively contribute about 18 kcal mol^{-1} of stabilization energy.[36] This suggests that the concept of a trifurcated hydrogen bond as a means for enhancing basicity appears worth further pursuits, if one can overcome the congestion problem.



92

Solution-Phase (THF) Basicity. Solution-phase basciity was modeled by computing the energy for the reactions shown in Schemes 3 and 4. Each species was reoptimized at IEFPCM/PBE1PBE/6-31G(d,p) with parameters for THF, a common organic solvent. Use of these reaction energies obviates the need for computing the energy of the solvated proton and provides solution-phase proton affinities relative to pyridine. The computed relative reaction energies are listed in Tables 3−6.

Inspection of the solution-phase energies identifies a major effect of solvent—the range in values is suppressed relative to gas phase results. Within the PCM treatment, solvent interaction with solute is solely through its dielectric, stabilizing polar substrates. In the context of our work, solvent will stabilize the bases little, since they tend to have small dipole moments. However, the charged conjugated acids will be significantly stabilized by the dielectric field. The result is that a simple base like pyridine or quinuclidine will be more basic in polar solution than in the gas phase.

We are interested in *relative* proton affinity and so we must consider the effect of solvent on the substituted base relative to its effect on pyridine. We have designed our bases to stabilize the charge of the conjugate acid by providing groups that can donate electron density to the proton. This action effectively delocalizes the charge. The dielectric field of the solvent is most effective in stabilizing *localized charge*, and so solvent will affect our designed bases to, in general, a lesser extent than pyridine. Thus, the increased basicity afforded by the substituents will be lessened (or screened) by the solvent.

Since many of the trends discussed in the gas-phase proton affinities of the pyridine and quinuclidine bases carry over to the solution phase, we instead focus our attention here to the very best solution-phase bases. The hydroxyethyl- and methoxyethylpyridines **40**, **42**, and **43** are 12−13 kcal mol^{-1} more basic than pyridine, a substantial improvement in basicity though about 20 kcal mol^{-1} less than the substituent effect on gas-phase proton affinity. Of the oxygen substituents, the strongest base is **53**. Unlike in the gas phase, where the 4-dimethylamino substituent enhances the PA over the 4-amino group (by about 2 kcal mol^{-1}), in THF solution the effect is reversed: **54** is 1.4 kcal mol^{-1} less basic than **53**. This trend is seen in most of the pyridine bases examined here.

Many of the alkylamino-substituted pyridines are quite basic. The two best are **58** and **60** which are 18.2 and 19.8 kcal mol^{-1} more basic than pyridine. These are on par or better than the basicities of some of the compounds from Scheme 1.

The substituted quinuclidines are also pretty fair bases. One must recognize that quinuclidine itself is a much stronger base (by about 7 kcal mol^{-1}) than pyridine. (The experimental aqueous pK_a difference between pyridine and quinuclidine[37] is 5.8, slightly larger than our computed difference in THF.) Hydroxymethyl-, hydroxyethyl-, and methoxyethyl-substituted quinuclidines (compounds **83**, **84**, and **86**) are 12 kcal mol^{-1} more basic than pyridine in THF. The aminomethyl-substitued quinuclidine is 15.6 kcal mol^{-1} more basic than pyridine, but the most basic quinuclidine is **90**. It is predicted to be 19.4 kcal mol^{-1} more basic than pyridine.

90 and **60** are the best bases in solution we found that involve the stabilization concept defined in Scheme 2. However, **81** is predicted to be quite basic (24.9 kcal mol^{-1} more basic than pyridine) and matches up with the best previous solution-phase bases proposed.

Conclusions

Superbases, those molecules more basic than 1,8-bis-(dimethylamino)naphthalene, have been a popular pursuit. The primary strategy for constructing superbases is to force amines or other nitrogen groups in close proximity. The repulsion between the closely allayed lone pairs destabilizes the base, and the "sharing" of the proton stabilizes the conjugate acid. Our approach to superbases is to construct molecules with a central basic site with two or three "arms", each possessing an atom with a lone pair. Upon protonation of the central basic site, the arms can wrap inward, bringing the lone pairs near the proton to stabilize this positive charge (Scheme 2). We propose a variety of disubstituted pyridines and trisubstituted quinuclidines as potential strong bases.

If we take the definition of "superbase" to be one that is more basic than DMAN **1**, then many of the computed compounds in this study qualify as superbases. Both oxygen and nitrogen substituents can be utilized as electron donors that can rotate inward to stabilize a protonated pyridine or quinuclidine. The strongest gas-phase bases possessing oxygen substituents are **43**, **48**, **53**, and **54**. Among the very strongest nitrogen-substituted bases are **58**, **60**, **61**, **67**, and **90**. All of these bases have proton affinities that are more than 35 kcal mol^{-1} greater than the PA of pyridine, or more than 12 kcal mol^{-1} greater than the PA of DMAN. For solution purposes, **58** and **60** and **90** are the most promising strong bases, being more than 18 kcal mol^{-1} more basic than pyridine. These computations further the notion of the hydrogen-bonding enhancement of basicity (and acidity) put forward by Kass.[12,18]

One of our aims was to identify strong bases that are less esoteric than many of the recently proposed superbases. The trisubstituted quinuclidines examined here are unknown, but

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some of the disubstituted pyridines are known compounds. Compound **62**, whose basicity is only moderately improved over pyridine (but can be significantly improved with a *p*-amino substituent), was prepared by Bercaw for use as a chelator to iron.[38] The dimesityl derivative complexes with iron such that all three nitrogen bind to iron, mimicking the stabilization mechanism proposed for our superbases. **57** has been prepared and also used for chelating metals.[39] It is fairly basic, and with small alterations (methylating the amines and adding a *p*-amine group) a very potent base (**61**) can be had. The X-ray crystal structure of **44** has been determined.[40] While **44** is not a particularly potent base, the crystal structure of its conjugate acid **44H** was also reported, without any mention of its basicity. Of note in these two crystal structures is that the torsional angle between the phenoxy plane and the pyridine plane decreases from 45° in **44** to 25° in **44H**, reflecting the stabilizing role of the hydroxyl groups as in Scheme 2a. The methoxy analogue **46**, predicted to be a much stronger base, is also known.[41] It seems quite plausible that the very basic compounds identified in this work can be prepared and put to productive use.

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Supporting Information Available: Full citation for ref 23, Figure S1 showing a comparison of computed vs experimental proton affinity for bases listed in Table 1, and coordinates of all pyridine and quinuclidine bases and their conjugate acids optimized at PBE1PBE/6-311G(d,p). This material is available free of charge via the Internet at http://pubs.acs.org.

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