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Substituent Effects on the Basicity of 3,7-Diazabicyclo[3.3.1]nonanes

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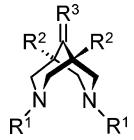


R^1 = Ph, Bn, Ph(Me)CH, Ph_2CH

R^2 = H, Me, CO_2Me

R^3 = H_2, O

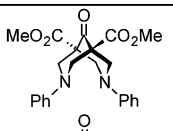
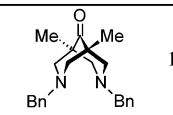
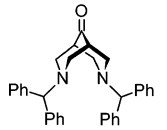
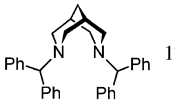
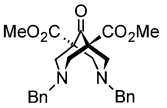
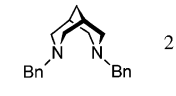
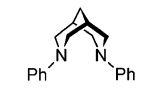
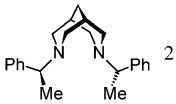
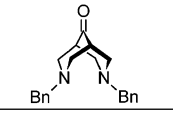
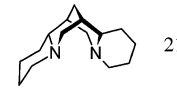
Basicity constants for a series of 3,7-diazabicyclo[3.3.1]nonane derivatives in acetonitrile with a variation over 13 orders of magnitude have been determined using a spectrophotometric titration technique. An excellent correlation between basicity and calculated proton affinities obtained at PCM-B3LYP/6-31+G-(d)//B3LYP/6-31G(d) level was found. The results are discussed in terms of substituent effects and compared to ^{15}N NMR chemical shifts.

Introduction

Acid−base interactions are a pivotal component in many chemical reactions both in organic chemistry and in biochemistry. Therefore, it is of general interest to be able to predict and modulate the strength of organic bases and to understand the different factors contributing to it. We here present a series of structurally similar and chemically stable organic bases, covering a wide range of pK_{BH^+} values (i.e., pK_a of the conjugated acids) of approximately 13 orders of magnitude (Table 1). The bases share the bispidine (3,7-diazabicyclo[3.3.1]nonane) skeleton, which is also found in the natural product sparteine. Bispidine as well as sparteine derivatives and isomers have been employed extensively as bases in synthesis[1] and as ligands for organometallic compounds.[2] Furthermore, they have interesting physiological properties as antiarrhythmic agents and as opioid receptor ligands.[3]

Basicities of organic compounds are also of interest regarding their complexation properties, since the correlation between metal ion complex stability and ligand basicity is well-established.[4] A linear relationship between the equilibrium constants for protonation and metal complexation can be expected within a series of structurally related ligands, i.e., log $K_{M/ML} = a \times pK_{BH^+} + b$.[4a] Acid−base properties are also one of the most important parameters of compounds with pharmaceutical interest, since protonation can modulate, for example, binding

TABLE 1. Observed pK_a Values for 3,7-Diazabicyclo[3.3.1]nonanes, Determined as pK_{BH^+} for the Conjugated Acid, Spectrophotometrically in AN Solution

Bispidine	Structure	pK_a	Bispidine	Structure	pK_a
1		8.13	**6**		17.48
2		13.48	**7**		17.79
3		13.81	**8**		21.25
4		13.97	**9**		21.38
5		16.93	**10**		21.66

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properties, lipophilicity, solubility, and transmission through membranes.[3c,5]

Basicity determination of organic compounds may be hampered by limited solubility, ionic or hydrogen-bond interactions, as well as by leveling effects of the solvent. Recently, acetonitrile (AN) has emerged as the solvent of choice for measurements in nonaqueous solvents.[6,7] A spectrophotometric titration method has been developed that allows the accurate pK_a determination over a large range of values.[7] Measurement in AN results in a self-consistent series of basicity values with little solvent effects. However, pK_a values obtained for AN solution (p$K_{a,AN}$) are different from those in other solvents, mainly because of different hydrogen-bonding properties.[8] As an example, p$K_{a,AN}$ values were ca. 7.5 units higher than the pK_a for aqueous solution and 6−10 units higher than the pK_a for DMSO solutions.[8b]

Since the basicity of organic nitrogen compounds is related (at least partially) to the availability of the nitrogen free electron pair for protonation, an alternative and convenient way to access the basicity might be measurement of ^{15}N NMR chemical shifts.[9] The p*H*-dependency of chemical shifts is a well-documented NMR phenomenon and has been used to determine pK_a values for a variety of compounds.[10]

Results and Discussion

In the present work, a UV−vis spectrophotometric titration technique for measurements of relative acidities (ΔpK_a) in acetonitrile was used.[7] A solution containing two bases, the base under investigation and a reference base, with known p$K_{a,AN}$ value, was titrated with a solution of methanesulfonic acid in acetonitrile. A UV−vis spectrum was recorded after each addition of the titrant. From the spectra, the relative basicity of the two bases could be calculated. The p$K_{a,AN}$ values were determined for the conjugate acid forms of several 3,7-diazabicyclo[3.3.1]nonanes and are summarized in Table 1.

The p$K_{a,AN}$ values for the bispidine derivatives **1**−**9** span a range of over 13 orders of magnitude. In contrast, previously potentiometrically measured pK_a values for DMSO solutions[2a] of **1** (4.4 vs 8.13, ΔpK_a = 3.73), **3** (5.3 vs 13.81, ΔpK_a = 8.51), and **6** (7.7 vs 17.48, ΔpK_a = 9.78) are considerably lower, in keeping with known literature trends.[8b] This applies also for a reported[11] value for (−)-sparteine **10** (17.50 vs 21.66, ΔpK_a = 4.16), determined potentiometrically for a solution in AN. These lower values might also be explained by the presence of moisture, which would generate a leveling effect.

A cursory overview of the relative basicities (p$K_{a,AN}$) shows the lowering effect of electron-withdrawing substituents on the nitrogen atoms. Replacement of Bn by Ph results in a decreased basicity, e.g., **3** vs **1**, ΔpK_a = −5.68; **8** vs **4**, ΔpK_a = −7.28. Addition of electron-withdrawing phenyl groups to a benzyl substituent decreases the basicity (**7** vs **8**, ΔpK_a = −3.46), whereas addition of methyl groups increases it (**8** vs **9**, ΔpK_a = 0.13). Interestingly, there is also a pronounced effect of more remote substituents. A carbonyl group in position 9 of the bispidine skeleton decreases the basicity: **2** vs **7**, ΔpK_a = −4.31; **5** vs **8**, ΔpK_a = −4.32. Carboxymethyl substituents in the 1- and 5-positions (bridgehead) also decrease the basicity: **3** vs **5**, ΔpK_a = −3.12. Furthermore, the effects appear to be additive: **3** vs **8**, ΔpK_a = −7.44 (≈−4.3−3.1); **1** vs **4**, ΔpK_a = −5.84 (lower than the expected value of −7.44 because the nitrogens are already electron-deficient). As expected, sparteine **10** has the highest basicity because it lacks any electron-withdrawing substituents.

The basicity is also affected by phenyl groups in the α-position on the carbon substituent of the nitrogen, in analogy to p$K_{a,AN}$ values measured for a series of primary amines: CH_3NH_2 (18.37), $PhCH_2NH_2$ (16.76), Ph_2CHNH_2 (14.91), and Ph_3CNH_2 (13.40).[12]

The effect of a carbonyl group in position 9 has been attributed to interactions between the nitrogen lone pairs and the π orbitals of the carbonyl group through σ bonds.[13] Furthermore, it has been shown that the reactivity of the carbonyl group is considerably increased upon nitrogen protonation[14] or complexation to metal ions.[2a]

Having established a relationship between the bispidine substitution pattern and basicity, it is desirable to find a model that can be used to predict this parameter quantitatively. Such a model would also be useful to identify further compounds with even higher basicity. As can be expected, the literature contains many theoretical studies on structure−basicity relationships of organic bases. Proton affinities can be calculated, including solvent effects. Several models for structure−basicity relationships have been proposed.[15]

To explore the possibility to rationalize the trend in measured pK_a values of the bases, we carried out quantum chemical calculations at the IEF-PCM/B3LYP/6-31+G(d)//B3LYP/6-31G(d) hybrid density functional theory (DFT) level.[16−18] In these

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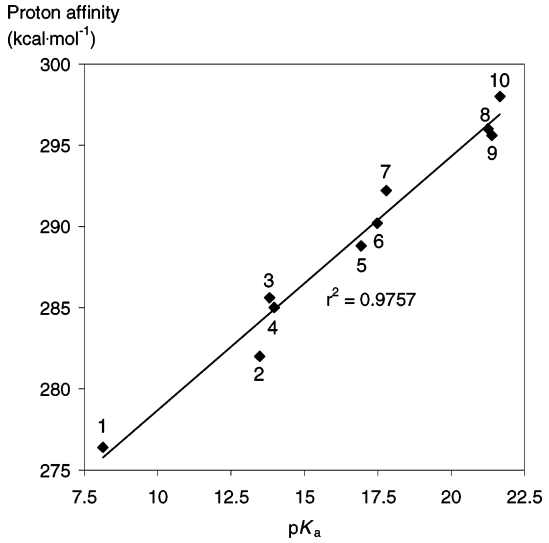

FIGURE 1. Correlation between measured p$K_{a,AN}$ values and calculated proton affinities (PA) obtained at the IEF-PCM/B3LYP/6-31+G(d)//B3LYP/6-31G(d) level using $\epsilon = \epsilon_{acetonitrile} = 36.64$. PA = 1.5728p$K_{a,AN}$ + 263.12, $r^2 = 0.9757$.

calculations, the polarized continuum model of Tomasi and coworkers (IEF-PCM) was used to simulate the nonspecific action of the surrounding solvent, with the dielectric constant set at 36.64, the value of the dielectric constant of acetonitrile. Results are summarized in Figure 1 and Table 2.

There is an excellent agreement between calculated proton affinities and observed basicities (Figure 1).

To find an explanation for the observed variation of basicity, several parameter correlations have been investigated. A linear correlation with $r^2 = 0.6315$ exists between the calculated N···N distance in the neutral species and the measured p$K_{a,AN}$ values (Figure 2). Among the investigated bispidines, those with a bridging carbonyl group have shorter N···N distances (2.829−2.958 Å) and lower p$K_{a,AN}$ (8.13−17.48) as compared to those with methylene bridges (N···N distances within the range 2.973−3.004 Å and pK_a within 13.97−21.66). Although the carbonyl group would be expected to flatten the six-membered ring, and thus move the two N atoms farther apart, the opposite seems to be the case.

The correlation between p$K_{a,AN}$ and N···N distance is only moderate ($r^2 = 0.67$), but increases to $r^2 = 0.9489$ when **1**, **2**, **4**, **7**, and **9** are excluded. These are the species with the bulkiest

TABLE 2. Selected Results from the Quantum Chemical Calculations for Compounds 1−10, Including Proton Affinities in AN

bispidine	p$K_{a,AN}$[a]	PA[b]	q(N)[c]	d(N···N)[d]	d(N···N$^+$)[e]	d(N−H)[f]
1	8.13	276.4	−0.506	2.829	2.668	1.809
2	13.48	282.0	−0.549	2.958	2.731	1.917
3	13.81	285.6	−0.542	2.884	2.715	1.935
4	13.97	285.0	−0.507	2.979	2.692	1.835
5	16.93	288.8	−0.552	2.937	2.709	1.897
6	17.48	290.2	−0.545	2.932	2.705	1.906
7	17.79	292.2	−0.555	2.978	2.761	1.977
8	21.25	296.0	−0.555	2.973	2.688	1.843
9	21.38	295.6	−0.559	2.979	2.743	1.925
10	21.66	298.0	−0.559	3.004	2.723	1.896

[a] Experimental values, this work. [b] Calculated proton affinities (kcal·mol^{-1}), at the IEF-PCM/B3LYP/6-31+G(d)//B3LYP/6-31G(d) level using $\epsilon = \epsilon_{acetonitrile} = 36.64$, given as energy differences between the protonated molecule and the free base. [c] Atomic charges at the N atoms calculated by natural population analysis (NPA) given in e. The average q(N) of the two N atoms in one molecule is tabulated. [d] N···N distance (Å) in free base. [e] N···N distance (Å) in protonated species. [f] N−H bond length (Å) in protonated species.

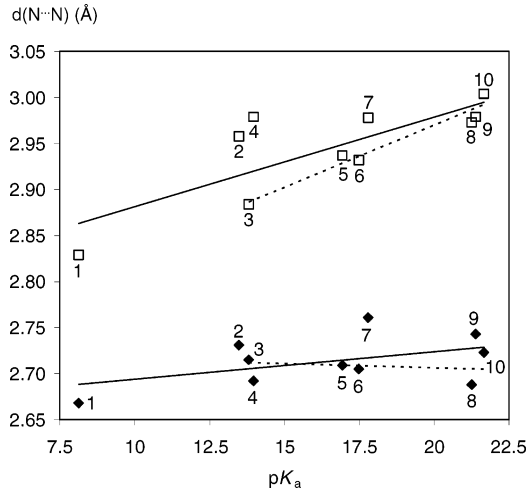

FIGURE 2. N···N distances at the B3LYP/6-31G(d) level plotted against measured pK_a values. (a) □, N···N distances in neutral species; −, all compounds included [d(N···N) = 0.0097pK_a + 2.784, r^2 = 0.6315]; - -, excluding compounds **1**, **2**, **4**, **7**, and **9** [d(N···N) = 0.0135pK_a + 2.6997, r^2 = 0.9489]. (b) ◆, N···N$^+$ distances in protonated species; −, all compounds included [d(N···N$^+$) = 0.003pK_a + 2.6642, r^2 = 0.2192]; - -, excluding compounds **1**, **2**, **4**, **7**, and **9** [d(N···N$^+$) = −0.0009pK_a + 2.7426, r^2 = 0.0519].

N-substituents. For the protonated species, this correlation is very poor, with $r^2 = 0.22$ (all included) and $r^2 = 0.05$ (**1**, **2**, **4**, **7**, and **9** excluded) (Figure 2).

A similar pattern is obtained when plotting the atomic charges at the N atoms of the neutral species against the experimental p$K_{a,AN}$ values (Figure 3). Again, correlation improves, from r^2 = 0.64 to $r^2 = 0.81$, when **1**, **2**, **4**, **7**, and **9** are excluded.

These findings indicate that the basicity is dependent on both electronic and steric factors. Initially, high electron density on the N atoms increases the p$K_{a,AN}$. The presence of a second nitrogen atom is responsible for much higher values than would be expected for corresponding monoamines, which is known as the chelate effect.[21] However, the presence of bulky substituents might disfavor the hydrogen-bond formation of N−H$^+$ with the second nitrogen atom or decrease the population of chair−chair conformers in which hydrogen bonding can occur

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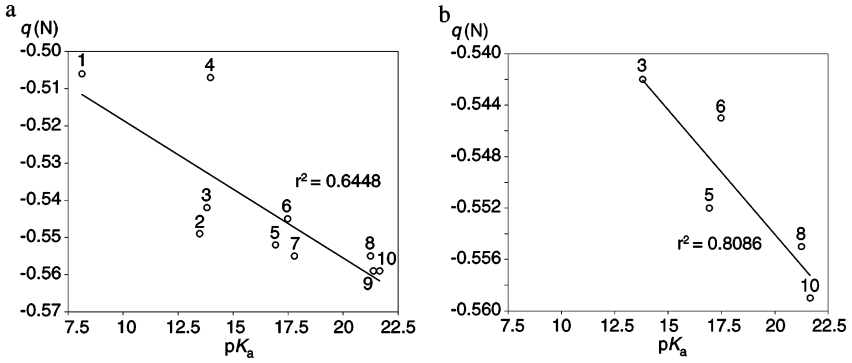

FIGURE 3. Atomic charges of the N atoms, q(N), in neutral species from natural population analysis at the IEF-PCM/B3LYP/6-31+G(d)//B3LYP/6-31G(d) level plotted against measured pK_a values. The q(N) plotted are averages of the charges of the two N atoms in a molecule. (a) All compounds, $q(N) = -0.0037pK_a - 0.482$, $r^2 = 0.645$. (b) **1**, **2**, **4**, **7**, and **9** excluded, $q(N) = -0.0019pK_a - 0.515$, $r^2 = 0.809$.

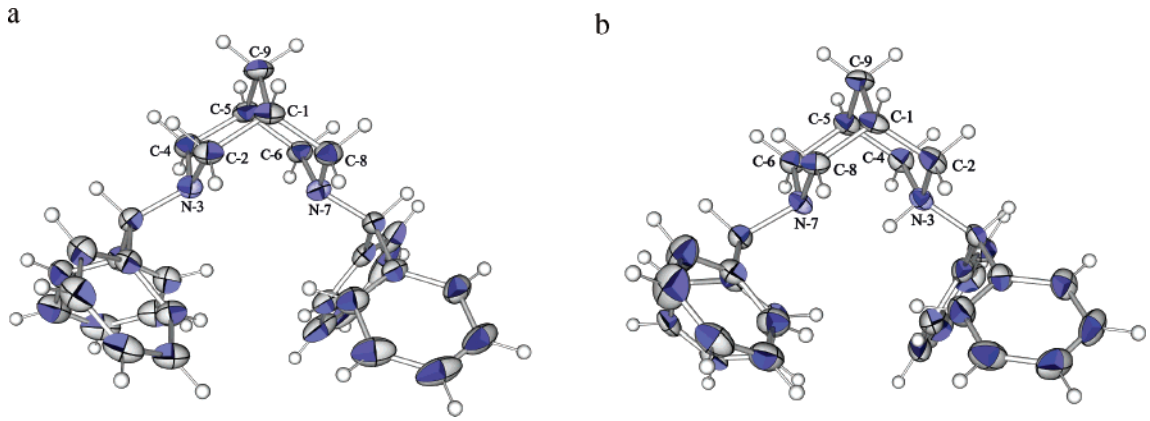

FIGURE 4. ORTEP view of (a) **7** and (b) $[\mathbf{7}\cdot H]^+\cdot CF_3SO_3^-$, with the counterion omitted for clarity.

without an extra entropy penalty. Protonation of chair−boat conformers might also involve solvation of the N−H$^+$ species, which would require desolvation prior to chelation.

Other parameters, such as hydrogen-bond length in the protonated species or the degree of pyramidalization of N, as measured by the sum of valence angles at N atoms ($\sum\alpha$(N)), show only poor correlation to the p$K_{a,AN}$ values.

The structures of bispidine derivative **7** and its monoprotonated[2d] form $[\mathbf{7}\cdot H]^+$ were investigated by X-ray crystallography (Figure 4).[22] Selected interatomic distances are summarized in Table 3.

Upon protonation of **7**, the N-3···N-7 distance decreases from 2.854 Å (**7**) to 2.727 Å ($[\mathbf{7}\cdot H]^+$), indicating the presence of a hydrogen bond (N$^+$−H···N). It is interesting to note that for compound **4**, an N-3···N-7 distance of 3.072 Å has been reported.[23] This fits well to the description above of the phenyl group as a bulky substituent. Furthermore, protonation of **7** introduces a substantial asymmetry into the molecule, which is most pronounced for the C−N bond lengths. For example, N-3−CHPh$_2$ = 1.523 Å (protonated N) as compared to N-7−CHPh$_2$ = 1.494 Å (nonprotonated N). An increase in bond length is observed for all N−C bonds, corresponding to a weakening (Figure 5). Notably, this applies also for the C-1−C-9 and C-5−C-9 bonds, which is in line with the observed effect of protonation or metal ion complexation on the carbonyl group reactivity (vide infra).

Protonation experiments in solution followed by ^{1}H NMR, using methanesulfonic acid, were in agreement with the assumptions made in the computations, i.e., protonation of one nitrogen

TABLE 3. Interatomic Distances Measured by X-ray Crystallography of the Bispidine 7 and the Protonated Bispidine $[\mathbf{7}\cdot H]^+\cdot CF_3SO_3^-$

atoms	d(**7**)[a]	$d([\mathbf{7}\cdot H]^+)$[b]	Δd[c]
C-1−C-2	1.539	1.522	−0.017
C-2−N-3	1.475	1.514	+0.039
N-3−C-4	1.477	1.524	+0.047
C-4−C-5	1.531	1.519	−0.012
C-5−C-6	1.537	1.531	−0.006
C-6−N-7	1.475	1.490	+0.015
N-7−C-8	1.475	1.500	+0.025
C-8−C-1	1.536	1.527	−0.009
C-1−C-9	1.529	1.535	+0.006
C-5−C-9	1.526	1.528	+0.002
N-3···N-7	2.854	2.727	−0.127
N-3−CHPh$_2$	1.473	1.523	+0.050
N-7−CHPh$_2$	1.470	1.494	+0.024

[a] Interatomic distances in **7** (Å). [b] Interatomic distances in $[\mathbf{7}\cdot H]^+$ (Å). [c] Difference = $d([\mathbf{7}\cdot H]^+) - d$(**7**) (Å).

(19) (a) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *106*, 5151. (b) Cancès, M. T.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032. (c) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253.

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(21) (a) Alder, R. W. *Chem. Rev.* **1989**, *89*, 1215. (b) Meot-Ner, M.; Hamlet, P.; Hunter, E. P.; Field, F. H. *J. Am. Chem. Soc.* **1980**, *102*, 6393.

(22) CCDC-600810 and CCDC-264284 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(23) Levina, O. I.; Potekhin, K. A.; Kurkutova, E. N.; Struchkov, Y. T.; Palyulin, V. A.; Zefirov, N. S. *Dokl. Akad. Nauk SSSR* **1984**, *277*, 367.

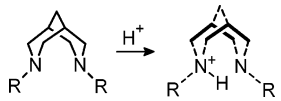
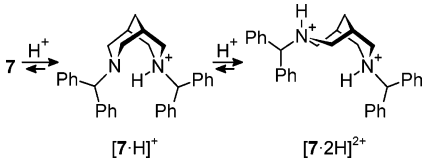


FIGURE 5. Changes in bond lengths of bispidine **7** upon protonation. R = Ph_2CH; --- = longer bond; − = shorter bond.

SCHEME 1. Protonation of 7 with $MeSO_3H$ in $CDCl_3$



atom results in the formation of an intramolecular hydrogen bond to the other nitrogen atom (Scheme 1). On the NMR time scale (at room temperature), the symmetry of the diamine ligand is preserved for this first protonation step. For the free base in solution, the symmetry is C_{2v} (as opposed to C_2 in the crystal). The positive charge is spread equally over the two N atoms, resulting in an adamantane-like structure with the proton positioned at equal distance from both nitrogen atoms, as proposed for monocationic 3,7-diazabicyclo[3.3.1]nonanes.[24] This apparent C_{2v} symmetry is most likely the result of rapid proton hopping between the two nitrogen atoms.[25,26] Cooling of the solution (to −70 °C) did not show any splitting or broadening of the signals. If an excess of acid is added, the second nitrogen atom is protonated. This releases the intramolecular hydrogen bond, and a nonsymmetric, diprotonated bispidine with chair−boat conformation is formed. The structure was confirmed by NOEs. This constitutes one example of the few documented, double-protonated bispidine derivatives. One of these is the commercial antiarrhythmic agent tedisamil dihydrochloride.[27]

The structural features of the bispidines and their protonated congeners were characterized using routine NMR techniques, including full assignment of all ^1H NMR and ^{13}C NMR signals, as has been described previously.[28] Ring conformations in bispidines were derived from NOEs and homonuclear coupling constants and from $^3J_{CH}$ as indicated in HMBC spectra. An example of conformationally significant NOEs is shown for the doubly protonated bispidine derivative [**7**·2H]$^{2+}$·2($MeSO_3^-$) in Figure 6.

Bispidinones behaved differently than bispidines upon protonation under similar conditions. For example, the bispidinone **2** formed a mixture of two monoprotonated species. The ratio between these species depended on the amount of moisture in the sample. Upon closer scrutiny, the mixture was shown to contain the salt [**2**·H]$^+$ $MeSO_3^-$ and the salt of the corresponding 9,9-diol (Scheme 2).

The formation of such diols is likely to proceed via protonation of the carbonyl oxygen atom, followed by a nucleophilic addition of water. However, this reaction occurs more readily in the bispidinones than in comparable ketones, indicating that initial protonation of the nitrogen atom has an activating effect.

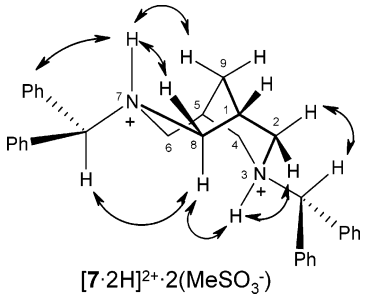


FIGURE 6. Stereochemically significant NOEs (arrows) used for the assignment of bispidine ring conformations for [**7**·2H]$^{2+}$·2($MeSO_3^-$).

SCHEME 2. Protonation of Bispidinone 2 with $MeSO_3H$ in $CDCl_3$

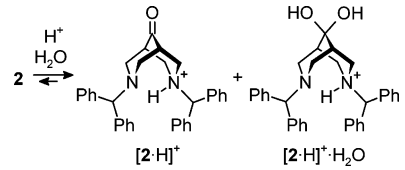
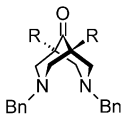


TABLE 4. Selected Taft's σ_I Values[29a,29b] and the Measured p$K_{a,AN}$ Values



Compound	R	σ_I	p$K_{a,AN}$
3	CO_2Me	0.31	13.81
5	H	0.00	16.93
6	Me	-0.05	17.48

This effect would involve an increase of the electron deficit at the carbonyl carbon (via an inductive effect), as has been claimed by others.[14]

To further rationalize the observed basicities, we applied the Taft model. This divides substituent effects on basicity into different contributions, i.e., field effects, polarizability effects, resonance effects, and steric effects.[6b,15a,15b,29,30] In the Taft equation (eq 1),

$$pK_a = pK_a^\circ + \rho\sigma_I + \delta E_s \qquad (1)$$

the two last terms express the independent contributions from polar (inductive) and steric effects, respectively.

Parameter sets for the bispidine substituents (in the case of 1,5-disubstituted-3,7-dibenzylbispidinones **3**, **5** and **6**) are collected in Table 4. The σ_I values measure the polar effects of substituents. A large positive σ_I value implies high electron-withdrawing power by inductive and/or resonance effects, relative to H, whereas a large negative σ_I value implies high electron-releasing power relative to H. The parameter σ_I is supposedly free of steric influences and dependent on only electronic factors. This allows an estimation of basicity for the given set of substituents.

The correlation between p$K_{a,AN}$ and σ_I (Figure 7) appears to be rather good for this small selection of compounds (1,5-disubstituted-3,7-dibenzylbispidinones). For the other compounds, a good correlation could not be found. Most likely,

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(30) MacPhee, J. A.; Panaye, A.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 3553.

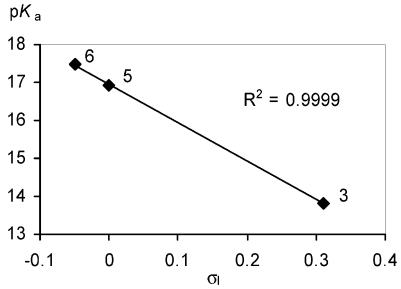


FIGURE 7. Correlation between Taft parameter σ_I and $pK_{a,AN}$ for 1,5-disubstituted-3,7-dibenzylbispidinones. $pK_a = 16.95 - 10.15 \cdot \times \sigma_I$, $r^2 = 0.9999$.

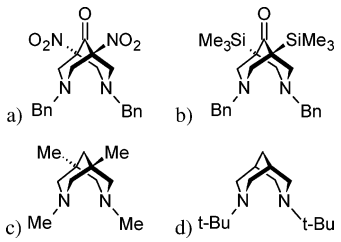


FIGURE 8. Suggestions for new bispidines with different basicity. Using the Taft equation: (a) $\sigma_I(NO_2) = 0.76$, $pK_a = 16.95 - 10.15 \times 0.76 = 9.24$; (b) $\sigma_I(SiMe_3) = -0.13$, $pK_a = 16.95 - 10.15 \cdot \times -0.13 = 18.27$. Using computations and proton affinity−pK_a correlation: (c) PA = 296.67 kcal·mol^{-1}, $pK_a = 21.33$; (d) PA = 299.67 kcal·mol^{-1}, $pK_a = 23.19$.

they would require the use of steric parameters. However, our tests with such parameters[30] did not improve the fitting. One reason could be that the literature parameters are not well-suited for the property under consideration or that conformational effects of the bispidine skeleton are involved.

Using the results from the correlations between structure and basicity, we are now able to rationally design new bispidines with a range of pK_a values, in particular bispidines with pK_a's outside the present range. In particular, it should be possible to propose further derivatives of these bispidinones with higher basicity by using 1,5-substituents with lower σ_I values. A few examples are shown in Figure 8.

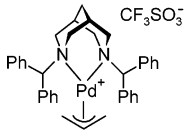
^{15}N NMR Chemical Shifts. ^{15}N NMR chemical shifts, with a range of >1000 ppm, provide valuable information about the shielding of nitrogen atoms, giving access to structural information as well as molecular interactions. Lower chemical shift indicates higher electron density around the nucleus, which in turn should be an indicator of its electron donor capability and, hence, its basicity. This has also been exploited for a variety of simple organic molecules. Thus, the relationships between ^{15}N NMR chemical shifts and the pK_a values of 2,4-dinitroanilinium salts were found to be linear, indicating that these properties are influenced by the same factors.[25] Correlation between basicity and calculated ^{15}N NMR chemical shifts has been established for iminoamines and other compounds.[31] However, these usually are calculations for isolated molecules in the gas phase. Observed chemical shifts for the bispidine derivatives and some of their salts and complexes are summarized in Table 5.

TABLE 5. ^{15}N Chemical Shifts[a] of Compounds 1−12, Including Protonated Species for 2, 6, and 7

bispidine	$\delta(^{15}N)$	bispidine	$\delta(^{15}N)$
1	−322.5	**7**	−326.3
2	−329.9	[**7**·H]$^+$ $MeSO_3^-$	−314.4
[**2**·H]$^+$ $MeSO_3^-$	−316.5	[**7**·2H]$^{2+}$ $2MeSO_3^-$	−322.5, −325.4
3	−337.0	**8**	−335.9
4	−315.5	**9**	−328.6
5	−336.9	**10**	−325.4, −326.6
6	−333.5	[**2**·H]$^+$ $MeSO_3^-$·H_2O	−315.0
[**6**·H]$^+$ $MeSO_3^-$	−323.0	**11**[32,b]	−341.2
		12[33]	−340.0

[a] Referenced to 0.37 M CH_3NO_2 ($\delta = 0.0$ ppm) in $CDCl_3$ and measured for $CDCl_3$ solutions. [b] Solution in acetone-d_6 at −70 °C.

The ^{15}N chemical shift values do not show any general correlation with the calculated q(N) charges, indicating that several counteracting factors might be involved. The higher chemical shifts for compounds **1** and **4** are likely due to the combined deshielding effect of the phenyl substituent anisotropy and lower electron density. For the remaining compounds, the correlation is the reverse of what would be expected. Protonation has the expected effect of increasing the chemical shift (i.e., deshielding), but double protonation ([**7**·2H]$^{2+}$) decreases the chemical shift (which is still higher than in the free base), indicating that also further conformational effects are involved (vide infra). This is also indicated by the different chemical shifts for the two sparteine nitrogens and for the nitrogens in the dication [**7**·2H]$^{2+}$. On a qualitative level, substitution of the nitrogen atoms with groups having stronger electron-withdrawing effect results in deshielding [e.g. **8** (−335.9 ppm) → **7** (−326.3 ppm), **5** (−336.9 ppm) → **2** (−329.9 ppm)]. A carbonyl group (C-9) results in shielding, e.g., **8** (−335.9 ppm) → **5** (−336.9 ppm); **7** (−326.3 ppm) → **2** (−329.9 ppm), **4** (−315.5) → **1** (−322.5). This is the opposite of what should result from entirely electronic effects and might indicate some conformation-related anisotropy effects or a change in solvation. On the other hand, the thiolane derivative **12** has a higher shielding than the



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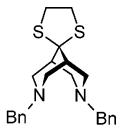

12

related carbonyl derivative **5**. To rationalize the effect of metal coordination, the ligand trans to the nitrogen atoms must be considered, i.e., its trans influence: In the series [**7**·H]$^+$ (−314.4 ppm) → **7** (−326.3 ppm) → **11** (−341.2 ppm), the shielding effect increases, the protonated ligand being most deshielded. Obviously, the π-allyl ligand transfers electrons toward the nitrogens. In the series [**7**·2H]$^{2+}$ (−322.5, −325.4) → [**7**·H]$^+$ (−314.4 ppm) → **7** (−326.3 ppm), the double protonated species does not fit in, possibly indicating effects of its different conformation (chair−boat instead of chair−chair). In summary, the ^{15}N chemical shifts can be rationalized well on a qualitative level, with the exception of the carbonyl compounds. However, correlation with the basicity of the bispidine derivatives is poor. It should also be noted that the variation of our experimental chemical shifts is of the same magnitude ($\Delta\delta \leq 25$) as typical error margins of values derived from quantum chemical ^{15}N NMR chemical shift calculations. Furthermore, reported excellent correlations between ^{15}N chemical shifts and basicities or

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proton affinities often refer to calculated, not observed, chemical shifts, obviously avoiding complications due to conformational and, in particular, solvation effects.

Conclusions

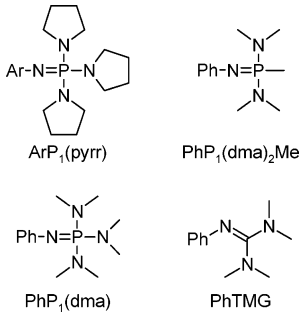
We have shown that the influence of substituent effects on the basicity of bispidine derivatives covering a wide range of values can be predicted by computations with high accuracy. Substituent effects can also be rationalized considering electronic effects. A correlation between ^{15}N chemical shifts and basicity could, however, not be proven, indicating that this parameter is influenced by further effects that are not easily predicted. Therefore, pK_a values should provide a better indication of ligand performance.

Experimental Section

Quantum Chemical Calculations. The quantum chemical calculations were carried out with the Gaussian03 program package using the B3LYP hybrid density functional theory (DFT) method.[16,17] Geometries were optimized using the 6-31G(d) valence double-ζ basis set of Pople and Hariharan,[18] with subsequent single-point energy calculations using the 6-31+G(d) basis set with diffuse functions on all atoms except hydrogen. Frequency calculations were performed on symmetric structures to ascertain that these structures correspond to minima on the potential energy surfaces. The nonspecific action of a surrounding solvent was simulated using the polarizable continuum model in the integral-equation formalism (IEF-PCM) of Tomasi and co-workers.[19] Atomic charges were calculated with natural population analysis (NPA) as implemented by Weinhold.[20]

General Experimental Details. Melting points were determined in open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 400 or 500 MHz (^1H) and 100.6 or 125.7 MHz (^{13}C). Chemical shifts (^1H and ^{13}C) were indirectly referenced to TMS via the residual solvent signal ($CDCl_3$, 7.26 and 77.0). ^{15}N NMR chemical shifts were obtained from ^1H detected $^1H-^{15}N$ gHMBC[34] spectra at 500 MHz. The ^{15}N chemical shifts were referenced externally to the signal of CH_3NO_2 ($\delta = 0.0$ ppm, 0.37 M solution of CH_3NO_2[35] in $CDCl_3$). NMR signals were assigned from gHSQC,[36] gHMBC,[34] gNOESY,[37] and TOCSY[38] spectra. Reactions were monitored by TLC on silica gel F_{254} or neutral alumina F_{254}, and compound visualization was achieved with UV-light (254 nm) or by developing the plates with a 5% phosphomolybdic acid solution in ethanol, followed by heating. Flash column chromatography was performed on silica gel 60 (35−70 μm) or on neutral activated γ-Al_2O_3 (60 mesh). All commercially available chemicals were of reagent grade and used without further purification unless otherwise noted. 3,7-Diphenyl-1,5-dicarbomethoxy-3,7-diazabicyclo[3.3.1]nonan-9-one **1**,[2a] 3,7-dibenzyl-1,5-dicarbomethoxy-3,7-diazabicyclo[3.3.1]nonan-9-one **3**,[2a] 3,7-diphenyl-3,7-diazabicyclo[3.3.1]nonane **4**,[39] 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]-nonan-9-one **5**,[1a] 3,7-dibenzyl-1,5-dimethyl-3,7-diazabicyclo[3.3.1]-nonan-9-one **6**,[2a] and (*S*,*S*)-3,7-bis(1′-phenylethyl)-3,7-diazabicyclo-[3.3.1]nonane **9**[2c] were prepared according to literature procedures. The crystallographic analysis procedure is described in the Supporting Information.

CHART 1. Selected Structures of the Reference Compounds



Chemicals for pK_a Determination. The synthesis and purification of the reference compounds (Chart 1) are described elsewhere.[40−44] Acetonitrile [>99.9%, super purity solvent (far UV), water content <0.005%] was the same as used in previous works[40,41] and was used without further purification. The water content of pure solvent was determined by coulometric Karl Fischer titration to be about 0.004%. Solutions of methanesulfonic acid ($MeSO_3H$, >99%) and trifluoromethanesulfonic acid (TfOH, 99+%) were used as acidic titrants. A solution of phosphazene base *t*-BuP_1(pyrr) (≥98%) was used as basic titrant.

3-(*tert*-Butyloxycarbonyl)-7-(1,1-diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (13). A suspension of coarsely grained paraformaldehyde (1.00 g, 33.3 mmol) in methanol (50 mL) was slowly added to a refluxing solution of *N*-(*tert*-butyloxycarbonyl)-piperidin-4-one (3.00 g, 15.1 mmol), benzhydrylamine (2.98 g, 16.3 mmol), and acetic acid (0.92 g) in methanol (80 mL). During 1 h another portion of paraformaldehyde (1.00 g, 33.3 mmol) was added and the mixture was refluxed overnight. Water (500 mL) and 1 M KOH solution (30 mL) were added, and the aqueous phase was extracted with diethyl ether and CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and filtered, and the solvent was evaporated. The yellow foamy residue was purified by flash chromatography on silica gel (pentane/CH_2Cl_2/EtOAc 10:3:2) to yield an amorphous solid (3.78 g, 9.30 mmol, 62% yield). R_f = 0.40 (pentane/CH_2Cl_2/EtOAc 10:3:2). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.49 (m, 4H, Ph), 7.29 (m, 4H, Ph), 7.19 (m, 2H, *p*-Ph), 4.64 (dm, J = 13.3 Hz, 1H, C*H*-N−CO), 4.47 (dm, J = 13.3 Hz, 1H, C*H*-N−CO), 4.06 (s, 1H, Ph_2CH), 3.42 (dm, J = 13.3 Hz, 1H, C*H*NCO), 3.32 (dm, J = 13.3 Hz, 1H, C*H*NCO), 3.27 (m, 2H, 6,8-C*H*), 2.52 (dm, J = 11.5 Hz, 2H, 6,8-C*H*), 2.39 (m, 1H, 1-C*H*), 2.33 (m, 1H, 5-C*H*), 1.64 (s, 9H, CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 214.0 (*C*-9), 154.5 (N−*C*═O), 142.6 (ipso-*C*), 142.5 (ipso-*C*), 128.8 (Ph), 128.6 (Ph), 127.6 (Ph), 127.4 (Ph), 127.2 (Ph), 80.3 (CMe_3), 76.0 (Ph_2-*C*H), 58.4 (CH_2-6,8), 50.2 (CH_2-2 or CH_2-4), 49.8 (CH_2-4 or CH_2-2), 47.4 (*C*H-1), 47.3 (*C*H-5), 28.6 (CH_3).

3-(1,1-Diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (14). A suspension of **13** (4.06 g, 9.98 mmol) and anhydrous $ZnBr_2$[45] (4.50 g, 20.0 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 13 h. The mixture was poured into dilute aqueous NaOH solution, and the aqueous phase was extracted with CH_2Cl_2. The organic phase was concentrated to yield a yellowish amorphous solid (2.58 g, 8.43 mmol, 84% yield). The product was

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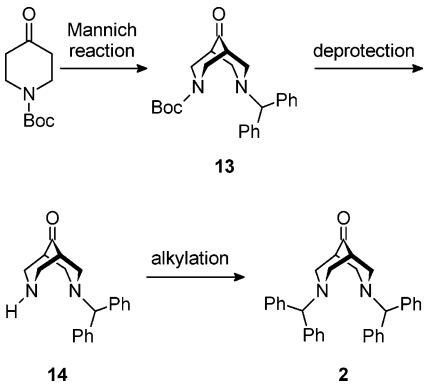
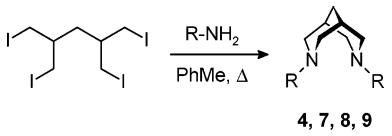
SCHEME 3. Synthesis of Compound 2



SCHEME 4. General Method for the Syntheses of Compounds 4, 7, 8, and 9



found to be unstable on silica and neutral alumina; therefore, it was used without further purifications directly in the next step. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (m, 4H, 2′,6′-C*H*), 7.31 (m, 4H, 3′,5′-C*H*), 7.21 (m, 2H, 4′-C*H*), 4.01 (s, 1H, Ph_2C*H*), 3.56 (dm, J = 13.9 Hz, 2H), 3.34 (m, 2H), 3.19 (dm, J = 13.9 Hz, 2H), 2.56 (m, 2H), 2.31 (m, 2H, 1,5-C*H*).

3,7-Bis(1,1-diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (2) (Scheme 3**).** To a mixture of **14** (2.00 g, 6.53 mmol), benzhydryl bromide (1.86 g, 7.53 mmol), K_2CO_3 (9.0 g, 65.1 mmol), KOH (1.83 g, 32.7 mmol), and Bu_4NBr (0.40 g, 1.24 mmol) were added CH_2Cl_2 (100 mL) and water (40 mL). After stirring at room temperature for 45 h, the mixture was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phases were dried over Na_2SO_4, filtrated, and concentrated to yield 4.2 g of yellow oil. Purification with flash chromatography on silica gel (pentane/CH_2Cl_2/EtOAc/TEA 100:20:7:6) and recrystallization from acetone gave 2.99 g of colorless crystals (6.33 mmol, 97% yield). Mp: 187−189 °C. R_f = 0.65 (pentane/CH_2Cl_2/EtOAc/TEA 100:20:7:6). IR (neat): 3026, 2951, 2793, 1734 (C=O), 1492, 1450, 985, 757, 709 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (m, 8H, 2′,6′-C*H*), 7.31 (m, 8H, 3′,5′-C*H*), 7.22 (m, 4H, 4′-C*H*), 4.42 (s, 2H, Ph_2C*H*), 3.10 (dm, J = 11.3 Hz, 4H, 2,4,6,8-CH_2-eq), 2.73 (dm, J = 11.3 Hz, 4H, 2,4,6,8-CH_2-ax), 2.52 (m, 2H, 1,5-C*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 215.0 (*C*=O), 142.0 (*C*-1′), 128.5 (Ph), 127.9 (Ph), 127.1 (*C*H-4′), 74.7 (Ph_2*C*H), 56.6 (*C*H_2-2,4,6,8), 47.0 (*C*H-1,5). ^{15}N NMR (50.7 MHz, $CDCl_3$): δ = −329.9 (*N*-3,7). Anal. Calcd for $C_{33}H_{32}N_2O$: C, 83.86; H, 6.82; N, 5.93. Found: C, 84.03; H, 6.81; N, 5.81.

3,7-Bis(1,1-diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonane (7).[46] This compound was prepared by an alternative (Scheme 4) to the literature procedure. 1,5-Diiodo-2,4-bis(iodomethyl)pentane[39] (1.00 g, 1.66 mmol) and benzhydrylamine (2.00 g, 10.9 mmol, 6.6 equiv) were weighed into a glass ampule, dry toluene (6 mL) was added, and the ampule was sealed. After heating at 125 °C for 100 h and cooling to room temperature, the ampule was opened, and the formed crystals were separated, extracted with 10% NaOH solution (15 mL), and re-extracted with CH_2Cl_2 (4 × 15 mL). The combined organic phases were extracted with brine (4 mL) and dried over anhydrous Na_2SO_4. The resulting oil was treated with a mixture of pentane and ether and left in a refrigerator to crystallize. Crystals were separated, and the mother liquid was concentrated and purified by column chromatography using pentane/ether/TEA (50:7:3) as the solvent. Crystallization from acetone afforded the title product (**7**) as white crystals (345 mg, 0.75 mmol, 45% yield). A byproduct was also isolated; see Supporting Information (compound **15**). Mp: 174−175 °C (lit.[46a] mp: 170 °C). R_f = 0.64 (pentane/ether/TEA 50:5:3). IR (neat): 3021, 2890, 2748, 1597, 1491, 1267, 995, 748, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.70 (m, 8H, 2′,6′-C*H*); 7.40 (m, 8H, 3′,5′-C*H*), 7.27 (m, 4H, 4′-C*H*), 4.19 (s, 2H, Ph_2−C*H*), 2.99 (dm, J = 11.1 Hz, 4H, 2,4,6,8-CH_2-eq), 2.20 (dm, J = 11.1 Hz, 4H, 2,4,6,8-CH_2-ax), 1.84 (m, 2H, 1,5-C*H*), 1.55 (m, 2H, 9-CH_2). ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ: 143.6 (*C*-1′), 128.34 (Ph), 128.28 (Ph), 126.6 (*C*H-4′), 78.0 (Ph_2-*C*H), 57.0 (*C*H_2-2,4,6,8), 32.6 (*C*H_2-9), 30.7 (*C*H-1,5). ^{15}N NMR ($CDCl_3$, 50.7 MHz) δ: −326.3 (*N*-3,7).

3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane (8).[47] 1,5-Diiodo-2,4-bis(iodomethyl)pentane[39] (1.00 g, 1.66 mmol) and benzylamine (1.06 g, 9.89 mmol, 6 equiv) were dissolved in toluene (6 mL) and sealed into a glass ampule. After heating at 125 °C for 3 days, the ampule was cooled to room temperature, and the contents were extracted with 10% NaOH solution, followed by re-extraction of the aqueous phase with toluene, evaporation of the organic phase, and drying under vacuum. Flash chromatography was carried out by using silica gel and pentane/ether/TEA (7:0.5:0.6) as the mobile phase, resulting in isolation of the title product as a transparent oil (0.23 g, 0.75 mmol, 45% yield). A byproduct was also isolated; see Supporting Information (compound **18**). R_f = 0.50 (pentane/ether/TEA 7:0.5:0.6). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.47 (m, 4H, 2′,6′-C*H*), 7.34 (m, 4H, 3′,5′-C*H*), 7.27 (m, 2H, 4′-C*H*), 3.50 (Ph-CH_2), 2.84 (dm, J = 11.0 Hz, 4H, 2,4,6,8-CH_2-eq), 2.36 (dm, J = 11.0 Hz, 4H, 2,4,6,8-CH_2-ax), 1.91 (m, 2H, 1,5-C*H*), 1.58 (m, 2H, 9-CH_2). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 139.8 (*C*-1′), 128.8 (Ph), 128.0 (Ph), 126.5 (*C*H-4′), 63.4 (Ph-*C*H_2), 57.9 (*C*H_2-2,4,6,8), 30.9 (*C*H_2-9), 29.9 (*C*H-1,5). ^{15}N NMR ($CDCl_3$, 50.7 MHz): δ = −335.9 (*N*-3,7).

General Procedure for NMR Titration Experiments. Bispidine derivative was dissolved in $CDCl_3$ (0.7 mL) in an NMR tube. A solution of $MeSO_3H$ in $CDCl_3$ (ca. 0.5 M) was prepared immediately prior to use. After recording the spectrum of the free bispidine derivative solution, aliquots of the acid solution were added and the ^{1}H NMR spectra recorded after each addition. After the disappearance of the signals corresponding to the free bispidine derivative, other NMR spectra (^{13}C, NOESY, HMBC, etc.) were recorded in order to assign the structures of the formed protonated species.

(3-*endo*,7-*exo*)-3,7-Bis(1,1-diphenylmethyl)-3,7-diazoniabicyclo-[3.3.1]nonane dimethane-sulfonate ([7·2H]$^{2+}$·2MeSO$_3^-$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.93 (bs, 1H, chair-side N*H*), 7.81 (bs, 1H, boat-side N*H*), 7.70−7.80 (several multiplets), 7.33−7.49 (several multiplets), 5.95 (d, J = 9.0 Hz, 1H, boat-side Ph_2C*H*), 5.41 (d, J = 8.1 Hz, 1H, chair-side Ph_2C*H*), 3.61 (m, 2H, boat-side CH_2-eq), 3.53 (m, 2H, boat-side CH_2-ax), 3.37 (m, 2H, chair-side CH_2-eq), 3.22 (m, 2H, chair-side CH_2-ax), 3.03 (s, CH_3), 2.74 (m, 2H, 1,5-C*H*), 2.56 (m, 1H, boat-side 9-C*H*), 1.99 (m, 1H, chair-side 9-C*H*). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 133.6, 133.0, 130.0, 129.9, 129.7, 129.1, 128.8, 128.5, 80.2 (chair-side Ph_2*C*H), 75.9 (boat-side Ph_2*C*H), 56.9 (chair-side *C*H_2), 51.5 (boat-side *C*H_2), 39.5 (*C*H_3), 24.5 (*C*H-1,5), 20.6 (*C*H_2-9).

pK_a Determination. The spectrophotometric titration method used in this work is the same as that described earlier,[7,40,42] i.e., simultaneous titration of two free bases, one bispidine derivative, and a reference base of comparable basicity. After each addition of acidic titrant the UV−vis spectrum was recorded. Also, both bases were titrated separately. A glovebox was used to ensure the absence of humidity and oxygen. A UV−vis spectrophotometer

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TABLE 6. Results of UV−Vis Spectrophotometric Titration Experiments in AN Solution and Assigned p$K_{a,AN}$ Values for the Conjugate Acid Forms of the Compounds 1−10

	reference base		concn,[b] 10^5 M						
bispidine	identity	pK_a[a]	bispidine	reference base	acid[c] used	calcn method[d]	ΔpK_a[e]	*s*	assigned pK_a value
1	3-NO_2-aniline	7.68	1.59	4.74	T	S	0.44	0.05	8.13
	3-NO_2-4-F-aniline	7.67	2.56	5.67	T	S	0.42	0.04	
	2,6-$(MeO)_2$-pyridine	7.64	2.49	7.11	T	S	0.48	0.07	
	2,4-F_2-aniline	8.39	2.58	8.33	T	S	−0.23	0.03	
	2-Cl-pyridine	6.79	3.29	13.25	T	S	1.38	0.05	
2	2,6-Cl_2-4-NO_2-C_6H_2-P_1(pyrr)	14.43	1.73	3.67	M	NV/S	−0.95	0.1	13.48
	2,6-$(NO_2)_2$-C_6H_3-P_1(pyrr)	14.12	1.50	5.22	M	NV/S	0.65	0.05	
3	2,4-$(NO_2)_2$-C_6H_3-P_1(pyrr)	14.88	3.57	3.19	M	NV/S	−0.95	0.1	13.81
	2,6-$(NO_2)_2$-C_6H_3-P_1(pyrr)	14.12	2.78	7.53	M	NV	−0.35	0.05	
	2,6-Cl_2-4-NO_2-C_6H_2-P_1(pyrr)	14.43	2.74	4.03	M	NV	−0.62	0.05	
	3-NH_2-pyridine	14.17	1.67	6.63	M	NV/S	−0.44	0.1	
4	2,4-$(NO_2)_2$-C_6H_3-P_1(pyrr)	14.88	2.31	3.07	M	S	−0.90	0.03	13.97
	2,6-$(NO_2)_2$-C_6H_3-P_1(pyrr)	14.12	1.91	2.91	M	S	−0.17	0.01	
	2,6-Cl_2-4-NO_2-C_6H_2-P_1(pyrr)	14.43	2.50	3.68	M	S	−0.47	0.01	
5	2-NO_2-4-CF_3-C_6H_3-P_1(pyrr)	16.54	2.45	1.78	M	NV	0.39	0.05	16.93
	2-NO_2-5-Cl-C_6H_3-P_1(pyrr)	17.27	3.00	2.08	M	NV	−0.34	0.05	
	2-NO_2-4-Cl-C_6H_3-P_1(pyrr)	17.68	2.66	2.83	M	NV	−0.76	0.05	
6	2-NO_2-4-CF_3-C_6H_3-P_1(pyrr)	16.53	1.98	3.61	M	NV	0.96	0.05	17.48
	2-NO_2-5-Cl-C_6H_3-P_1(pyrr)	17.27	4.16	1.85	M	NV/S	0.19	0.07	
	4-NMe_2-pyridine	17.95	1.43	4.50	M	NV/S	−0.47	0.1	
	4-NMe_2-pyridine	17.95	2.67	5.02	T	NV/S	−0.46	0.1	
	2-NO_2-4-Cl-C_6H_3-P_1(pyrr)	17.68	1.88	3.87	M	NV/S	−0.19	0.1	
7	2,5-Cl_2-C_6H_3-P_1(pyrr)	18.52	1.13	1.86	M	S	−0.70	0.04	17.79
	4-pyrrolidinylpyridine	18.33	1.04	3.23	M	NV/S	−0.59	0.1	
	4-NMe_2-pyridine	17.95	1.42	3.32	M	NV	−0.17	0.06	
	4-NO_2-C_6H_4-P_1(pyrr)	18.51	1.12	2.85	M	S	−0.70	0.06	
8	PhP_1(dma)	21.25	1.24	2.49	M	NV	0.03	0.06	21.25
	4-Br-C_6H_4-P_1(pyrr)	21.19	1.84	1.14	M	NV/S	0.08	0.06	
	PhP_1(dma)Me	21.03	1.14	2.04	M	NV/S	0.23	0.1	
	4-CF_3-C_6H_4-P_1(pyrr)	20.16	1.49	1.61	M	NV/S	1.01	0.1	
	PhTMG	20.84	1.54	2.71	M	NV	0.43	0.06	
9	2-Cl-C_6H_4-P_1(pyrr)	20.17	2.34	2.74	M	NV/S	1.2	0.1	21.38
	PhP_1(dma)	21.25	1.79	3.62	M	NV/S	0.11	0.05	
	4-Br-C_6H_4-P_1(pyrr)	21.19	1.79	2.99	M	NV/S	0.21	0.05	
	$PhP_1(dma)_2Me$	21.03	2.17	2.67	M	NV	0.36	0.05	
	PhTMG	20.84	2.05	3.40	M	NV/S	0.52	0.1	
10	PhP_1(pyrr)	22.34	4.39	3.87	M	NV/S	−0.63	0.1	21.66
	PhP_1(dma)	21.25	4.07	3.17	M	NV/S	0.41	0.05	
	PhP_1(dma)	21.25	6.45	3.53	T	NV/S	0.42	0.05	
	4-Br-C_6H_4-P_1(pyrr)	21.19	3.58	3.14	M	NV/S	0.49	0.1	
	$PhP_1(dma)_2Me$	21.03	4.11	2.67	M	NV/S	0.60	0.07	
	PhTMG	20.84	3.97	4.32	M	NV/S	0.77	0.07	

[a] Reference 44. [b] Concentration of bispidine and reference base in mixture. [c] Abbreviation of the acid titrated with: M = CH_3SO_3H, T = CF_3SO_3H. [d] Calculation method: NV, bispidine as "nonvisible", ΔpK_a calculated on molar basis; S, calculated from UV−vis spectra. [e] ΔpK_a = pK_a(bispidine) − pK_a(reference base).

was connected to an external sample compartment that was situated in the glovebox by means of two quartz fiber optic cables. Glassware used during the experiments was heated at 150 °C for at least 6 h and then cooled in a desiccator over P_2O_5 or in the glovebox. Concentrations of bases used in the titration experiments were around 10^{-5} M and never exceeded 14×10^{-5} M; concentrations of acidic and basic titrants were usually in the 5×10^{-4} M range. The solutions were transferred by means of Pasteur pipets or syringes. A solution of $MeSO_3H$ in AN was used as acidic titrant in most cases. In some experiments (see Table 6), a solution of TfOH was used because the acidity of $MeSO_3H$ was too low. Two basicity equilibriums were measured using both acids to make sure that ΔpK_a does not depend on anions of the acids (Table 6). The water content of collected titrated waste solutions was determined by coulometric Karl Fischer titration to be about 0.005−0.006%.

Calculation Methods. UV−vis spectra were used to determine the ΔpK_a values for those pairs of bases that have both good as well as different UV−vis spectra of the free base and the protonated form ("pure" spectrophotometric method). The details of the calculation methods have been reported previously.[7,40,42,48] From each titration experiment of the mixture of bases, the ΔpK_a was determined as the mean of 10−20 values. As most of the bispidines have only small differences between the UV−vis spectra of the free base and the protonated form, an alternative method was used as well. In this method,[42] available spectra as well as the exact amount of moles of the compounds in the titration vessel and of the added titrant are used ("based on moles" method; see ref 42 for details). Good agreement between these two different approaches (pure spectrophotometric and based on moles method) was not always obtained. In this case the result with better standard deviation (usually the method that was based on moles) was used. The absolute pK_a values were calculated as reported previously[7,40] by minimizing the sum of squares of differences between directly measured ΔpK_a values and assigned pK_a values while the pK_a values of reference bases were kept constant (Table 6). However, it should

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be stressed that the absolute pK_a values of bases given in Table 6 are not as accurate as the relative pK_as. The precision and the consistency of the results can be assessed using a standard deviation s as defined by eq 2:

$$s = \sqrt{\frac{u}{n_m - n_c}} \quad (2)$$

where $n_m = 42$ is the number of measurements and $n_c = 10$ is the number of pK_as determined. For our results, $s = 0.04$ pK_a units, u = sum of squares of differences between directly measured ΔpK_a values and the assigned pK_a values.

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Supporting Information Available: Experimental procedures, identified byproducts, characterization data, and spectra for compounds, X-ray CIF files, tables of bond lengths, angles, calculated Cartesian coordinates, and UV−vis spectra from pK_a determination experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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