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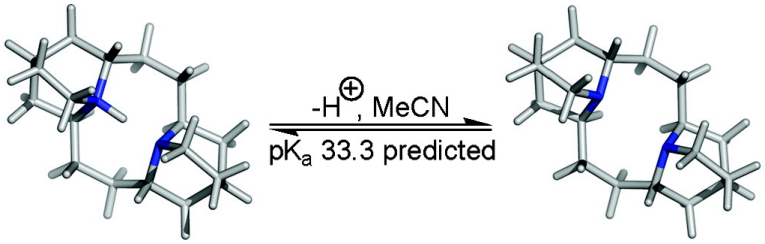

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Design of C_2-Chiral Diamines That Are Computationally Predicted To Be a Million-fold More Basic than the Original Proton Sponges

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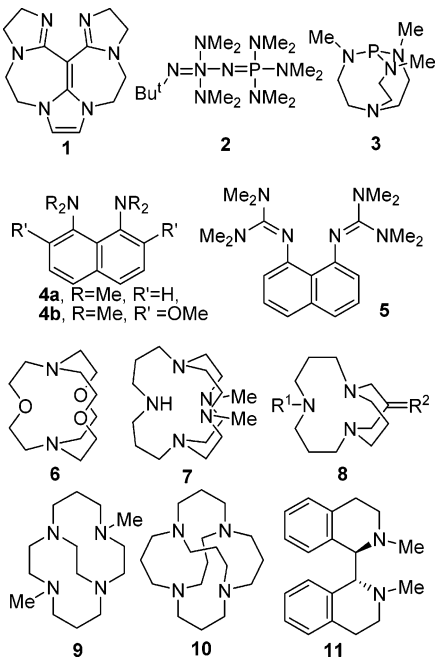
Abstract: A set of C_2-chiral diamines **18**−**21** based on 1,6-diazacyclodecane have been identified whose conjugate acids are predicted by B3LYP/6-31G* calculations to have pK_a values of ∼23−6 on the water scale (pK_a = 30−33 in MeCN); they are also expected to be kinetically active, but essentially nonnucleophilic. Strain relief on protonation largely determines the basicity of these compounds, and the key to the design of stronger bases is limiting conformational freedom, especially by preventing nitrogen inversion, through the introduction of additional ring fusions. 15,16-Dimethyl-15,16-diazatricyclo[9.3.1.1^{4,8}]hexadecane (**20**) is examined in detail and shown to exist in 10 diastereomeric forms as a result of in-/out-isomerism. The predicted pK_a values for these diastereomers range over 14 log units.

Several types of unusually strong neutral bases have been developed. These include Schwesinger's vinamidine[1,2] and phosphazene bases,[3] the proazaphosphatrane bases developed by Verkade,[4] and the proton sponges originally introduced by our group[5,6] and extensively developed by Staab[7,8] and others.[9,10] Schwesinger's[2] best vinamidine base **1** has a pK_a in acetonitrile (MeCN) of 31.9 (the common practice of citing the pK_a value of the conjugate acid will be followed in this paper). It should be noted that pK_a values in MeCN are typically 7−8 units higher than in water, while those in dimethyl sulfoxide (DMSO) are 1−3 units lower (pK_a values for Me_3NH^+ are 9.81 in water, 17.61 in MeCN, and 8.4 in DMSO). Schwesinger's P_2−t-Bu−phosphazene base **2** has a pK_a in MeCN of 33.45,[11] and Verkade's proazaphosphatrane base **3** has a pK_a in MeCN of 32.9.[12] The original proton sponge **4a** is much weaker than these (pK_a 12.1 in H_2O,[5] 18.62 in MeCN,[13] and 7.5 in DMSO[14]), while the most powerful naphthalene-based proton sponges known to date are probably **4b** (pK_a 16.1 in 60% DMSO/H_2O[15] and 11.5 in DMSO[9]) and **5** (pK_a 25.1 in MeCN).[10]



The causes of enhanced basicity in these compounds are of considerable interest, but they are also of significance as practical reagents where three desirable properties are (a) high thermodynamic basicity (pK_a), (b) nonnucleophilicity, to avoid side reactions competing with deprotonation, and (c) kinetic

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activity, i.e., adequate rates of proton transfer to and from the basic site. With the current need to develop technology to produce chemical substances in a pure enantiomeric form, a fourth desirable attribute is good chiral discrimination.

In addition to these types of base, a number of medium-ring di-and polyamines have been found to have enhanced basicities. Lehn's [1.1.1]cryptand, **6**, has an estimated pK_a in H_2O of 17.8, based on the known rate of protonation and an upper limit for the rate of deprotonation (which could not be detected).[16] Of course, a compound with these properties is of no practical use as a base, and this is true of a number of bicyclic medium-ring diamines prepared by Alder and discussed in more detail later. Variations on the cryptand structure developed by the Ciampolini and Micheloni groups, such as **7**, are kinetically active however.[17] Bell[18] has developed a series of bicyclic triamines **8**, R^1 = H or Me, R^2 = H_2 or CH_2, which show enhanced basicities. The cross-bridged cyclam **9** prepared by Weisman is a stronger base than DBU with pK_a 24.9 in MeCN.[19] Several related tetraamine bases were prepared by Springborg and others and have been christened bowl adamanzanes.[20] Springborg also prepared tricyclic tetramines such as **10** (adamanzanes) that fully encapsulate one proton; unsurprisingly, rates of proton transfer in and out of the cage are extremely slow in these examples.[20]

Existing neutral strong bases meet the three practical criteria set out above to varying degrees. There is no doubt that the Schwesinger P_3, P_4, and P_5 bases are thermodynamically the strongest neutral nitrogen bases known, and their position in this respect is unlikely to be challenged. They also appear to be relatively nonnucleophilic and to have fast enough rates of proton transfer that this is not an issue. Thus these are the strong neutral bases of choice for many practical applications. Useful chiral versions are not available however. The proazaphosphatrane bases are approximately equal in basicity to the Schwesinger P_2 bases thermodynamically, and chiral versions have been reported.[21] Proton sponges are generally excellent from the point of view of low nucleophilicity, but many suffer from very low rates of proton transfer,[15] and they are also weaker than the Schwesinger and Verkade bases. The C_2-chiral diamine **11** has pK_a = 18.2 in MeCN, but this represents a quite modest enhancement relative to 2-methyl-1,2,3,4-tetrahydroisoquinoline, since the hydrogen bond formed is far from linear.[22] From a physical organic point of view, there is continuing debate about whether the enhanced basicity in proton sponges is due mainly to strain relief on protonation,[6,7,23] or to the special properties of the hydrogen bonds in their monoprotonated ions.[24] The hydrogen bonds in the monoprotonated ions have also excited much interest as models for low-barrier hydrogen bonds whose role in enzyme catalysis has been hotly debated.

This paper discusses the design of new, chiral diamines with pK_a values > 6 log units higher than existing proton sponges according to density functional theory (DFT) calculations. It will be asserted that strain relief on monoprotonation is overwhelmingly the main cause of the extreme basicity, and it will be suggested that these bases should be kinetically active, but essentially nonnucleophilic.

Theoretical Methods

All DFT calculations were performed with the Jaguar program package,[25] using Becke's three-parameter exchange functional[26] with the correlation functional of Lee, Yang, and Parr (B3LYP).[27] All species were characterized by full geometry optimization with the standard 6-31G* basis set, and minima were characterized by analytical frequency calculations. Single-point calculations were then carried out with the 6-311+G** basis set. Calculations simulating the solvents water, MeCN, and DMSO employed the Poisson−Boltzmann continuum solvent model as implemented in the Jaguar program, with the assumption that geometries, zero point energy, and thermodynamic parameters could be transferred from the gas-phase calculations. Cartesian coordinates, self-consistent field (SCF) energies, and zero point corrections for all the species discussed in this paper are available in the Supporting Information.

The global minimum conformation for most species discussed in this paper cannot be safely predicted. Monte Carlo multiple minimum conformational searches[28] were therefore carried out for all species, using the MMFFs force field in MacroModel.[29] The MMFFs force field does not accurately reflect lone pair/lone pair repulsions, so, where these might be significant, conformational searches were also carried out with the PM3 semiempirical method in Spartan.[30] Where several conformations were found to have similar energies by these methods, these were each submitted to B3LYP/6-31G* calculation, and the lowest energy conformation from this was used in proton affinities (PA) and pK_a calculations. No attempt has been made, however, to allow for conformational mixtures, since the error resulting from ignoring this is likely to be small compared with other errors.

There have been extensive developments in the calculation of PA, gas-phase basicities (GB), and solution pK_a values in recent years. In particular, Liptak and Shields[31] have shown that it is now possible to calculate absolute aqueous pK_a values with chemical accuracy, and their methods have been applied with considerable success to calculate pK_a values in several solvents for one special class of strong neutral bases, the diaminocarbenes, by Magill et al.[32] Unfortunately the most reliable methods (e.g. CBS-QB3) are far too computationally intensive to be applied to molecules of the size discussed in this paper. Magill and Yates[33] have recently discussed the choice of methods in this situation.

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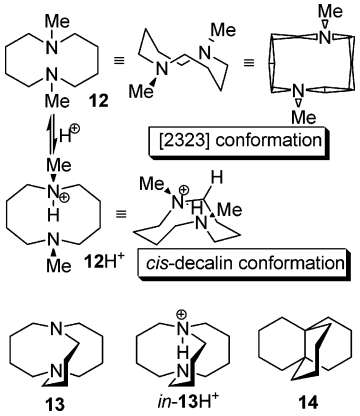
Scheme 1. Medium-Ring Diamines and Their Protonated Ions



Their results suggest that two good options for larger species are (a) CBS-4M and (b) B3LYP/6-311+G**, and method b has been used throughout here. This procedure uses geometries, zero point energies, and thermal and entropy corrections from the well-established B3LYP/6-31G* level of theory. pK_a values have been calculated relative to Me_3NH^+ whose pK_a value has been assumed to be 9.81 in water, 17.61 in MeCN, and 8.4 in DMSO. These procedures lead to pK_a values of 11.9 (H_2O), 18.1 (MeCN), and 8.5 (DMSO) for the original proton sponge **4a** compared with experimental values of 12.1,[5] 18.62,[13] and 7.5,[14] respectively. The pK_a value of **4b** in DMSO is calculated to be 11.1 (experimental, 11.5[9]). While the general level of agreement seems relatively good, it is worth noting that the calculated pK_a difference between **4b** and **12** in DMSO is 3.9, compared with a measured value of 0.4. Nevertheless, the calculations appear reliable enough that the major effects described in this paper can be clearly demonstrated.

Results and Discussion

In 1988, we reported[34] that the simple alicyclic diamine **12** was a slightly stronger base than **4b** in DMSO ($\Delta pK_a = 0.4$). Diamine **12** was the strongest of a series of medium-ring diamines examined, essentially because the 1,6-diazacyclodecane framework provides an ideal geometry for a transannular hydrogen bond. We suggested at the time that the enhanced basicity of **12** relative to simple tertiary amines and acyclic diamines reflected steric inhibition of solvation, leading to gas-phase-like behavior. Unlike **4b** and other proton sponges, there is not much strain relief when **12** is protonated, since the nitrogen lone pairs in the free base are accommodated on opposite sides of a relatively strain-free [2323] or boat−chair−boat cyclodecane ring conformation, as shown in Scheme 1. In this conformation the lone pairs are transannular to a C−H bond and cannot interact with solvent molecules (there may be weak N···H−C bonding). The diamond lattice represents the ideal structure for sp^3 carbon, and the conformation of **12**H$^+$ can be seen as derived from a diamond lattice *cis*-decalin structure by replacement of a C−C bond by an N···H−N$^+$ hydrogen bond. It may come as a surprise that a *cis*-decalin-like structure is preferred to the *trans*-decalin alternative. However, it should be noted that (a) the advantage enjoyed by the trans-isomer of decalin almost disappears when both bridgehead atoms are substituted with methyl groups and (b) stretching the *trans*-decalin to accommodate the longer N···H−N$^+$ hydrogen bond results in a disrotatory twist of the N−Me groups so that the dipoles associated with the hydrogen bond are much less well-aligned. The preference for *cis*-decalin-like structures containing N···H−N$^+$ hydrogen bonds becomes very clear in the analysis of the isomers of **20** below.

Table 1. Calculated (B3LYP/6-311+G**//B3LYP/6-31G*) PA and pK_a Values

diamine	gas-phase PA (kJ mol^{-1})	pK_a (H_2O)[a]	pK_a (MeCN)[b]	ΔE(i) (kJ mol^{-1})	ΔE(ii) (kJ mol^{-1})
4a	1028	11.9	18.1		
4b	1089	20.1	23.2		
12	1046	15.8	23.5	1	−9
13	1078	21.0	28.3	42	−6
15	1056	9.2	16.3	82	58
16	1018	15.4	22.8		
17	1060	24.5	30.9	0	−23
18	1124	25.9	33.3	47	−36
19	1112	23.4	31.3	27	−52
20	1105	23.6	30.4	43	−23
21	1103	24.2	31.0	104	41

[a] Relative to Me_3N, pK_a = 9.81. [b] Relative to Me_3N, pK_a = 17.61.

Table 2. Calculated (B3LYP/6-311+G**//B3LYP/6-31G*) PA and pK_a Values for diastereomers of 15,16-dimethyl-15,16-diazatricyclo[9.3.1.1^{4,8}]hexadecane

diamine	gas-phase PA (kJ mol^{-1})	pK_a (H_2O)[a]	pK_a (MeCN)[b]	ΔE(i) (kJ mol^{-1})	ΔE(ii) (kJ mol^{-1})
syn-RRRR	1105	23.6	30.4	43	−23
anti-RRRR	1022	9.8	16.7	16	33
Syn-RRRS	1091	21.4	28.0	36	−18
Anti-RRRS	1025	10.4	16.9	13	24
Syn-RSRS	1082	19.9	26.5	41	−3
Anti-RSRS	1071	19.1	25.4	45	13
Syn-RRSS	1107	24.5	30.9	93	24
Anti-RRSS	1031	10.9	17.8	2	7
Syn-RSSR	1093	21.5	28.9	59	2
anti-RSSR	1014	9.5	16.1	−1	22

[a] Relative to Me_3N, pK_a = 9.81. [b] Relative to Me_3N, pK_a = 17.61.

A more tightly constrained structure than **12**H$^+$ is that of inside-protonated 1,6-diazabicyclo[4.4.4]tetradecane, in-**13**H$^+$, which can be derived from diamond lattice [4.4.4]propellane **14** by replacement of a C−C bond by an N···H−N$^+$ hydrogen bond (Scheme 1). The hydrogen bond in in-**13**H$^+$ (N···N distance, 2.56 Å) is undoubtedly under compression but is more easily accommodated than two nitrogen lone pairs (which strongly repel each other) in the free base **13** (N···N distance, 2.81 Å).[35] However **13** is completely ineffective as a base, because the inside proton can be neither inserted nor removed by conventional proton transfers.[36] The PA of **13**, defined as the negative of the enthalpy change for protonation in the gas phase, can be calculated of course,[37] and it is much higher than that of **12**, due to strain relief on protonation; B3LYP/6-311+G**//B3LYP/6-31G* PA values are for **12** 1046 and for **13** 1078 kJ mol-^{1}. Using the Poisson−Boltzmann continuum solvent model in the Jaguar program, aqueous pK_a values of 15.8 and 21.0 can be estimated for **12** and **13**, respectively (see Table 1). In the remainder of this paper (see Tables 1 and 2), calculated pK_a values are reported for water, but also for MeCN solution since the best data for neutral bases are in the latter solvent.[13] Calculated pK_a values in DMSO are given in the Supporting Information.

Table 1 includes an analysis of strain effects in the free bases and the protonated ions. For this purpose the energy changes

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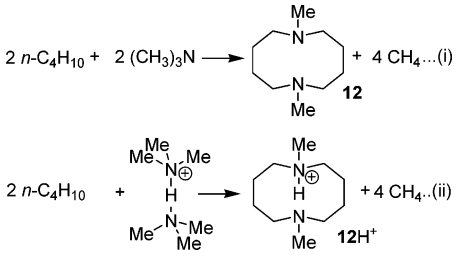
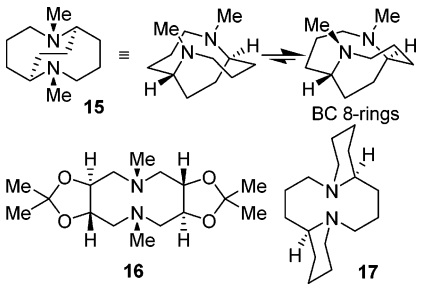
for isodesmic equations in which each C−N bond in the diamine or protonated ion was formally constructed from Me_3N or Me_3NH^+ were calculated using B3LYP/6-31G*. These isodesmic equations are exemplified for the case of **12** and **12**H^+ in (i) and (ii); note that the protonated ions are compared with the hydrogen-bonded $Me_3N\cdots H-NMe_3^+$ species. The B3LYP/6-31G* calculated hydrogen bond strength in the latter is 94.1 kJ mol^{-1}.

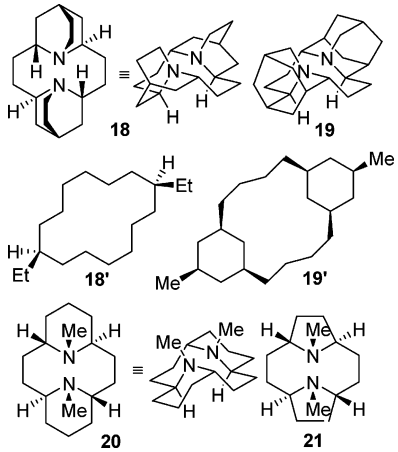


Comparison of the ΔE(i) and ΔE(ii) values for **12** and **13** shows that it is the severe strain in diamine **13** which is the cause of its enhanced (thermodynamic) basicity. By the criterion of the ΔE(ii) value, in-**13**H^+ is marginally more strained than **12**H^+, even though it contains the shortest known $N\cdots H-N^+$ bond which is perfectly linear and may be of the single minimum type.

A prescription for the ultimate alicyclic proton sponge might therefore be to design a protonated ion with a diamond lattice structure which was unable to escape lone pair/lone pair repulsion when deprotonated but still gave reasonable access to the proton from the outside, unlike in-**13**H^+ (proton transfer to and from **12** appears to be normal). Thus if it was possible to devise structures related to **12** which were unable to adopt the relatively strain-free [2323] conformation, enhanced basicities might result. The conformational changes required to get from **12** to **12**H^+ include inversion at one nitrogen atom and extensive rotation about the bonds in the 10-membered ring. The most effective way to restrict the conformational freedom of **12** is to introduce additional bridges or rings. Diamine **15** is certainly unable to reach a [2323] conformation for the 10-membered ring. It can adopt a diamond lattice structure with BB cyclooctane rings, but calculations show that the preferred structures for both **15** and **15**H^+ have BC cyclooctane rings, and it appears that strain in this system is not effectively relieved by protonation, since the calculated PA = 1056 (Table 1), only a little higher than that for **12**. C_2-chiral diamines **16** and **17** are unfortunately quite flexible, and the 1,6-diazacyclodecane rings are able to achieve [2323] conformations. The calculated PA of **17** is 1060 kJ mol^{-1}, very little higher than that of **3**, while that for **16**, attractive synthetically since it might be made in C_2-chiral form from tartrate, is only 1018 kJ mol^{-1}, presumably due to the electron-withdrawing acetal groups.



At the other extreme, diamines such as **18** and **19**, in which each nitrogen atom is built into a bicyclic framework, such as quinuclidine or 1-azaadamantane, are extremely rigid, although, as will be shown later, they do retain enough conformational freedom to allow one of the lone pairs to interact with external hydrogen bond donors. This is vital if they are to be kinetically active as bases. Diamines **18** and **19** are C_2-chiral, and they may be expected to be almost nonnucleophilic, as there is very little room for anything larger than a proton between the nitrogen atoms.



Diamines **18** and **19** are calculated to have PA values of 1124 and 1112 kJ mol^{-1}, respectively. These values are truly remarkable; they are comparable to those calculated[38] for a set of diaminocarbenes (1113−1184 kJ mol^{-1}). The calculated pK_a values in MeCN are close to vinamidine base **1**, P_2–t-Bu−phosphazene base **2**, and proazaphosphatrane base **3**.

It is initially surprising that these diamines are predicted to be stronger bases than **13**, which might have been expected to be (thermodynamically) the ultimate base of this type. However the hydrogen bond in in-**13**H^+ is probably shorter than ideal, as has already been pointed out. Comparison of the ΔE(i) and ΔE(ii) values (Table 1) shows that there is substantially greater strain relief when **18** and **19** are protonated than in the case of **13**. It should be noted that the absolute values for ΔE(i) and ΔE(ii) may be in some doubt in the case of **18** and **19**, as they are based on B3LYP/6-31G* calculated energies for the hydrocarbons **18′** (*cis*-1,8-diethylcyclotetradecane) and **19′**, respectively. Nevertheless, the difference [ΔE(i) − ΔE(ii)] which measures the strain relief resulting from protonation is not in doubt.

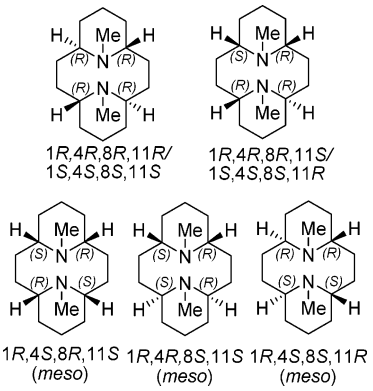
It is worth noting that the C−N−C angles in **18** average 109.8° signifying perfect sp^3 hybridization and that these hardly change on protonation (C−N−C, 110.3°). Thus the suggestion that flattened amines will be unusually strong bases,[39] which

(38) Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, J. N.; Paolini, F. P. V.; Schütz, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5896−5911.
(39) (a) Korzhenevskaya, N. G.; Dustmukhamedov, T. T.; Umarov, K. S.; Chotoi, K. Y.; Mirzoev, M. S. *Zh. Obshch. Khim.* **1991**, *61*, 1539−1542. (b) Korzhenevskaya, N. G.; Mestechkin, M. M.; Matveev, A. A. *Zh. Obshch. Khim.* **1992**, *62*, 626−628. (c) Korzhenevskaya, N. G. *Dopov. Akad. Nauk Ukr.* **1993**, 123−126. (d) Korzhenevskaya, N. G. *Ukr. Khim. Zh. (Russ. Ed.)* **1994**, *60*, 193−198. (e) Korzhenevskaya, N. G.; Mestechkin, M. M.; Lyashchuk, S. N. *Zh. Org. Khim.* **1996**, *32*, 498−502. (f) Korzhenevskaya, N. G.; Kovalenko, V. V. *Zh. Org. Khim.* **1999**, *35*, 270−274. (g) Korzhenevskaya, N. G.; Rybachenko, V. I.; Kovalenko, V. V. *Russ. Chem. Bull.* **2003**, *52*, 893−899.

has recently been called up as a contributing factor to the high basicity of proton sponges,[9,40] receives no support in this case.

Diamines **18** or **19** are certainly challenging synthetic targets, and it is worth asking if simpler structures might have similar properties. In fact tricyclic diamines **20** and **21** are only slightly weaker bases than **18** and **19** and are still stronger than **13** (Table 1). To understand the features of these diamines that make them such strong bases, a detailed analysis of the structure and conformation of all the stereoisomers of **20** has been undertaken (**21** should be essentially similar).

Configurations, Conformations, and Protonation Behavior for 15,16-Dimethyl-15,16-diazatricyclo[9.3.1.14,8]hexadecane. 15,16-Dimethyl-15,16-diazatricyclo[9.3.1.1^{4,8}]hexadecane (**20**) has seven configurational stereoisomers, two pairs of enantiomers, and three *meso*-forms. Each of the configurational stereoisomers has many possible conformations: nitrogen invertomers, alternative chair forms, and twist boat forms in the six-membered rings, and a range of conformations in the ten-membered ring are all possible. The barriers for interconversion between these forms could be quite varied, but it is likely that equilibration between all these conformers will be achieved at ambient temperature with one important exception. The potential for in-/out-isomerism[41] exists, and homeomorphic isomerization to interconvert in- and out-isomers requires pushing an N−Me group through the cyclodecane ring, which is clearly impossible. Thus for each configurational isomer there will be two distinct species (formally conformational diastereomers), most easily identified by whether the N−Me groups are on the same or opposite sides of the molecule and referred to here as syn and anti. [While it is possible to use in-/out-nomenclature, the in/out nature of the bridgehead protons is actually far from obvious in some of the conformations.] There are therefore 10 diastereomeric species whose proton affinities and pK_a values could be determined; these will be referred to below as *syn-RRRR*, *anti-RSRS*, etc.



The results from DFT calculations on all 10 isomers are summarized in Table 2; remarkably, calculated PA values for the diastereomers of **20** vary by >80 kJ mol^{-1} and pK_a values by >14 logarithmic units! These striking variations in PA and pK_a are usefully analyzed in terms of strain effects in the free bases and the protonated ions using eqs i and ii as before (the hydrocarbon used as a basis for comparison is cyclotetradecane, which is essentially strain-free).

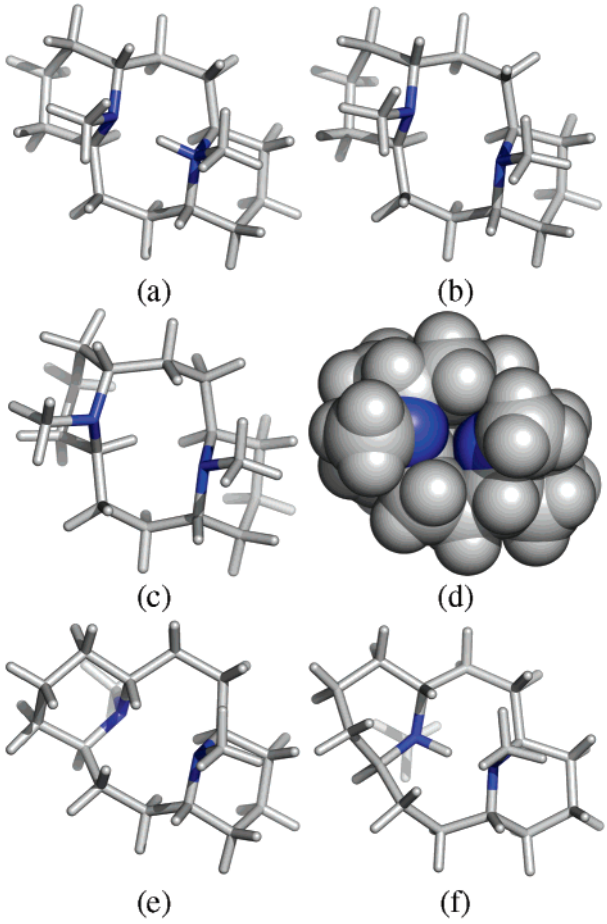


Figure 1. Structures for (a) *syn-RRRR*H$^+$, (b) *syn-RRRR*, (c and d) opened conformation for *syn-RRRR*, (e) *anti-RRRR*, and (f) *anti-RRRR*H$^+$.

Chiral Isomers *syn-* and *anti-RRRR* and *syn-* and *anti-RRRS*. The 1*R*,4*R*,8*R*,11*R*/1*S*,4*S*,8*S*,11*S*-enantiomer pair **20** (called *syn-RRRR* below) has potential C_2 symmetry and is the most interesting in many respects. The *syn-RRRR*H$^+$ is the most stable of all the protonated ions (ΔE(ii), −23 kJ mol^{-1}). It adopts the diamond lattice structure with C_2 symmetry shown in Figure 1a with an N···H−N$^+$ distance of 2.64 Å; the hydrogen bond is close to linear (N−H−N, 167.5°). The free base *syn-RRRR* is found to prefer the same basic conformation (Figure 1b). Lone pair repulsion is relieved by opening up the N···N distance to 2.96 Å, but at the cost of increased strain elsewhere (ΔE(i), 43 kJ mol^{-1}). Note especially that the two in-bridgehead hydrogen atoms are forced close together (H···H, 1.91 Å). There is a second "opened" conformation, 24 kJ mol^{-1} less stable and shown in Figure 1c, in which one CH−CH$_2$–CH$_2$–CH torsion angle has changed sign. This conformation is significant, since the nitrogen atoms are much more open for interaction with external hydrogen bond donors (see the space-filling model, Figure 1d) and thus provides a route for proton transfer to *syn-RRRR* (see below). Changing the sign of the torsion angle of the remaining CH−CH$_2$–CH$_2$–CH results in a severe increase in strain, and the lone pairs actually become less accessible again. The main point however is that the strain in *syn-RRRR* is very effectively relieved by protonation, leading to the prediction of an extraordinarily high PA value.

(40) (a) Korzhenevskaya, N. G.; Schroeder, G.; Brzezinski, B.; Rybachenko, V. I. *Russ. J. Org. Chem. (Zh. Org. Khim.)* **2001**, *37*, 1603−1610. (b) Korzhenevskaya, N. G.; Rybachenko, V. I.; Schroeder, G. *Tetrahedron Lett.* **2002**, *43*, 6043−6045.
(41) Alder, R. W.; East, S. P. *Chem. Rev.* **1996**, *96*, 2097−2111.

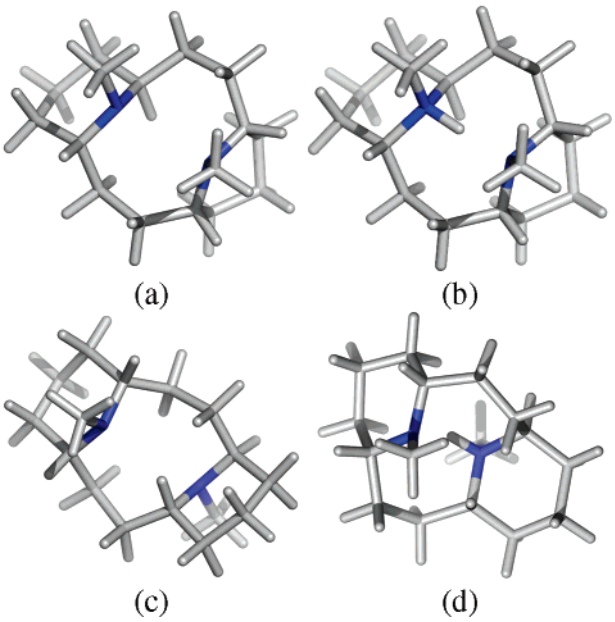


Figure 2. Structures for (a) *syn-RRRS*, (b) *syn-RRRS*H$^+$, (c) *anti-RRRS*, and (d) *anti-RRRS*H$^+$.

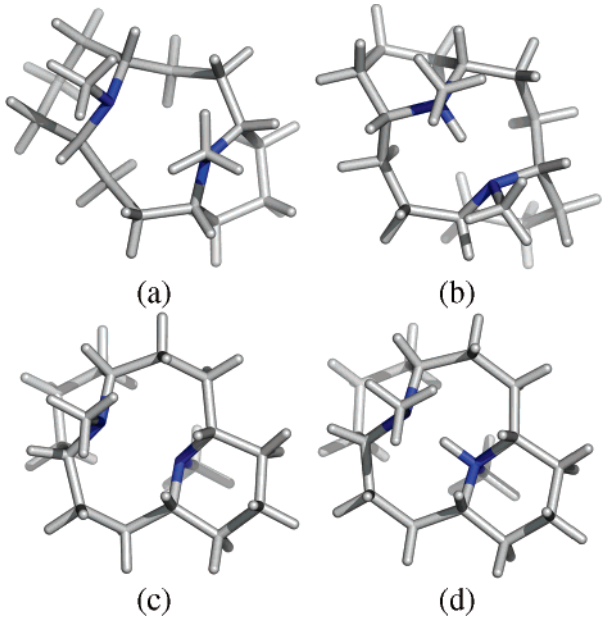


Figure 3. Structures for (a) *syn-RSRS*, (b) *syn-RSRS*H$^+$, (c) *anti-RSRS*, and (d) *anti-RSRS*H$^+$.

The situation is quite different for *anti-RRRR*, which also has C_2 symmetry; see Figure 1e. While this is somewhat strained (ΔE(i), 16 kJ mol^{-1}), due to a relatively poor conformation for the 10-membered ring, the nitrogen atoms are far apart (N···N, 3.28 Å), and protonation actually results in an increase in strain, to judge by the ΔE(i) and ΔE(ii) values. In *anti-RRRR*H$^+$, one of the piperidine rings is flipped into a twist-boat conformation in order to orient the lone pairs better for hydrogen bonding; see Figure 1f. As a result, the calculated PA for *anti-RRRR* is 85 kJ mol^{-1} lower than for *syn-RRRR* which corresponds to a drop in pK_a values of >14 log units.

The situation for *syn-* and *anti-RRRS* is rather similar to that for the *RRRR* isomers, although the contrast between the isomers is not quite so stark. The *syn*-isomer should be a strong base (Table 2), while the *anti*-isomer is predicted to be about 11 log units weaker. Preferred conformations for both free bases and protonated ions are illustrated in Figure 2.

***meso*-Isomers *syn-RSRS* and *anti-RSRS*.** This is the only case where the PA values of the *syn-* and *anti*-forms are relatively similar (Table 2). Preferred conformations for both free bases and protonated ions are illustrated in Figure 3a−d.

In the preferred conformation for *syn-RSRS*, which has C_s symmetry, one piperidine has an axial N−Me and the other is equatorial, and in both the C−N−C angle within each piperidine ring is enlarged, to 117.0° with ax-NMe and to a remarkable 125.1° with eq-NMe. On the other hand, both piperidine rings in *syn-RSRS*H$^+$ are twist-boat; this permits a N···H−N$^+$ distance of 2.64 Å. In the corresponding double-chair structure (6 kJ mol^{-1} less stable) the N···H−N$^+$ distance is 2.80 Å. In *anti-RSRS*, there is again one piperidine with an ax-NMe and one with eq-NMe; the C−N−C angles within the piperidine rings are 107.6 and 120.5°, respectively. Inside protonation of this isomer preserves the C_s symmetry, and the N···N distance decreases from 2.84 to 2.61 Å.

***meso*-Isomers *syn-RRSS* and *anti-RRSS*.** Preferred conformations for both free bases and protonated ions are illustrated in Figure 4a−d. The *syn-RRSS* free base lacks the potential C_s symmetry and is the most strained of all (ΔE(i), 93 kJ mol^{-1}) with extremely severe lone pair interactions resulting from a calculated N···N distance of only 2.80 Å. The short N···H−N$^+$ distance of 2.60 Å in the protonated ion permits substantial strain relief, and this is calculated to be the most basic isomer with PA = 1107 kJ mol^{-1}. The *anti-RRSS* free base adopts an almost strain-free diamond lattice structure (ΔE(i), 2 kJ mol^{-1}) with C_s symmetry, in which two chair-form piperidine rings are fused to a [2323] 10-membered ring so that the nitrogen atoms are 4.19 Å apart. In the protonated ion, *anti-RRSS*H$^+$, the ring fusions at the piperidine have flipped from all-axial to all-equatorial so that the N···H−N$^+$ bond spans a *trans*-decalin-like ring (N···H−N$^+$ distance, 2.71 Å). Strain actually increases slightly on protonation so the PA value is quite low (Table 2). It is worth noting that the conformational

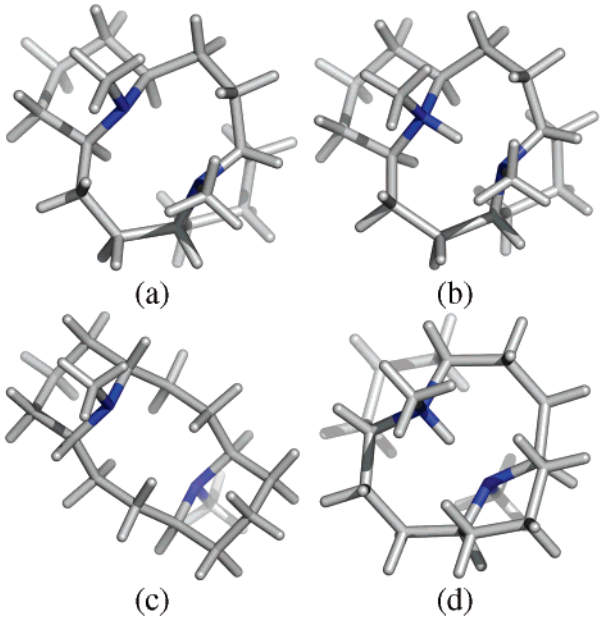


Figure 4. Structures for (a) *syn-RRSS*, (b) *syn-RRSS*H$^+$, (c) *anti-RRSS*, and (d) *anti-RRSS*H$^+$.

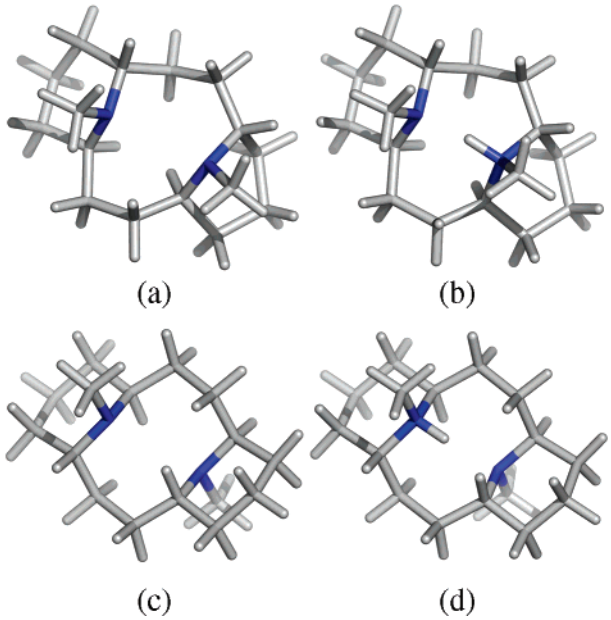


Figure 5. Structures for (a) *syn-RSSR*, (b) *syn-RSSR*H$^+$, (c) *anti-RSSR*, and (d) *anti-RSSR*H$^+$.

processes needed to get from the *anti-RRSS* conformation to that of *anti-RRSS*H$^+$ could well require substantial activation. Dynamic NMR studies of the protonation of this isomer might be interesting.

***meso*-Isomers *syn-RSSR* and *anti-RSSR*.** Preferred conformations for both free bases and protonated ions are illustrated in Figure 5a−d. The preferred conformation of *anti-RSSR* has the lowest strain of all. It resembles that proposed for **12**, with a [2323] 10-membered ring conformation that includes transannular C−H···N distances of 2.30 Å, which may be weakly bonding. Note that this conformer has an inversion center (C_i) and is structurally analogous to the tricyclic bisaminal 1,4,8,-11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane studied by Weisman and Alder.[42] Topomerization of *anti-RSSR* to realize the potential C_s symmetry (thus rendering all the bridgehead hydrogens equivalent) requires a double homeomorphic isomerization and is never likely to occur. This is the only isomer where protonation does not result in any N···H−N$^+$ bonding. The preferred conformation of *anti-RSSR*H$^+$ retains the same general structure as free *anti-RSSR*, with only a minor change in N···N distance (from 3.21 to 3.13 Å), but one C−H···N interaction is replaced by C−H···H−N$^+$ repulsion with an H···H distance of only 1.74 Å. Not surprisingly, therefore, *anti-RSSR* is calculated to be the weakest base of all (Table 2).

The *syn-RSSR* isomer is severely strained (ΔE(i), 59 kJ mol^{-1}) and the preferred conformation has one twist-boat piperidine (the double chair conformation is 16 kJ mol^{-1} less stable). The protonated form retains a preference for one twist-boat, but considerable strain is relieved (ΔE(ii), 2 kJ mol^{-1}), so this diamine is strongly basic.

In summary, all the *syn*-isomers are predicted on the basis of DFT calculations to be stronger bases than **12**, with PA values of 1082−1107 kJ mol^{-1} and calculated pK_a values in MeCN ranging from 26.5 to 30.9. In all cases protonation is accompanied by formation of a good hydrogen bond and major release of strain: ΔE(i) > ΔE(ii) by 44 kJ mol^{-1} or more. Four of the *anti*-isomers are normal bases, with calculated pK_a values in MeCN (16.1−17.8) closely similar to Me_3N, but *anti-RSRS* is stronger than **12** (pK_a, 25.4 in MeCN). It is clear that blocking of nitrogen inversion by linking it to in-/out-isomerism in these species is vital to the design of bases such as *syn-RRRR* **20** and **21**.

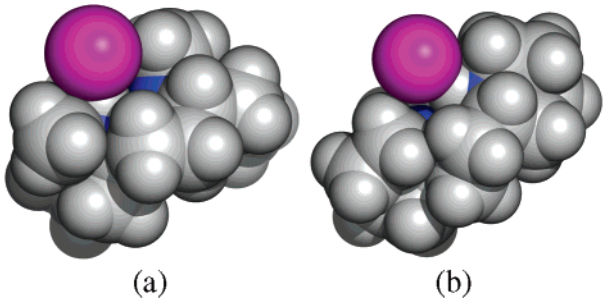


Figure 6. Structures for HCl complexes with the opened conformations of (a) **20** and (b) **18**.

Kinetics of Protonation. The discussion so far has concentrated on the thermodynamics of protonation of the various diamines and stereoisomers of 15,16-dimethyl-15,16-diazatricyclo-[9.3.1.1^{4,8}]hexadecane. If pure enantiomers of **18**−**21** can be prepared, they could prove to be practical chiral bases so long as they are kinetically active. Based on the examination of models and some calculations, it seems likely that this will be the case. Figure 6 shows space-filling models of complexes of HCl with the opened conformations of **20** (*syn-RRRR*) and the di(quinuclidine) base **18**. Surprisingly, as minimized with B3LYP/6-31G* in the gas phase, both these structures are contact ion pairs with H−N distances of 1.09 and 1.08 and H···Cl distances of 1.98 and 2.02 Å, respectively. Attempts to minimize structures in which the protons had not been transferred failed, so attempts to locate transition states for proton transfer into **18** and **20** were discontinued. Nevertheless it seems unlikely that proton transfer from external acids into these diamines will be associated with prohibitive barriers.

If protonation of **20** (*syn-RRRR*) takes place when it is in conformation b, this will be at the cost of CH_2CH_2 bridge flipping (24 kJ mol^{-1}), and subsequent conversion to the stable form of *syn-RRRR*H$^+$ will involve flipping back. The transition state for this flipping lies 68 kJ mol^{-1} above *syn-RRRR*H$^+$. Thus *syn-RRRR* may be reactive but behave kinetically as if it was a rather weaker base (a PA calculation based on the opened conformations for *syn-RRRR* and *syn-RRRR*H$^+$ gives a value of 1052 rather than 1111 kJ mol^{-1}, which translates into an aqueous pK_a of about 15). While reasonable rates of proton transfer to **18** and **20** are obviously required for practical use, some extra activation for proton transfer to and from these bases could actually render them more selective, although this is certainly a speculative proposal.

It is also worth noting that the proton in *anti-RRRR*H$^+$ is almost as inaccessible as in in-**13**H$^+$; it seems possible that *anti-RRRR* would not inside-protonate by conventional proton transfers. Moreover, outside protonation with concomitant nitrogen inversion would entail a huge increase in strain, so this diamine could well be kinetically nonbasic; a striking contrast with its *syn*-isomer.

(42) (a) Gabe, E. J.; Lepage, Y.; Prasad, L.; Weisman, G. R. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1982**, *38*, 2752−2754. (b) Alder, R. W.; Heilbronner, E.; Honegger, E.; McEwen, A. B.; Moss, R. E.; Olefirowicz, E.; Petillo, P. A.; Sessions, R. B.; Weisman, G. R.; White, J. M.; Yang, Z.-Z. *J. Am. Chem. Soc.* **1993**, *115*, 6580−6591.

Conclusions

The extreme basicities of diamines **18**−**21** appear to arise very largely from strain relief on protonation. They also represent a new type of chiral base that could have very desirable properties. They are probably close to the limit of development of the proton sponge idea, but are likely to retain reasonable kinetic activity, while being essentially nonnucleophilic. The methyl groups in diamines **20** and **21** could presumably be modified without significantly affecting the base properties. Thus other alkyl or aralkyl groups might be introduced to tune the chiral discrimination, or one of these groups could be modified to attach the base to a polymer support. It is also worth pointing out that replacing one or both of these methyl groups by hydrogen could provide amines whose alkali metal derivatives could have interesting properties as chiral anionic bases. While a discussion of synthetic approaches to these bases is not appropriate here, it is worth noting that the monomethyl analogue of **20** is predicted to prefer a *cis*-decalin-like geometry containing a trans-annular N−H···N(Me) bond, and it should therefore undergo methylation to afford *syn-RRRR*H^+ (**14**H^+) directly.

Acknowledgment. I thank the Leverhulme Trust for an Emeritus Fellowship 2002−4 and the University of Bristol for a Senior Research Fellowship.

Supporting Information Available: The complete ref 3d and Cartesian coordinates, SCF energies, and zero point corrections for all species described (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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