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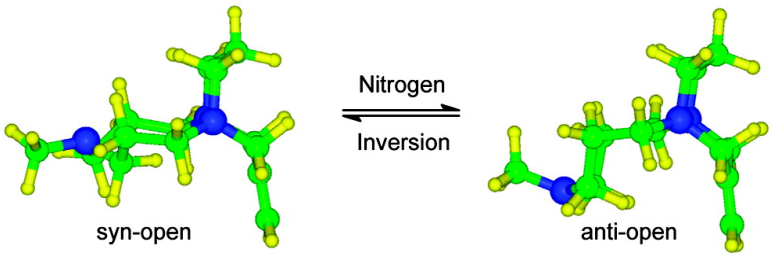

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Syntheses, Conformations, and Basicities of Bicyclic Triamines

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Abstract: The multistep syntheses of several bicyclic triamines are described, all of which have an imbedded 1,5,9-triazacyclododecane ring. In 1,5,9-triazabicyclo[7.3.3]pentadecanes **12**, **13**, **15**, and **16**, two nitrogens are bridged by three carbons. The monoprotonated forms of these triamines are highly stabilized by a hydrogen-bonded network involving the bridge and both bridgehead nitrogens, producing a difference of more than 8 pK_a units in acidities of their monoprotonated and diprotonated forms. The one- and zero-carbon bridges in 1,5,9-triazabicyclo[9.1.1]tridecane (**23)** and 7-methyl-1,5,9-triazabicyclo[5.5.0]dodecane (**39)** do not enhance the stabilities of their monoprotonated forms. X-ray crystal structures and computational studies of **12**·HI and **16**·HI reveal similar, but somewhat weaker, hydrogen-bonded networks, relative to **15**·HI. The activation free energies for conformational inversion of **13**·HI (14.4 ± 0.2 kcal/mol), **16**·HI (15.0 ± 0.1 kcal/mol) and **16** (8.8 ± 0.3 kcal/mol) were measured by variable-temperature ^{1}H and ^{13}C NMR spectroscopy. These experimental barriers give an estimate of 6.2 kcal/mol for the strength of the bifurcated hydrogen bond between the bridge nitrogen and cavity proton in **16**·HI. Computational studies support the hypothesis that N-inversion occurs in an open conformation, leading to an estimate of 10.32 kcal/mol for the enthalpy of the bifurcated hydrogen bond in **16**·HI in the gas phase.

Introduction

Polyamines in which two or more nitrogen atoms lie in close proximity are of interest from both theoretical and practical points of view. The enhanced basicities of proton sponges,[1] such as **1**,[2] **2**,[1a] and **3**,[3] have stimulated numerous experimental and theoretical studies.[4] Proton sponge **1** (X = H),[2a,d] in particular, is useful in synthetic organic chemistry because it is quite basic (pK_a = 12.1), but it is not nucleophilic. Nitrogen bridgehead bicyclic diamines (**4**)[1b,5] are another structural class of molecules in which interaction between lone-pair electrons is dictated by the carbon framework. Of particular interest is 1,6-diazabicyclo-[4.4.4]tetradecane (**4**, $k = l = m = 4$), for which the single-well potential, inside-protonated form cannot be formed by proton transfer in acidic media.[5,6] Such findings may seem esoteric, but proton sponges and bicyclic diamines have made available a series of $[N-H\cdots N]^+$ cations of various hydrogen bond strengths, stabilities and barriers. These species may be useful, for example, as models for evaluating the role of low-barrier hydrogen bonds in enzyme catalysis.[7]

This article concerns the synthesis, basicities, and protonated structures of bicyclic triamines of type **5**, which are similar to **4**, but contain an additional basic site in one of the three bridges.

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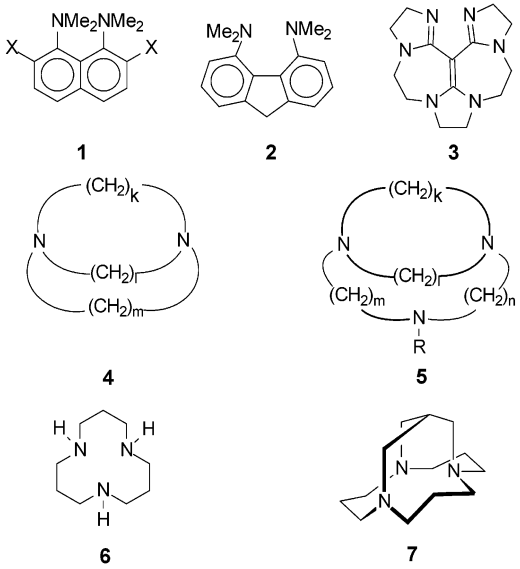
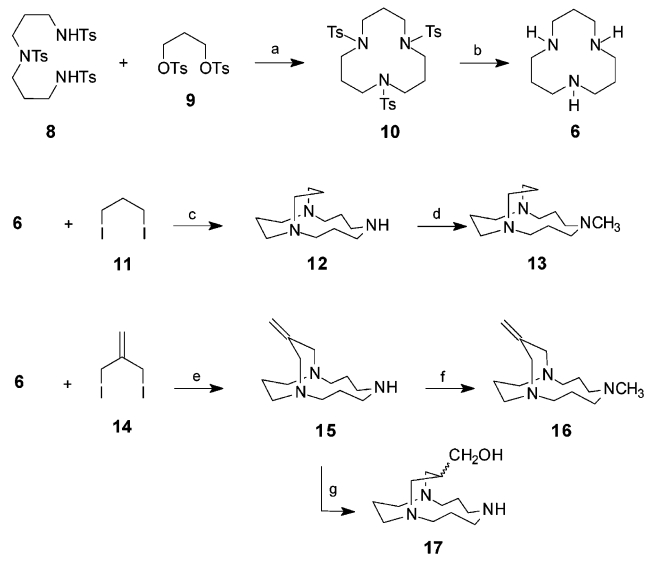
The key molecular framework of interest (**5**, $k = l = m = n = 3$), is a bicyclic analogue of 1,5,9-triazacyclododecane (**6**),[8] which is relatively basic ($pK_a = 12-13$) and forms complexes with various transition metals. Linking two nitrogens of **6** with a three-carbon bridge has been reported to significantly enhance basicity but retain rapid proton-transfer kinetics.[9] Other rapidly protonating bicyclic polyamines contain two[10] or three[11] nitrogen atoms in the bridges, but **5** may represent the simplest molecular architecture exhibiting such properties. Interestingly, [1.1.1]-cryptand is extremely basic, but protonates very slowly.[12] The present studies were originally aimed at the synthesis of tricyclic triamine **7**, which is a substructure of a previously targeted tetrahedrally symmetric tetramine.[13] Triamine **7** was viewed as a potential ionophore for lithium, and several known azacages are known to bind this cation.[14] The current results on basicities of triamines of type **5** are relevant to the question of cation selectivity (H^+ vs Li^+) for **7** and related hypothetical structures. Many of the compounds reported here might also be of use in future syntheses of more elaborate cage polyamines.



Results

Synthesis. Following the Atkins−Richman method for macrocyclic polyamine synthesis,[15] *N*,*N*′,*N*″-tritosylbis(3-aminopropyl)amine **8**[8a,e] was prepared from commercial bis(3-aminopropyl)amine, tosyl chloride and aqueous $NaOH/CH_2Cl_2$,

Scheme 1 [a]



[a] (a) NaH, DMF, 100 °C (50%); (b) H_2SO_4, 100 °C (55%); (c) $KHCO_3$, 2-butanol, reflux; KOH, H_2O, $CHCl_3$ (31%); (d) CH_2O, $NaCNBH_3$, CH_3CN, HOAc; KOH, H_2O, $CHCl_3$ (50%); (e) K_2CO_3, 2-propanol, reflux; NaOH, H_2O, $CHCl_3$ (70%); (f) HCO_2H, CH_2O (43%); (g) 9-BBN, THF; H_2O_2, NaOH, THF, H_2O, EtOH (97%, 4:1 mixture of diastereomers).

and obtained as a crystalline solid in 90% yield (Scheme 1). Cyclization by treatment of **8** with NaH, followed by slow addition of ditosylate **9**,[16] gave tritosyl macrocycle **10**.[8a,e,16b,17] A 50% yield of pure **10** was obtained after precipitation of higher-molecular weight material by addition of hexane to a hot toluene solution of the crude product, evaporation of the supernatant solution and recrystallization. Removal of the tosyl groups in hot sulfuric acid, followed by vacuum distillation from KOH, gave macrocycle **6**,[8a−e,17] the key intermediate for synthesis of all bicyclic triamines discussed in this article.

Reaction of macrocyclic triamine **6** with 1,3-diiodopropane (**11**) was carried out by simultaneous, slow addition of these reactants to a pot of hot solvent to minimize the formation of higher-molecular weight byproducts. A low yield of bicyclic triamine **12** was obtained when boiling 2-propanol was used, indicating that the rate of cyclization was too slow at this temperature. Substitution of boiling 2-butanol resulted in a 50% yield of **12**·HI after removal of impurities by trituration, followed by recrystallization. Treatment of this salt with 5 M aqueous KOH gave free base **12** in 61% yield after distillation.

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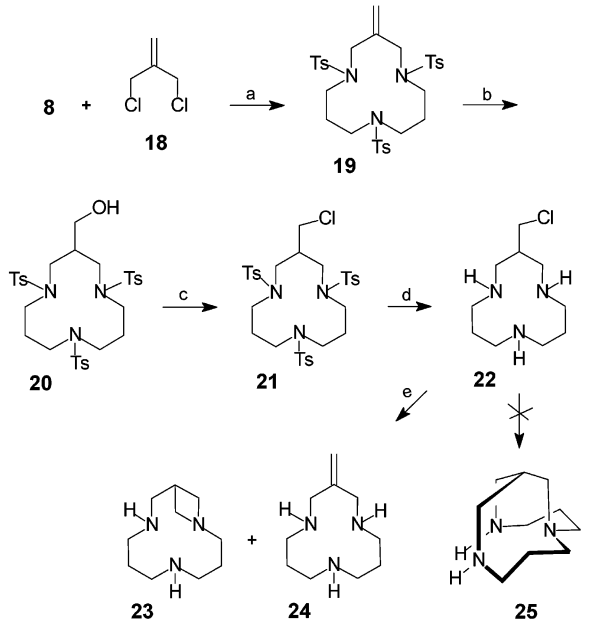
Scheme 2 [a]



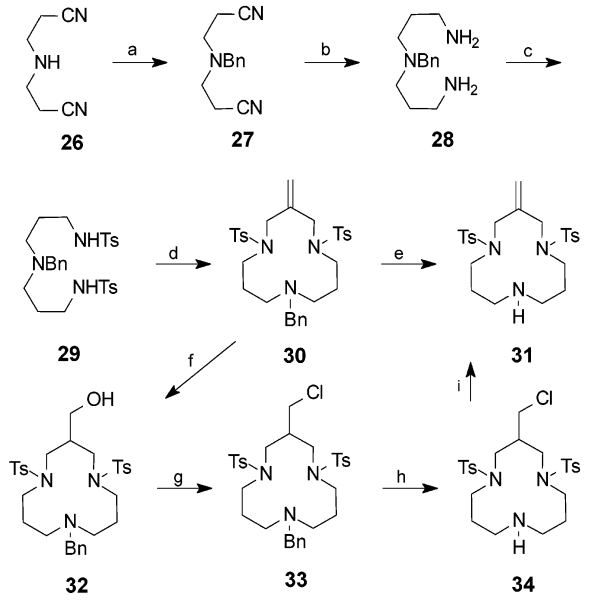
[a] (a) NaH, DMF, 100 °C (59%); (b) thexylborane, THF, reflux; H_2O_2, NaOH, THF, H_2O, EtOH (66%); (c) PPh_3, CCl_4, DMF (64%); (d) H_2SO_4, 100 °C; (e) K_2CO_3, 2-propanol, reflux (58%, two steps).

Methylation of **12** to **13** could be carried out in ca. 60% yield by means of the Eschweiler−Clarke reaction (formaldehyde/formic acid),[18] but a higher yield was obtained when the HI salt was treated with formaldehyde and sodium cyanoborohydride[19] (Scheme 1).

As previously communicated,[9] simultaneous addition of macrocycle **6** and 2-iodomethyl-3-iodo-1-propene (**14**)[20] to boiling 2-propanol gave bicyclic triamine **15**, which could be isolated from the reaction mixture in good yield as the free amine. Eschweiler−Clarke methylation of **15** gave **16** in moderate yield. Reaction of **15** with various organoboranes was also investigated in order to produce potential intermediates for the synthesis of tricyclic triamine **7**. Best results were obtained with 9-BBN in THF, which gave a 4:1 mixture of stereoisomeric primary alcohols (**17**). The relative configurations of these two products (**17a** and **17b**) were not determined.

In an approach to bicyclic triamine **25**, a series of 3-substituted 1,5,9-triazacyclododecanes were synthesized (Scheme 2). Entry to this series was provided by cyclization of tritosyltriamine **8** with 2-chloromethyl-3-chloro-1-propene (**18**) by the Atkins−Richman method.[15] Hydroboration of the exocyclic methylene group of the product (**19**) with BH_3·THF and oxidation with alkaline hydrogen peroxide gave a 1:1 mixture of primary alcohol **20** and the corresponding tertiary alcohol. Use of thexylborane cleanly gave **20**, which was used in the next step without purification. The planned bicyclization required that the hydroxyl group of **20** be transformed into a leaving group that would be stable to the conditions of detosylation. Reaction of **20** with triphenylphosphine and CCl_4[21] gave chloromethyl derivative **21**, which was detosylated in hot sulfuric acid to give chloromethyl triamine **22** as an oil. In an attempt to effect displacement of chloride by N9, a solution of crude **22** in 2-propanol was heated with K_2CO_3. Distillation of the crude product of this reaction from KOH gave a pure sample of bicyclic triamine **23**, rather than the desired product (**25**). In the presence of potassium hydroxide, a small amount of alkene **24** was formed in addition to bicycle **23**. Bicyclic target **25** was not detected under any reaction conditions, indicating the following order of decreasing reactivity for **22**: four-membered ring formation > elimination ≫ eight-membered ring formation.

Scheme 3 [a]



[a] (a) BnCl, $NaHCO_3$, H_2O, reflux (68%); (b) H_2, Ni, NaOH, EtOH (81%); (c) TsCl, NaOH, CH_2Cl_2, H_2O (95%); (d) NaH, **18**, DMF, 100 °C (55%); (e) 1. ACE-Cl, $ClCH_2CH_2Cl$, reflux; 2. CH_3OH (78%); (f) 1. thexylborane, THF, reflux; 2. H_2O_2, NaOH, THF, EtOH, H_2O; (g) PPh_3, CCl_4, DMF; (h) H_2, Pd/C, 2-propanol (25%); (i) K_2CO_3, 2-propanol, reflux (100%).

An alternate approach to triamine **25** involved protection of N9 by a group that could be removed in the presence of tosylamide substituents at N1 and N5. The benzyl protection group was chosen, and various transformations were carried out (Scheme 3). *N*,*N*-Bis(2-cyanopropyl)benzylamine (**27**) was prepared previously[22] by conjugate addition of benzylamine to acrylonitrile at 140 °C. We employed a two-step procedure that was more amenable to larger-scale preparations involving reaction of acrylonitrile with ammonia at room temperature,[23]

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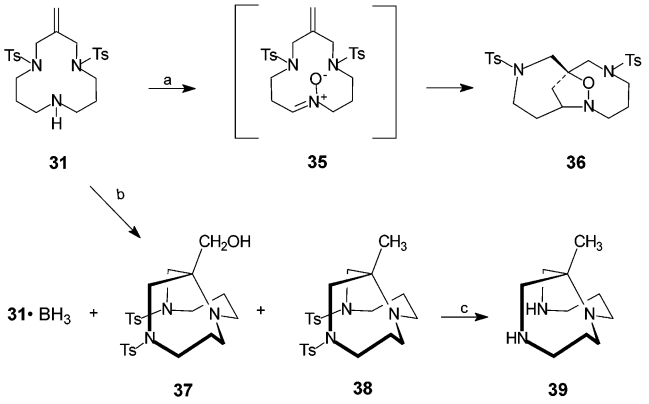
Scheme 4 [a]



[a] (a) *m*-CPBA, K_2CO_3, CH_2Cl_2; (b) 1. $Hg(OAc)_2$, EtOAc; 2. $NaBH_4$; 3. NaOH, H_2O; (c) H_2SO_4, 100 °C (46%).

followed by alkylation with benzyl chloride. Raney nickel catalyzed hydrogenation of **27** gave *N*,*N*-bis(2-aminopropyl)-benzylamine **28**[22] in good yield. Other protecting groups, including *t*-BOC, acetyl, benzoyl, and *p*-anisoyl, were investigated but were either too labile under the alkaline hydrogenation conditions (step b) or were too stable toward deprotection in step e (cf. Scheme 3).

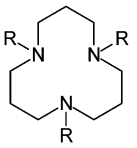
Tosylation of triamine **28**, macrocyclization of **29** with 3-chloro-2-chloromethyl-1-propene (**18**), hydroboration/oxidation of alkene **30**, and conversion of alcohol **32** to chloride **33** were carried out as described for synthesis of tritosyl analogue **21** (cf. Scheme 2). The benzyl protecting group in **33** was cleaved by means of catalytic hydrogenolysis.[24] Removal of the benzyl group in alkene **30** was accomplished in good yield by means of α-chloroethyl chloroformate (ACE-Cl).[25] Both of the resulting ditosyl macrocycles (**31** and **34**) were considered potential precursors to triamine **25**. Attempted conversion of **34** to **25** by reaction with K_2CO_3 in hot 2-propanol resulted in quantitative formation of alkene **31**. These same conditions gave the least amount of alkene **24** in the cyclization of **22** to **23**, again indicating that elimination is much faster than bicyclization via eight-membered ring formation in the 1,5,9-triazacyclododecane ring system.

Several attempts were made to cyclize **31** by intramolecular attack of N9 on the exocyclic methylene carbon atom (Scheme 4). The general strategy was to produce an electrophilic three-membered ring intermediate (e.g., an epoxide or mercurinium ion), which might undergo nucleophilic displacement at the less hindered position. Alternately, attack by nitrogen at the tertiary position would afford bicyclic isomers containing seven-membered, rather than eight-membered rings. An attempt to epoxidize the double bond of **31** with *m*-CPBA instead gave tricyclic isoxazolidine **36**, apparently via intramolecular 1,3-dipolar cycloaddition of nitrone **35**, produced by oxidation of the corresponding hydroxylamine intermediate.[26] Bromination of **31** was also investigated, but a complex mixture of products was obtained. Several attempts were made to produce the bicyclic skeleton of amine **25** by intramolecular aminomercuration[27] of **31**, followed by reduction of the organomercury product with sodium borohydride. Regardless of the Hg^{2+} counterion ($CF_3CO_2^-$, $CH_3CO_2^-$, Br^-, Cl^-, NO_2^-, or O^{2-}) or solvent (acetonitrile, benzene, ether, ethyl acetate, DME, dioxane, or THF), borane complex[28] **31**•BH_3, bicyclic alcohol **37**, and bridgehead methyl analogue **38** were the only isolable products. Product **38** was anticipated from nucleophilic attack at the tertiary carbon of the mercurinium intermediate, but **37** likely arises from solvolysis of a tricyclic aziridinium intermediate.[29] To compare the basicity of bicyclic amine **39** with those of **12**, **13**, **15**, and **16**, the tosylamide groups of **38** were cleaved in hot sulfuric acid.

Table 1. Basicities of Triamines **6**, **12**, **13**, **15**, **16**, **23**, and **40**; pH Values of Aqueous solutions (5 mM, 25 °C) and pK_a Values Measured by Titration with 0.1 M HCl, 25 °C

	pH	pK_{a1}	pK_{a2}	pK_{a3}
6[a]	12.8	12.6 ± 0.1 (12.2)[f]	7.49 ± 0.02	2.07 ± 0.07
6[b]	11.8	(11.4)[f]	7.41 ± 0.01	2.17 ± 0.02
6[c]		12.60 ± 0.05	7.57 ± 0.02	2.41 ± 0.03
6[d]		13.15 ± 0.05	7.97 ± 0.02	
6[e]		12.3 ± 0.1	7.3 ± 0.1	2.4 ± 0.1
12	11.4	(11.1)[f]	4.50 ± 0.01	(2.8)[g]
13	11.4	(11.0)[f]	4.89 ± 0.01	(2.9)[g]
15	11.8	(11.3)[f]	4.36 ± 0.06	(2.7)[g]
15[a]	13.1	(12.6)[f]	4.29 ± 0.08	(1.8)[g]
15[b]	11.7	(11.2)[f]	4.16 ± 0.08	(2.6)[g]
16	11.8	(11.3)[f]	4.88 ± 0.07	(2.7)[g]
23	11.7	(11.3)[f]	6.24 ± 0.01	(2.6)[g]
39	10.6	9.7 ± 0.1	7.16 ± 0.01	1.71 ± 0.02
40[e]		12.8 ± 0.1	5.7 ± 0.1	2.9 ± 0.1

[a] Concentration 0.1 M (25 °C). [b] Concentration 5 mM (20 °C). [c] Reference 8c, potentiometric titration of **6**•3HCl in 0.1 M aq KNO_3 (25 °C). [d] Reference 8d, ^{1}H NMR titration of **6**•3HCl in 0.05 M aq KNO_3 (25 °C). [e] Reference 8f, ^{1}H NMR titration of free base in D_2O, corrected for isotope effect (25 °C). [f] Estimated from pH at 0.5 equiv point. [g] Estimated from pH at 2.5 equiv point.



6 R = H
40 R = CH_3

Basicities. The basicities of the six bicyclic triamines **12**, **13**, **15**, **16**, **23**, and **39** were compared to that of the parent monocyclic triamine **6** in two ways. First, the pH values of aqueous solutions were measured (Table 1). At concentrations of 5 mM, all pH values fell in the range of 11.4−11.8, except for that of triamine **39** (10.6). More concentrated solutions (0.1 M) of **6** and **15** gave pH values of 12.8 and 13.1, respectively, indicating that **15** is a significantly stronger base than **6**. A second comparison was made by potentiometric titration of the free amines (5 mM) with 0.1 N HCl. By this procedure, the pH remained below 12, avoiding alkaline error in the glass pH electrode measurements. The titration curves showed that the ionization constants of the monoprotonated and triprotonated forms (pK_{a1} and pK_{a3}, respectively) could not be measured potentiometrically for triamines **12**, **13**, **15**, **16**, and **23** because

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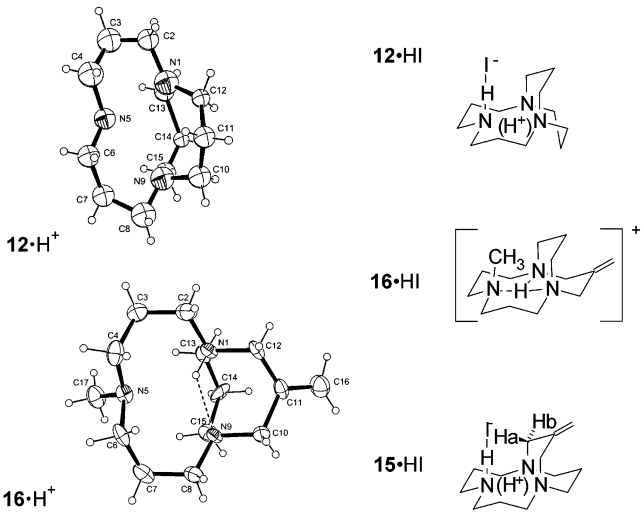

Figure 1. Conformations of HI salts of **12**, **15**, and **16** observed in the X-ray crystal structures. Cavity hydrogen atoms not located crystallographically are shown in parentheses in the skeletal diagrams. Crystal structure diagrams of **16**·H$^+$ and **12**·H$^+$ (one of two equivalent cations in the asymmetric unit) are shown with ellipsoids at 25% probability.

the pK_{a1} values were too large and the pK_{a3} values were too small. The titration curve of a 0.1 M solution of **15** matches that of 0.1 M sodium hydroxide. Table 1 lists the pK_{a2} values for **12**, **13**, **15**, **16**, and **23** and all three values measured for **39** and **6**. These thermodynamic pK_a's were calculated from protonation curves with correction for the activities of all ions in solution. The pK_a's calculated for macrocycle **6** are consistent with previously reported pK_a values[8c,d,f] when the latter are corrected for ionic strength.

Crystallography. The HI salts of triamines **12** and **16** were crystallized and their structures were determined by X-ray diffraction at the University of Reading. The conformations of the triamines in the crystal structures are compared in Figure 1 with that of **15**·HI, the crystal structure of which was previously reported.[9] There are two conformationally equivalent molecules of **12**·HI in the asymmetric unit and one is represented in Figure 1 as **12**·H$^+$. The structure of **12**·HI is not very accurate because the crystal diffracted weakly, but the essential features are clear. The conformations of the two cations in the asymmetric unit are almost identical, but they differ from those of **15**·HI and **16**·HI in one major way. One of the three-carbon bridges of **12**·HI is bent away from the other, while both bridges are bent toward each other in the HI salts of **15** and **16**.

Apart from the orientation of one of the small bridges, there are very minor differences between the crystal conformations of **12**·HI, **15**·HI, and **16**·HI. The presence of an exocyclic double bond in **15** and **16** alters bond angles according to the different requirements of sp^2 and sp^3 carbon. The four structures are numbered as shown in Figure 2. This figure also displays the N−N distances; the torsion angles are compared in Table 2. Particularly striking is the equivalence of the conformations of **15**·HI and **16**·HI; no torsion angle differs by more than 15°. An approximate mirror plane bisects each structure, passing through N5, C14, and C11, which is part of the exocyclic double bond in **15** and **16**. Staggering of all ethylene units produces a cyclohexane-like conformation in which adjacent atoms of the long bridge alternate above and below the best plane of the macrocycle. In **15**·HI the unsaturated bridge is on the same side as C3 and C7 of the long bridge, whereas in **16**·HI it is on the opposite side. Only for **16**·HI could a hydrogen atom be located in the cavity by difference Fourier maps, and it is covalently bonded to bridgehead nitrogen N1.

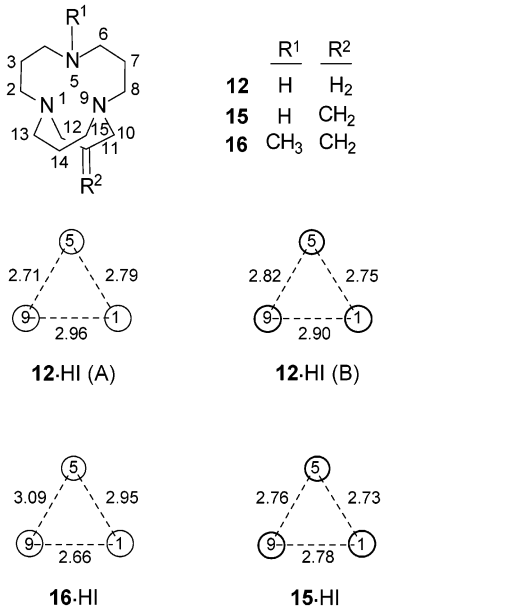

Figure 2. Scale diagram showing N−N distances observed in X-ray crystal structures of HI salts of **12**, **15**, and **16**. Arrangement: N1 (bottom right), N5 (top), N9 (bottom left).

Table 2. Torsion Angles (deg) in the Crystal Structures of the HI Salts of Bicyclic Triamines **12**, **15**, and **16**

torsion	**16**·HI	**15**·HI	**12**·HI(A)	**12**·HI(B)
N(1)−C(2)−C(3)−C(4)	57.7	59.5	50.9	64.6
C(2)−C(3)−C(4)−N(5)	−71.8	−71.7	−66.7	−81.1
C(3)−C(4)−N(5)−C(6)	154.9	175.0	−179.4	−178.1
C(4)−N(5)−C(6)−C(7)	−161.6	−177.8	−176.7	−176.1
N(5)−C(6)−C(7)−C(8)	77.9	71.5	67.8	62.4
C(6)−C(7)−C(8)−N(9)	−57.0	−58.7	−58.5	−40.6
C(7)−C(8)−N(9)−C(15)	−68.9	−74.7	−80.4	−88.9
C(8)−N(9)−C(15)−C(14)	169.5	169.7	177.9	168.9
N(9)−C(15)−C(14)−C(13)	−50.8	−44.2	−61.8	−45.3
N(1)−C(13)−C(14)−C(15)	47.9	41.0	66.2	53.8
C(12)−N(1)−C(13)−C(14)	63.2	66.4	44.6	52.3
C(2)−N(1)−C(13)−C(14)	−172.2	−167.9	−175.4	−168.2
C(13)−N(1)−C(12)−C(11)	−61.6	−58.2	−110.1	−111.7
C(13)−N(1)−C(2)−C(3)	67.7	75.1	78.5	73.6
C(14)−C(15)−N(9)−C(10)	−65.3	−60.4	−48.9	−60.9
C(15)−N(9)−C(10)−C(11)	69.6	57.6	106.5	103.4
N(9)−C(10)−C(11)−C(12)	44.1	54.6	−65.4	−60.8
C(10)−C(11)−C(12)−N(1)	−48.7	−53.8	69.9	65.3

NMR Spectroscopy. Bicyclic triamines **12**, **13**, **15**, and **16** have very similar structures, differing only in the presence of an exocyclic double bond at C11 and a methyl group on the bridge nitrogen atom (N5, cf. Figure 2 for numbering scheme). The NMR spectra of these triamines and their HI salts are of interest for comparing their solution and crystal conformations, particularly with respect to interaction of the bridge nitrogen with the protonated cavity. As reported previously,[9] the results of two-dimensional ^{1}H and ^{13}C NMR studies (COSY, CSCM, and NOESY) indicate that the crystal and solution ($CDCl_3$) conformations of **15**·HI are very similar. The conformational bias of the C10−12 bridge bearing the exocyclic double bond is toward the smaller (C13−15) bridge. This is revealed by a significant NOE interaction between the vinylic protons and an axial proton on C14. Moreover, allylic coupling is observed for only one pair of protons on C10/12 (δ 3.88, ^4J = 1.7 Hz),

Table 3. ^{13}C and ^{1}H NMR Peak Assignments for Bicyclic Triamines **12**, **13**, **15**, **16**, and Their HI Salts

		C2	C3	C4	C10	C11	C13	C14	$=CH_2$	CH_3
12	(^{13}C)[a]	52.7	27.7	61.8	53.3	30.0	53.3	30.3	–	–
12·HI	(^{13}C)[b]	49.2	23.6	60.5	53.3	27.9	53.3	27.9	–	–
	(^{1}H)[b]	2.95	2.05	2.79	2.59, 2.95	1.74	2.59, 2.95	1.74	–	–
13	(^{13}C)[a]	56.3	29.4	58.9	54.4	31.4	54.4	31.4	–	44.6
13·HI	(^{13}C)[a]	59.0	22.6	59.4	54(br)	24(br)	54(br)	24(br)	–	42.8
15	(^{13}C)[b]	59.9	26.3	51.7	60.1	149.5	55.0	29.31	114.5	–
15·HI	(^{13}C)[b]	58.5	22.4	48.6	60.2	145.5	54.6	27.2	115.5	–
	(^{1}H)[b]	2.5−3.5	1.9, 2.2	2.5−3.5	3.05, 3.88	–	2.5−3.5	1.5, 2.1	5.00	–
16	(^{13}C)[b]	53.8	27.1	57.4	62.0	150.9	53.8	31.0	114.2	43.8
16·HI	(^{13}C)[b]	57.8	21.5	55.6(br)	58.3	139.6	55.6(br)	21.5	115.3	42.1

[a] CD_3CN, 25 °C; [b] $CDCl_3$, 25 °C.

and the other pair of protons on C10/12 (geminal to the first pair) is shielded (δ 3.05) by the antiperiplanar bridgehead nitrogen electron pairs.[30]

Better spectral dispersion was observed in the ^{1}H NMR spectra of the salts than the neutral forms of these triamines, suggesting that their conformational rigidity increases upon protonation. The ^{1}H and ^{13}C NMR peaks of **12**·HI were assigned to specific nuclei by means of two-dimensional NMR techniques (COSY and CSCM). ^{1}H and ^{13}C NMR assignments for **12**·HI and **15**·HI are given in Table 3, along with ^{13}C assignments for **12**, **13**, **13**·HI, **15**, **16**, and **16**·HI made by comparison. Broad peaks were observed in the NMR spectra of *N*-methylated salts **13**·HI and **16**·HI, suggesting the presence of conformational exchange processes with coalescence occurring near room temperature. Variable-temperature (VT) NMR studies were performed, anticipating that the activation energies for inversion of the bridge nitrogen could be related to the strength of interaction between N5 and the proton in the cavity.

VT ^{1}H NMR spectra of **13**·HI were complicated by overlapping multiplets, but clean two-site exchange was observed in the temperature range of −20 to +60 °C in CD_3CN for the ^{13}C resonances C10, 12, 13, and 15, the α-carbons of the smaller bridges. At −20 °C two peaks of equal intensity occur at 51.6 and 54.4 ppm, which coalesce into a single peak at 38 °C. Complete bandshape analysis of the ^{13}C NMR spectra obtained at 10, 20, 30, 35, 38, 40, and 50 °C by iteratively fitting curves calculated for a system of two uncoupled nuclei in exchanging magnetic environments gave a series of rate constants that were used to calculate a free energy of 14.4 ± 0.2 kcal/mol. No significant variation of the calculated energy was seen over a 40 °C temperature range, so the enthalpic and entropic contributions could not be measured.

The observation of two-site exchange for atoms of the smaller bridges of **13**·HI is consistent with a solution conformation similar to that observed in the solid-state structure of **12**·HI (cf. Figure 1), with the exception that the axial hydrogen on N5 in the large bridge is replaced by a methyl group. The different magnetic environments of the two smaller bridges interchange upon inversion of both N5 and the gauche conformations about the C−C and C−N bonds in the large bridge. In **16**·HI, the two three-carbon bridges are differentiated by the exocyclic methylene group; the N5 methyl group is either syn or anti to the bridge bearing the double bond. Interconversion of these nonequivalent conformations requires both cleavage of the N5 hydrogen bond and nitrogen inversion. These are postulated as

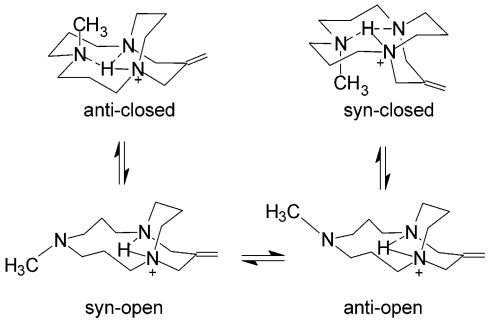

Figure 3. Proposed mechanism for conformational inversion of **16**·HI via hydrogen bond cleavage, followed by nitrogen inversion.

discrete steps in Figure 3, showing "opening" of the hydrogen-bonded anti-closed conformation to form the syn-open, N5 inversion to the anti-open, and reformation of the hydrogen bond to the protonated cavity to produce the syn-closed conformation.

The ^{1}H NMR spectrum of **16**·HI in $CDCl_3$ showed broad peaks at room temperature, but they resolved to two sets of sharp resonances at −30 °C. Integration of the vinylic proton signals at δ 5.088 and 5.183 ppm gave a ratio of 47:53, respectively. Complete line shape analysis of 12 spectra recorded in the range of 6−40 °C (T_c 20 °C) gave 15.1 ± 0.1 kcal/mol as the activation free energy for interconversion of the syn-closed and anti-closed conformations. The resonances of the two sp^2 carbon atoms (C11 and CH_2) were also used to measure this activation energy. At −60 °C in $CDCl_3$, these singlets occurred at δ 113.6 and 115.2 ppm for the CH_2 carbon, and at 138.3 and 139.8 ppm for C11. Curve-fitting of seven spectra recorded in the range of 10−50 °C gave $\Delta G^{\ddagger} = 14.9 \pm 0.2$ kcal/mol from the CH_2 line shapes and 14.8 ± 0.3 kcal/mol from C11. A coalescence temperature of 38 °C was observed in both cases. Slight temperature dependence of the chemical shifts was observed. This was corrected by adjusting the slow-exchange chemical shifts, but not the chemical shift separation, used for the two sites in calculating the curves.

The mechanism for conformational exchange shown in Figure 3 is strictly unimolecular, so experiments were performed at different concentrations to test whether intermolecular proton-transfer processes might be involved. For example, VT-NMR studies of **16**·HI were performed in $CDCl_3$ at different concentrations in the range of 12−55 mM, but no variation of the 20 °C coalescence temperature was observed. Moreover, a 1:1 mixture of **13** and **13**·HI (both 0.13 M in $CDCl_3$ at 25 °C) produces a slow-exchange ^{13}C NMR spectrum showing separate signals for the syn and anti forms of **13**·HI.[31] This indicates that even if low concentrations of the free base forms of **13**

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and **16** are present in solutions of their HI salts, this would not significantly affect the rate of conformational exchange.

Dynamic NMR studies were also performed on free base **16** to observe the effect of cavity protonation on the activation energy for nitrogen inversion. At −120 °C in $CD_2Cl_2/CDCl_3$ (2:1, v/v) two sets of ^{13}C NMR resonances were observed corresponding to a population ratio of 35:65. A coalescence temperature of −93 ± 3 °C was measured for the C11 carbon resonating at δ values of 148.9 and 149.6 ppm at −120 °C. Line-shape analysis at six temperatures in the range of −100 to −85 °C gave an activation free energy of 8.8 ± 0.3 kcal/mol for nitrogen inversion. This value is similar to that observed for medium ring amines, e.g., *N*-methylhomopiperidine (6.8 kcal/mol).[32]

Modeling. To address the hydrogen bonding pattern in **15**·HI, for which the position of the hydrogen atom in the cavity was not crystallographically determined, ab initio calculations at the HF/6-31+G* level using Gaussian98 were first used to model **16**·HI. The structure of the salt was minimized starting with the geometry observed in the crystal structure, including the identified location of the hydrogen atom bonded to bridgehead nitrogen atom N1 but omitting the iodine atom (cf. Figs. 1, 2). The calculated structure differed little from the crystal structure; N1−N9, and N1−N5 distances increased by only 0.06 and 0.03 Å, respectively, whereas the N5−N9 distance increased by 0.09 Å. This result is consistent with the presence of a strong hydrogen bond between N1 and N9 (2.72 Å) and a weaker hydrogen bond to the bridge nitrogen (N5). When the geometry was minimized after moving the hydrogen atom in the crystal structure from N1 to N5, the resulting distances were: N1−N5, 2.93 Å; N5−N9, 2.93 Å; and N1−N9, 2.85 Å. The calculated energy also increased by 4.5 kcal/mol. When the proton was removed from **16**·H^+ the distances were calculated as follows: N1−N5, 3.27 Å; N5−N9, 3.27 Å; and N1−N9, 2.85 Å.

These quantum mechanics calculations were then repeated on the crystal geometry of **15**·H^+, placing the second hydrogen atom first on N5, then on N1. In both cases the N−N distances increased, but the deviation was less with the hydrogen atom on N5. Relative to the crystal geometry in **15**·HI, the N−N distances increased by the following increments with the hydrogen on N5: N1−N5, 0.09 Å; N5−N9, 0.06 Å; N1−N9, 0.06 Å. With the hydrogen on N1, the increases were: N1−N5, −0.05 Å; N5−N9, 0.32 Å; N1−N9, 0.13 Å. The results of these calculations are thus in better agreement with a structure of **15**·H^+ in which the internal hydrogen atom is covalently bonded to the bridge nitrogen (N5), rather than to a bridgehead nitrogen (N1 or N9), although the calculated energy of the latter is lower by 3.8 kcal/mol.

The inversion process observed in **16** and **16**·HI by dynamic NMR spectroscopy was then modeled using Gaussian98. Attempts to invert N5 followed by geometry optimization with Gaussian98 gave extended conformations in which one or both of the C3−C4 and C6−C7 torsions went from gauche (<120°) to trans (>120°). Both results suggest that inversion of N5 in conformations similar to that of **16**·HI is prohibited by steric interaction between the bridge methyl group and the C13−C15 bridge. We were also unable to generate a transition state based on the crystal conformation in which N5 had a trigonal environment.

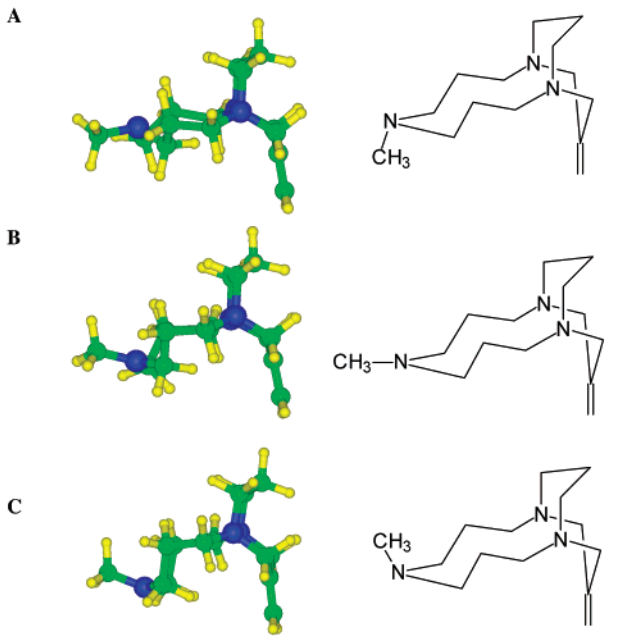


Figure 4. Conformational models of inversion in **16**. Relative energies determined at the HF/6-31+G* level (kcal/mole): A (syn-open, −6.34); B (planar TS, 00.0); C (anti-open, −1.31). Color scheme: C, green; H, yellow; N, blue.

It therefore seems likely that N5 inversion will occur within a different conformation. One major conformation in which N5 inversion can occur easily in **16** is shown in Figure 4. This conformation has mirror symmetry and differs from that in **16**·HI mainly at the C3−C4 and C6−C7 bonds, which are anti rather than gauche. Planar transition state **B** was obtained using the QST2 method in Gaussion98 using structures A and C as input structures. The obtained structure was confirmed as a transition state by the presence of one negative frequency. The structures of **A**, **B**, and **C** had energies of −709.13655, −709.12644, and −709.12853 au at the HF/6-31+G* level. In all of these structures N5 is 4.2−4.3 Å from either bridgehead atom, indicating that there could be no direct interaction between N5 and a proton located on N1 or N9 in the inversion transition state.

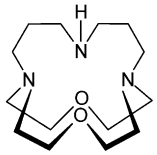
We then repeated this calculation with N1 protonated using the three structures in the same conformations as shown in Figure 4. We obtained a significantly different result. The structures of **B** and **C** were geometry optimized at the HF/6-31+G* level with converged energies of −709.53805 and −709.53815 au, respectively. Structure **B** was confirmed as being a transition state by the presence of one negative frequency. The negligible difference between the energies of **B** and **C** can readily be explained by examining the two structures. In **B** the nitrogen atom is trigonal, in **C** it becomes tetrahedral but with very little movement of other atoms. This is because the presence of the proton on N1 holds the bridge in a chairlike conformation, and pseudoaxial β-hydrogens prevent the methyl group on N5 from approaching the cavity of the macrocycle. Geometry optimization of **A** proved more difficult. The input structure almost converged to a structure close to the input structure with an energy of −709.52960 au, but only three of

(31) At equal concentrations in $CDCl_3$ **12** and **12**·HI give a rapid-exchange ^{13}C NMR spectrum, even down to −40 °C.
(32) Lambert, J. B. In *Topics in Stereochemistry*; Allinger, N. E., Eliel, E. L., Eds.; Wiley-Interscience: NY, 1975; Vol. 6, pp 19−105.

the four default convergence criteria in Gaussian98 were satisfied. After continued geometry optimization the structure converged to the anti-closed structure of Figure 3 with an energy of −709.55854 au. The closeness of the energies of **C** and **B** indicates that the barrier to inversion from **C** to **A** is negligible in **16**·HI, but that the syn-open structure of **A** is unstable to ring closure to form the anti-closed structure, which is stabilized by hydrogen bond formation.

Discussion

Strong N−N interaction in proton sponges not only enhances the basicity of the neutral form, it also decreases the basicity of the monocation.[1a,b] Cooperation between all three nitrogens of a triamine in stabilizing a single proton should accordingly increase the pK_a of the monoprotonated form (pK_{a1}) and decrease the pK_a of the dication (pK_{a2}).[1c] An example is 12,17-dioxa-1,5,9-triazabicyclo[7.5.5]nonadecane (**41**), with pK_{a1} > 13 and pK_{a2} = 6.20.[33] The resulting pK_a difference (ΔpK_a = pK_{a1} − pK_{a2}) of more than 6.8 log units results from the necessity of breaking a strong N···H$^+$ hydrogen bond during the second protonation. For comparison, the pK_{a1} and pK_{a2} values for 1,3-diaminopropane are 10.56 and 8.76, respectively (ΔpK_a = 1.8).[1c]



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All six triamines studied here (**12**, **13**, **15**, **16**, **23**, and **39**) have the 1,5,9-triazacyclododecane ring embedded in their bicyclic structures; thus the pK_a's of these systems reflect the consequences of bridging and substitution on the stability of the monoprotonated form. The average ΔpK_a value for 1,5,9-triazacyclododecane (**6**) calculated from the pK_a's listed in Table 1 is 5.1, indicating that the macrocyclic framework conformationally stabilizes interaction between the nitrogen atoms. The tri-*N*-methyl derivative **40** has a similar pK_{a1} value (ca. 12.8), but the monoprotonated form is a weaker base (pK_{a2} 5.7 vs ca. 7.5). This suggests that at least one of the three nitrogens is responsible for greater stabilization in **40**·HI$^+$ than in **6**·HI$^+$. Bicyclic triamines **12**, **13**, **15**, and **16** all contain a three-carbon bridge across two nitrogens of 1,5,9-triazacyclododecane. Their pK_{a1} values could not be measured accurately by potentiometric titration in water, but the pH of a 0.1 M aqueous solution of **15** (13.1) is greater than that of a 0.1 M aqueous solution of **6** (12.8). The pK_{a1} of **15** must be at least 13, while the pK_{a2} (4.4) is lower than that of **6**. The ΔpK_a of **15** is thus at least 3.5 units greater than that of **6**, showing that the three-carbon bridge considerably stabilizes the monocation. The ΔpK_a values for **12**, **13**, and **16** are slightly smaller than that for **15**, indicating a somewhat lower degree of stabilization of the monoprotonated form.

Bicyclic triamines **23** and **39** are isomeric structures containing a one-carbon bridge from N1 to C3 (in **23**) or a zero-atom bridge from N1 to C7 (in **39**). The pK_a values of **23** are similar to those of **6** and **40**, indicating that the incorporation of an azetidine ring in **23** does not strongly affect the N−N interactions present in **6** and **40**. Triamine **39** has a smaller pK_{a1} (9.7) and a ΔpK_a of only 1.4 units. Thus, the bicyclo[5.5.0] skeleton of **39** does not facilitate interaction between the three nitrogens; the bridgehead nitrogen may even prefer "out" pyramidalization,[5b] with the electron pair oriented away from the two bridge nitrogens.

Previous NMR and crystallographic studies established similarity between the solution- and solid-state conformations of **15**·HI.[9] The crystal structures of **12**·HI and **16**·HI reflect weaker observed stabilization of the monoprotonated form. The cavity proton of **15**·HI was not located crystallographically, but the nearly perfect equilateral triangle formed by the three nitrogens (cf. Figure 2) suggests that they are participating almost equally in a hydrogen-bonded network. In **12**·HI, the N1−N9 distance is lengthened by ca. 0.15 Å. Another difference is that in **12**·HI one of the three-carbon bridges is oriented away from the other, while in **15**·HI they are oriented together, possibly because of less steric hindrance between the sp^2 carbon at C11 and the "axial" hydrogen on C14. This conformation may permit more effective hydrogen bonding between the bridge nitrogen (N5) and both bridgehead nitrogens (N1 and N9). In **16**·HI, weaker stabilization of the monocation is manifested by lengthening of both bridge−bridgehead nitrogen distances (N1−N5 and N5−N9) by 0.2−0.3 Å. In **16**·HI, the cavity proton was crystallographically localized on one bridgehead nitrogen (N1); thus, bifurcation of the hydrogen bond occurs unequally between N5 and N9.

The Gaussian calculations at the HF/6-31+G* level carried out on **12**·H$^+$, **13**·H$^+$, **15**·H$^+$, and **16**·H$^+$ all show that the structure with the internal hydrogen atom bonded to the bridgehead nitrogen atom N1 (or N9) has a lower energy by 3.35, 4.32, 4.69, and 3.95 kcal/mol, respectively, relative to the structure with the internal hydrogen atom bonded to N5. However, the correlation between these results and the crystal structures of **12**·H$^+$, **15**·H$^+$, and **16**·H$^+$ is not straightforward. In the crystal structure of **16**·H$^+$ the extra hydrogen atom was located on the bridgehead N1, and the internal N−N distances obtained from the cation optimized in Gaussian98 are comparable with those obtained experimentally. The shortest distance, and apparently the strongest hydrogen bond, is between N1 and the other bridgehead (N9). The longer N1−N5 distance implies unequal bifurcation of the hydrogen bond between bridge and bridgehead positions. However, in **15**·HI the experimental structure and, in particular, the N−N distances are more comparable with the theoretical structure obtained when the hydrogen is located on the bridge (N5). This equally bifurcated hydrogen-bonded structure is supported by shorter distances for *both* N1−N5 and N5−N9 (see Figure 2), and the expansion of the N1−N9 distance is apparently a consequence of H-localization on N5. The resulting N_3 triangle in **15**·HI is nearly equilateral, permitting rapid migration of the proton between the three basic sites in solution. Steric hindrance caused by the methyl group in **16**·HI apparently reduces stabilizing interaction between the bridge and bridgehead sites, and this is reflected by the smaller ΔpK_a for **16**·HI than for **15**·HI. The experimental dimensions in **12**·HI are similar to those obtained in **15**·HI, and the N−N distances are compatible with the theoretical structure in which N5 is protonated rather than N1.

The results of dynamic NMR studies on the HI salts of *N*-methylated triamines **13** and **16** gave 14.4 ± 0.2 and an

(33) Bianchi, A.; Ciampolini, M.; Micheloni, M.; Chimichi, S.; Zanobini, F. *Gazz. Chim. Ital.* **1987**, *117*, 499−502.

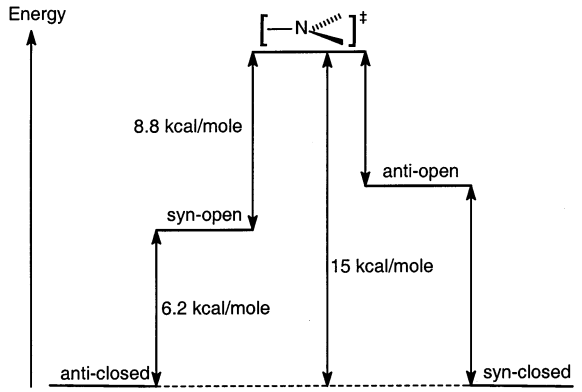

Figure 5. Energy profile for conformational inversion of **16**·HI, assuming equivalent inversion barriers of free amine **16** and the open conformations of **16**·HI (see Figure 3), based on experimental (VT NMR) inversion barriers ($\Delta G^{\ddagger}$).

average of 15.0 ± 0.1 kcal/mol for the activation free energies for ring inversion of **13**·HI and **16**·HI, respectively. These experiments were performed in different solvents, but the smaller value for **13**·HI is consistent with weaker bridge nitrogen stabilization, as revealed by basicity, crystallography, and computational studies. The latter, which have neglected solvent, have also established that bridge nitrogen inversion must occur via an open conformation (cf. Figure 3), even for free base **16**, for which an inversion barrier of 8.8 ± 0.3 kcal/mol was measured. Protonation of **16** clearly increases the inversion barrier by about 6 kcal/mol, a value which indicates the strength of the hydrogen bond between N5 and the proton covalently bonded to N1.

Figure 5 displays the energy profile for conformational inversion of **16**·HI, assuming that the barrier for N-inversion of the open forms (cf. Figure 3) is equal to that for free amine **16**. The actual barrier for interconversion of the syn-open and anti-open forms of **16**·HI may be smaller or larger than that of free base **16**. For example, conformational rigidity caused by interbridgehead hydrogen bonding might increase or decrease bond angle strain in the nitrogen inversion transition state. If we assume that these barriers are equal, as indicated in Figure 5, then the 6.2 kcal/mol free energy difference between the open and closed forms of **16**·HI is still only an estimate of the strength of the hydrogen bond between the bridge nitrogen and the cavity proton. This is because the open and closed forms should have different solvation and conformational energies. Moreover, removal of hydrogen bond bifurcation is likely to be partially compensated by an increase in the strength of the primary hydrogen bond between the bridgehead nitrogen atoms.

We investigated the proposed mechanism for the conformational inversion of **16**·HI via hydrogen bond cleavage followed by nitrogen inversion, as exactly shown in Figure 3. We first built the four conformations shown in the figure, which have different exo-methylene bridge conformations relative to Figure 4, and used Gaussian98 at the HF/6-31G* level to optimize their geometries. However, the syn-open conformation failed to converge but instead reverted to the anti-closed conformation. The relative energies of the other conformations, shown in Figure 6, were the following: anti-closed −709.55854, anti-open −709.53554, and syn-closed −709.55039 au. To understand the mechanism more fully we repeated the calculations using the unprotonated **16**. Here by contrast, but not unexpectedly, the anti-closed conformation now proved unstable and

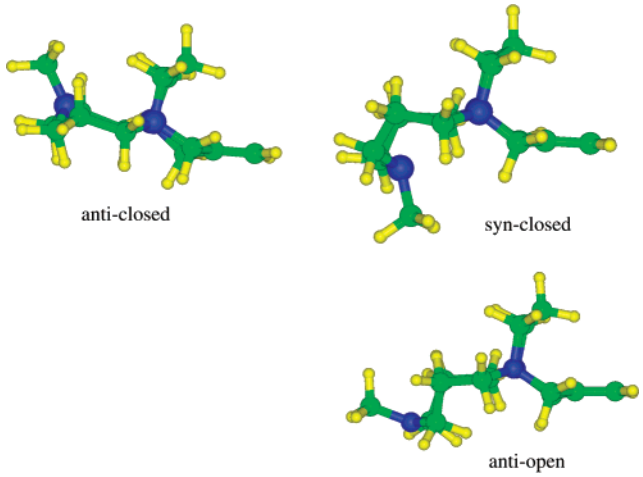

Figure 6. Structures of the anti-closed, anti-open, and syn-closed conformations of **16**·H^+ as calculated at the HF/6-31+G* level. The syn-open structure proved unstable to geometry optimization and reverted to the anti-closed conformation. Color scheme: C, green; H, yellow; N, blue.

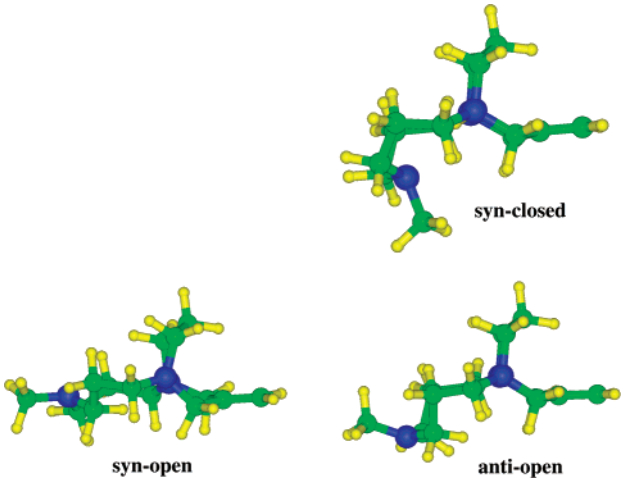

Figure 7. Structures of the syn-open, anti-open and syn-closed conformations of **16** as calculated at the HF/6-31+G* level. The anti-closed structure proved unstable to geometry optimization and reverted to the syn-open conformation. Color scheme: C, green; H, yellow; N, blue.

reverted to the syn-open conformation. The energies of the three structures, shown in Figure 7, were syn-open −709.12520, anti-open −709.11666, and syn-closed −709.11710 au. From these calculations we can compare the difference in energies between anti-open and syn-closed, which is 10.57 kcal/mol for **16**·H^+, but 0.25 kcal/mol for **16**. These values clearly show the importance of hydrogen bond formation to the stabilization of **16**·H^+ in the closed form. This calculation provides an estimate of 10.32 kcal/mol for the enthalpy of the hydrogen bond between the bridge nitrogen and the cavity proton in **16**·H^+ in the gas phase.

Conclusions

Effective routes have been developed for synthesis of three types of bicyclic triamines having the 1,5,9-triazacyclododecane ring embedded in their structures. Bridging two nitrogens with three carbons gives proton sponges **12**, **13**, **14**, and **15** having greatly stabilized monoprotonated forms, with pK_a values more than 8 units larger than those of their diprotonated forms. The one-carbon bridge in **23** and the zero-atom bridge in **39** do not

enhance the stability of the monoprotonated form. Structural studies involving X-ray crystallography and computational modeling reveal hydrogen-bonded networks that are apparently responsible for the stabilities of **12**·H^+, **13**·H^+, **15**·H^+, and **16**·H^+. The cavity proton is covalently bonded to the bridge nitrogen in **15**·HI, and the bridge nitrogens form equally bifurcated hydrogen bonding contacts. The bridge methyl group in **16**·HI decreases interaction of the bridge nitrogen with the cavity proton, which is covalently bonded to one of the bridgehead nitrogens. Dynamic (VT) ^{1}H and ^{13}C NMR studies, as well as molecular modeling, indicate that conformational inversion of **16**·HI ($\Delta G^{\ddagger} = 15.0$ kcal/mol) occurs after cleavage of the hydrogen bond between the bridge nitrogen and the cavity proton. Comparison with the 8.8 ± 0.3 kcal/mol activation energy for inversion of free base **16** leads to an estimate of 6.2 kcal/mol for the strength of this hydrogen bond. Computational results lead to an estimate of 10.32 kcal/mol for the enthalpy of the bifurcated hydrogen bond in the gas phase. These conclusions should be useful in the design of other highly basic compounds and for understanding hydrogen-bonded networks in biological systems.

Experimental Section

General Methods. All commercial solvents and reagents were used without purification, unless noted otherwise. Anhydrous tetrahydrofuran (THF) was obtained by distillation from sodium benzophenone ketyl immediately prior to use. Dichloromethane was either distilled from CaH_2 or passed through Woelm neutral alumina (activity I). Anhydrous, acid-free $CDCl_3$ was obtained by the latter method. Anhydrous benzene and dimethyl sulfoxide (DMSO) were obtained by distillation from CaH_2 (in vacuo for DMSO). Pyridine was dried over KOH, distilled from barium oxide and stored over 4Å molecular sieves. Tosyl (4-methylbenzenesulfonyl) chloride was purified by recrystallization from petroleum ether. 3,3′-Diaminodipropylamine (Eastman) was purified by vacuum distillation. Sodium hydride was obtained as a 60% dispersion in mineral oil and was washed with hexanes under N_2 prior to use. All reactions were conducted under dry nitrogen, unless noted otherwise. Thin-layer chromatography (TLC) was performed with Machery−Nagel plastic sheets coated with alumina or silica gel (0.25 mm). Spots were visualized under UV light or by heating after dipping in solutions of vanillin (9 g in 300 mL of ethanol and 1.5 mL of H_2SO_4) or phosphomolybdic acid (10% (w/w) in ethanol). Flash column chromatography was conducted with Merck Silica Gel 60 (230−400 mesh), and silica gel used for purification by filtration was ICN Silica TSC (activity III). Melting points are uncorrected and mass spectra (MS) were obtained by electron impact (70 eV).

***N,N′,N′′*-Tris(4-methylbenzenesulfonyl)bis(3-aminopropyl)-amine (8).**[8a,e] A solution of 65.6 g (0.5 mol) of 3,3′-diaminodipropylamine and 72 g (1.8 mol) of NaOH in 400 mL of water was added to a 2-L three-necked flask equipped with a mechanical stirrer, a condenser and a 1 L addition funnel. The reaction flask was placed in a water bath at room temperature. A solution of 292 g (1.53 mol) of *p*-toluenesulfonyl chloride in 750 mL of CH_2Cl_2 was added dropwise with vigorous stirring over 1 h. The mixture was then stirred for 2 h until it became clear. The CH_2Cl_2 layer was separated from the water layer and washed with water (3 × 400 mL), adding some $MgSO_4$ to aid separation of the layers. After the CH_2Cl_2 layer was dried with $MgSO_4$, it was concentrated to a volume of 450 mL, then 350 mL of Et_2O was added. The resulting solution was concentrated by slow evaporation. The crystalline product was collected by filtration, washed with a small portion of cold Et_2O, and dried under vacuum at room temperature, yielding 266 g (90%), mp 112.5−113.5 °C (lit.[8e] 114 °C); R_f 0.57 (alumina, CH_2Cl_2). ^{1}H NMR (80 MHz, $CDCl_3$): δ 7.72 (d, J = 8 Hz, 6 H), 7.30 (d, J = 8 Hz, 6 H), 3.00 (m, 8 H), 2.41 (s, 9 H), 1.74 (m, 4 H). IR (film): 3325 (s), 3075 (s), 2975 (s), 2900 (m), 1619 (s), 1450 (br, s), 1350 (br, s), 1175 (s) cm^{-1}.

1,3-Propanediol bis(4-methylbenzenesulfonate) (9).[16] A solution of 38.5 g (0.5 mol) of 1,3-propanediol in 100 mL of pyridine was added dropwise over 2 h to a solution of 228 g (1.2 mol) of tosyl chloride in 400 mL of anhydrous pyridine, which was cooled in an ice−salt bath at 0−10 °C. The reaction mixture was stirred for 4 h, then poured into 1 L of ice water. The solid product was collected by filtration, washed with water, dilute sulfuric acid, dilute sodium carbonate, and again with water. The wet product was recrystallized from acetone. The resulting white, crystalline product was filtered and dried under vacuum at room temperature, yielding 190 g (98%), mp 90−91 °C (lit.[16b] 94 °C). ^{1}H NMR (80 MHz, $CDCl_3$): δ 7.75 (d, J = 8 Hz, 4 H), 7.33 (d, J = 8 Hz, 4 H), 4.07 (m, 4 H), 2.45 (s, 6 H), 2.01 (m, 2 H).

1,5,9-Tris(4-methylbenzenesulfonyl)-1,5,9-triazacyclododecane (10).[8a,c,e,16b,17] NaH (6 g, 0.25 mol) was added under nitrogen to a solution of 59.4 g (0.1 mol) of *N,N′,N′′*-tris(4-methylbenzenesulfonyl)-bis(3-aminopropyl)amine (**8**) in 750 mL of anhydrous DMF. The resulting mixture was stirred at 80−100 °C for 1 h; it was then cooled to room temperature and filtered under nitrogen through a glass fiber filter into a 2-L three-necked round-bottomed flask equipped with a rubber septum and a thermometer. The insoluble material was washed with 250 mL of anhydrous DMF, which was also added to the 2 L reaction flask. The resulting solution was stirred at 100 °C under nitrogen as a solution of 39.4 g (0.1 mol) of 1,3-propanediol bis(4-methylbenzenesulfonate) (**9**) in 500 mL of anhydrous DMF was added slowly over 6 h. The reaction mixture was heated for an additional 6 h. The solvent was removed completely under vacuum on a rotary evaporator using a hot water bath. A solution of the viscous crude product in 300 mL of $CHCl_3$ was washed with an equal amount of water. The organic layer was separated, dried over $MgSO_4$, filtered to remove insoluble material, and concentrated by rotary evaporation. A solution of the residue in hot toluene was diluted with hexane and the clear supernatant liquid was decanted from the white precipitate. The residue was redissolved in toluene and the process was repeated until precipitation no longer occurred upon addition of hexane. The combined supernatant solutions were concentrated and the crude product was recrystallized from $CHCl_3$/EtOH, yielding 31.5 g (50%) of **10** as a white solid, mp 170−171 °C (lit.[8e] 171 °C); R_f 0.41 (silica gel, ethyl acetate/hexane (1:1, v/v)). ^{1}H NMR (80 MHz, $CHCl_3$): δ 7.64 (d, J = 8 Hz, 6 H), 7.29 (d, J = 8 Hz, 6 H), 3.17 (t, J = 6 Hz, 12 H), 2.40 (s, 9 H), 1.78 (m, 6 H). MS *m*/*z* (rel intens): 478 (100), 223 (43), 155 (78), 91 (98).

1,5,9-Triazacyclododecane (6).[8a−e,17] A solution of 31.7 g (50 mmol) of **10** in 100 mL of 98% H_2SO_4 was heated at 100 °C for 54 h under nitrogen. The solution was cooled in an ice bath and 200 mL of absolute ethanol was added slowly from an addition funnel, followed by 500 mL of anhydrous ether. The precipitate was collected by filtration and dried under nitrogen. It was dissolved in a minimum amount of water, and the pH was adjusted to >13 by addition of 10 M aqueous NaOH solution. The resulting solution was extracted with chloroform (2 × 200 mL). The combined extracts were dried over $MgSO_4$ and concentrated by rotary evaporation. After residual chloroform was completely removed under high vacuum overnight, the crude product was distilled under vacuum from powdered KOH to afford 4.70 g (55%) of a colorless liquid, bp 107 °C (1.0 mm), mp 8−9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (t, J = 5.4 Hz, 12 H), 2.22 (br, 3 H), 1.59 (p, J = 5.4 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 48.8, 27.5. IR (film): 3500−3200 (br, s), 2950 (s), 2830 (br) cm^{-1}. MS *m*/*z* (rel intens): 171 (M^+, 30), 143 (50), 84 (72), 70 (100).

1,5,9-Triazabicyclo[7.3.3]pentadecane hydriodide (12·HI). Separate solutions of 1.71 g (10 mmol) of 1,5,9-triazacyclododecane (**6**) in 50 mL of 2-butanol and 2.96 g (10 mmol) of 1,3-diiodopropane in 50 mL of 2-butanol were added over 8 h by syringe pump to a mixture of 3.3 g (33 mmol) of $KHCO_3$ and 900 mL of 2-butanol that was heated at reflux under N_2. The reaction mixture was then heated under reflux

for 15 h. The solvent was removed completely by rotary evaporation. A solution of the residue in 30 mL of 3 M aqueous NaOH solution was extracted with $CHCl_3$ (3 × 60 mL). The combined organic extracts were concentrated by rotary evaporation. A solution of the resulting oil was partially neutralized with dilute aqueous HI to pH ≈ 10 and extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ solutions were dried over $MgSO_4$ and concentrated by rotary evaporation. The product was purified by adding hexane to a hot solution of the residue in toluene and decanting the supernatant solution. The product (**12**·HI) crystallized from the supernatant at room temperature, yielding 1.68 g (50%) in two crops. Recrystallization from toluene/chloroform gave analytically pure material, mp 227−229 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.4 (br s, 2 H), 2.95 (m, 8 H), 2.79 (t, J = 5.7 Hz, 4 H), 2.59 (m, 4 H), 2.05 (p, J = 5.7 Hz, 4 H), 1.74 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 60.5, 53.3, 49.2, 27.9, 23.6. IR (KBr): 3330−3600, 2950, 2860, 2810, 2560, 2450, 1895, 1635, 1470, 1460, 1425, 1380, 1355, 1195, 1105 cm^{-1}. Anal. Calcd for $C_{12}H_{26}N_3I$: C, 42.48; H, 7.72; N, 12.38. Found: C, 42.67; H, 7.96; N, 12.27.

1,5,9-Triazabicyclo[7.3.3]pentadecane (12). A mixture of 0.66 g (1.9 mmol) of **12**·HI and 5 M aqueous KOH solution was stirred vigorously, and then the free amine was extracted with chloroform. The chloroform layer was dried over $MgSO_4$ and then concentrated by rotary evaporation. Residual solvent was completely removed under vacuum overnight, and the residue was then distilled under vacuum from powdered potassium hydroxide. The colorless oil (250 mg, 61%), which distilled at 110 °C (0.5 mm), was handled carefully under N_2. ^{1}H NMR (300 MHz, CD_3CN): δ 5.5 (br s, 1 H), 2.56 (m, 8 H), 2.42 (m, 8 H), 1.53 (m, 4 H), 1.45 (m, 4 H). ^{13}C NMR (75 MHz, CD_3CN): δ 61.8, 53.3, 52.7, 30.0, 27.7. IR (film): 3210 (br, s), 3170 (br, s), 2900 (br, s), 2850 (m), 2770 (br, s), 2700 (s), 1470 (s), 1440 (m), 1430 (m), 1345 (m), 1330 (m), 1275 (m), 1230 (m), 1190 (s), 1175 (m), 1125 (m), 1110 (m), 1030 (m), 985 (m), 750 (m) cm^{-1}. MS *m*/*z* (rel intens): 212 (3.2, M + l), 211 (26, M$^+$), 85 (21), 84 (100), 71 (30), 70 (62), 58 (41). Anal. Calcd for $C_{12}H_{25}N_3$: C, 68.20; H, 11.92; N, 19.88. Found: C, 67.85; H, 12.21; N, 19.96.

5-Methyl-1,5,9-triazabicyclo[7.3.3]pentadecane-HI Salt (13·HI). A mixture of 0.34 g (1.0 mmol) of 1,5,9-triazabicyclo[7.3.3]-pentadecane-HI (**12**·HI), 0.77 g (8 mmol) of 30% aqueous formaldehyde, 0.1 g (1.6 mmol) of $NaCNBH_3$ and 1 mL of acetonitrile containing a few drops of acetic acid was stirred for 3 h at room temperature. The reaction mixture was concentrated by rotary evaporation, basified to pH 13 by addition of aqueous NaOH solution, and extracted with $CHCl_3$. The $CHCl_3$ layer was concentrated by rotary evaporation. A solution of the crude product in water was adjusted exactly to pH 10 with 0.1 M aqueous HI solution and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated by rotary evaporation. The crude product was recrystallized from boiling toluene (***note:*** **13**·HI dissolves in cold toluene and crystallizes from hot toluene), yielding 0.24 g (70%) of white crystals, mp 272−273.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.0 (s, 1 H), 2.27 (s, 3 H), plus several broad peaks at room temperature. ^{13}C NMR (75 MHz, $CDC1_3$, 60 °C): δ 58.4, 57.8, 53.8, 42.4, 22.4, 21.8; (20 °C): δ 58.3, 57.8, 54.6, 52.3, 42.2, 22.8, 21.7. IR (KBr): 3330−3600, 2970, 2900, 1465, 1440, 1360, 1250, 1180, 1015, 995 cm^{-1}. Anal. Calcd for $C_{13}H_{28}N_3$: C, 44.19; H, 7.99; N, 11.89. Found: C, 43.82; H, 8.14; N, 11.67.

5-Methyl-1,5,9-triazabicyclo[7.3.3]pentadecane (13). A mixture of 0.71 g (2.0 mmol) of **13**·HI and 10 M aqueous KOH solution was stirred vigorously under N_2. The free amine was extracted with $CHCl_3$, and the extract was dried over $MgSO_4$. Chloroform was completely removed under vacuum overnight, and the residue was distilled from powdered KOH. A colorless oil (0.32 g, 71%) was obtained and handled carefully under N_2. ^{1}H NMR (300 MHz, CD_3CN): δ 2.8−3.2 (m, 16 H), 2.24 (s, 3 H), 1.4−1.7 (m, 8 H). ^{13}C NMR (75 MHz, CD_3CN): δ 58.9, 56.3, 54.4, 44.6, 31.4, 29.4. IR (film): 2920 (s), 2905 (s), 2880 (s), 2820 (s), 2770 (s), 2740 (s), 1500 (m), 1480 (m), 1350 (m), 1200 (m), 1175 (w), 1120 (w), 1050 (w) cm^{-1}. Anal. Calcd for $C_{13}H_{27}N_3$: C, 69.28; H, 12.08; N, 18.64. Found: C, 69.24; H, 12.32; N, 18.88.

11-Methylene-1,5,9-triazabicyclo[7.3.3]pentadecane (15). Separate solutions of 0.86 g (5 mmol) of 1,5,9-triazacyclododecane (**6**) in 50 mL of 2-propanol and 1.54 g (5 mmol) of 2-iodo-3-iodomethyl-1-propene[20] in 50 mL of 2-propanol were added over 3 h by syringe pump to a mixture of 1.66 g (12 mmol) of K_2CO_3, and 150 mL of 2-propanol that was heated at reflux under N_2. The reaction mixture was then heated under reflux for 3 h. The solvent was removed by rotary evaporation. A solution of the residue in 50 mL of $CHCl_3$ was washed with 5 M aqueous NaOH solution (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, concentrated by rotary evaporation, and dried completely under vacuum. The crude product was distilled under vacuum from powdered KOH, yielding 0.78 g (70%) of colorless oil, bp 110 °C (1.0 mm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.3 (br s, 1 H), 4.84 (t, J = 13 Hz, 2 H), 3.63 (dt, J = 1.8, 13 Hz, 2 H), 2.84 (d, J = 13 Hz, 2 H), 2.4−2.7 (m, 12 H), 1.7 (m, 3 H), 1.4 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.5, 114.5, 60.1, 59.9, 55.0, 51.7, 29.3, 26.3. IR (CCl_4): 3220, 2950, 2940, 2890, 2800, 1645, 1490, 1190, 1150, 925 cm^{-1}. MS *m*/*z* (rel intens): 223 (M$^+$, 50), 110 (60), 96 (100), 82 (70), 70 (80), 56 (70), 42 (50). Anal. Calcd for $C_{13}H_{25}N_3$: C, 69.90; H, 11.28; N, 18.81. Found: C, 69.96; H, 11.14; N, 18.90.

11-Methylene-1,5,9-triazabicyclo[7.3.3]pentadecane Hydriodide (15·HI). 11-Methylene-1,5,9-triazabicyclo[7.3.3]pentadecane (**15**) was dissolved in 0.1 M aqueous HI, and the pH of the solution was adjusted to 9−10. The monoprotonated product was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated by rotary evaporation. The crude HI salt was dissolved in boiling toluene/chloroform (1:1, v/v). Colorless crystals were obtained at room temperature, mp 199−200 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.50 (br s, 1 H), 10.50 (br s, 1 H), 5.00 (t, J = 2 Hz, 2 H), 3.88 (d, J = 14 Hz, 2 H), 3.05 (d, J = 14 Hz, 2 H), 2.5−3.5 (m, 12 H), 2.2 (m, 2 H), 2.1 (m, 1 H), 1.9 (m, 2 H), 1.5 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5, 115.5, 60.0, 58.5, 54.6, 48.6, 27.2, 22.4. IR (KBr): 2950, 2800, 2450, 1635, 1460, 1375, 1300, 1100 cm^{-1}.

5-Methyl-11-methylene-1,5,9-triazabicyclo[7.3.3]pentadecane (16). A mixture of 0.14 g (0.63 mmol) of **15**, 78 μL (1.5 mmol) of 90% formic acid and 54 μL (0.66 mmol) of 37% aqueous formaldehyde was heated in an oil bath at 120 °C for 16 h. The reaction mixture was basified with 10 M aqueous KOH solution and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated by rotary evaporation and dried under vacuum. The crude oily product was distilled from powdered KOH, yielding 65 mg (43%) of a colorless oil, bp 100−110 °C (0.3 mm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.88 (s, 2 H), 3.39 (d, J = 13 Hz, 2 H), 3.25 (d, J = 13 Hz, 2 H), 2.81 (m, 4 H), 2.62 (m, 4 H), 2.48 (m, 4 H), 2.25 (s, 3 H), 1.65 (m, 2 H), 1.53 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.9, 114.2, 62.0, 53.8, 57.4, 43.8, 31.0, 27.1. IR (film): 3075, 2750−2950, 1640, 1450, 1350, 1270, 1200, 1180, 1050, 760 cm^{-1}. MS *m*/*z* (rel intensity): 238 (M + l, 18), 237 (M$^+$, 85), 222 (15), 151 (25), 141 (30), 122 (35), 110 (60), 96 (90), 84 (100), 70 (80), 58 (90), 42 (90).

5-Methyl-11-methylene-1,5,9-triazabicyclo[7.3.3]pentadecane Hydriodide (16-HI). The procedure for preparation of (**16**·HI) from **16** is the same as for preparation of **15**·HI from **15**, giving a white solid, mp 246.5−247.5 °C (toluene/chloroform). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.8 (br s, 1 H), 5.16, 4.72, 4.00, 3.62, 3.42, 3.10, 2.82, 2.46, 2.25 (s, 3 H), 1.92, 1.85 (s), 1.60. All peaks are broad at room temperature (25 °C). ^{13}C NMR (75 MHz, $CDCl_3$ at 25 °C): δ 139.6, 115.3, 58.3, 57.8, 55.6, 42.1, 21.5. IR (KBr): 3400, 3050, 2950, 2800, 2100−2800, 1640, 1450, 1355, 1300, 1255, 1200, 1180, 1150, 1120, 1080, 1040, 990, 960, 940, 910, 860, 760 cm^{-1}. Anal. Calcd for $C_{14}H_{28}N_3I$: C, 46.01; H, 7.73; N, 11.50. Found: C, 46.01; H, 7.79; N, 11.48.

11-Hydroxymethyl-1,5,9-triazabicyclo[7.3.3]dodecane (17). A solution of 0.29 g (1.3 mmol) of 11-methylene-1,5,9-triazabicyclo-[7.3.3]pentadecane (**15**) in 15 mL of anhydrous THF was cooled to

−78 °C under N_2. A solution of 9-borabicyclo[3.3.1]nonane (9-BBN) in anhydrous THF (0.5 M, 7.7 mL) was added, and stirring was continued for 2 h at −78 °C. The reaction solution was allowed to warm to room temperature and stirred for 5 h; EtOH (3 mL), 3 M aqueous NaOH (3 mL), and 30% aqueous hydrogen peroxide (3 mL) were then added, and the resulting mixture was stirred for l h at room temperature. The mixture was saturated with K_2CO_3, and the THF layer was separated. The THF was removed by rotary evaporation, and 10 mL of 2 M aqueous HCl was added to the residue. The resulting solution was heated under reflux for 1 h to cleave any boramine complex, cooled, and continuously extracted overnight with methylene chloride. The pH of the aqueous solution was adjusted to >13 by addition of NaOH, and then it was extracted with chloroform. The chloroform extract was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo, yielding 0.30 g (97%) of the crude product as a crystalline, white solid. (***Note:*** Use of magnesium sulfate as a drying agent gave a complex that was insoluble in toluene and produced a very broad ^{1}H NMR spectrum ($CDCl_3$).) This 4:1 mixture of diastereomeric alcohols (**17a** and **17b**, respectively) was separated by repeated recrystallization from hexane, yielding small samples that gave the following data. **17a**: mp 124−125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73 (d, J = 6.1 Hz, 2 H), 2.2−3.2 (m, 18 H), 1.4−2.0 (m, 7 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.6, 60.7, 54.2, 52.6, 50.9, 41.1, 28.4, 25.4. IR (KBr): 3400 (br, s), 3125 (s), 2900 (s), 2875 (s), 1475 (s), 1340 (m), 1180 (m) cm^{-1}. MS *m*/*z* (rel intens): 241 (48), 84 (100), 70 (95), 58 (80). **17b**: mp 184−186 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.38 (d, J = 6.1 Hz, 2 H), 2.5−3.2 (m, 18 H), 1.4−2.4 (m, 7 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.6, 60.6, 57.2, 51.7, 49.7, 43.0, 25.5, 24.3. IR (KBr): 3425 (br, s), 2950 (s), 2800 (s), 1475 (s), 1350 (m), 1200 (m) cm^{-1}.

3-Methylene-1,5,9-tris(4-methylbenzenesulfonyl)-1,5,9-triazacyclododecane (19). To a solution of 59.4 g (0.1 mol) of **8** in 1 L of anhydrous DMF, was added 6 g (0.25 mol) of NaH under N_2. The resulting mixture was stirred at 80−100 °C for 1 h and then cooled to room temperature. It was then filtered under nitrogen through a glass fiber filter by means of a cannula into a 2-L three-necked round-bottomed flask equipped with a rubber septum and a thermometer. Transfer was completed with an additional 400 mL of anhydrous DMF. The resulting solution was heated at 100 °C, and a solution of 12.5 g (0.1 mol) of 3-chloro-2-chloromethyl-1-propene in 100 mL of anhydrous DMF was added by means of a syringe pump over 5 h. The reaction mixture was heated for 5 h; the DMF was removed completely by rotary evaporation using a boiling water bath. The resulting viscous crude product was dissolved in 150 mL of chloroform. This chloroform solution was washed with water (3 × 100 mL), dried over $MgSO_4$, and concentrated in vacuo. The yellow viscous product was purified in the same way as that described for tris(4-methylbenzenesulfonyl)-1,5,9-triazacyclododecane (**10**), yielding 38.3 g (59.3%) of solid, mp 168−169 °C (EtOH−CH_2Cl_2); R_f 0.42 (silica gel, ethyl acetate/hexane (1:1, v/v)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 8 Hz, 4 H), 7.58 (d, J = 8 Hz, 2 H), 7.31 (d, J = 8 Hz, 4 H), 7.28 (d, J = 8 Hz, 2 H), 5.19 (s, 2 H), 3.84 (s, 4 H), 3.23 (t, J = 7.2 Hz, 4 H), 3.10 (t, J = 6.3 Hz, 4 H), 2.43 (s, 6 H), 2.41 (s, 3 H), 1.89 (p, J = 6.8 Hz, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.53, 143.49, 138.2, 135.5, 134.3, 129.7, 129.6, 127.1, 127.0, 117.5, 50.8, 46.6, 44.6, 27.2, 21.4. IR ($CDCl_3$): 3060, 3030, 2950, 2920, 2860, 1730, 1650, 1595, 1490, 1450, 1330, 1300, 1285, 1150, 1085, 1035, 1015 cm^{-1}.

3-Hydroxymethyl-1,5,9-tris(4-methylbenzenesulfonyl)-1,5,9-triazacyclododecane (20). A solution of thexylborane (1.0 M, 100 mL, 0.1 mol) in THF was prepared by adding 8.4 g (0.1 mol) of 2,3-dimethyl-2-butene to 100 mL of cold 1.0 M BH_3·THF solution at 0 °C and stirring for an additional hour under nitrogen in an ice bath. It was added to a solution of 32.3 g (0.05 mol) of **19** in 300 mL of anhydrous THF at room temperature. The reaction mixture was stirred at room temperature for 4 h and then heated under reflux for 1 h. Ethanol (15 mL) was added cautiously to the cooled reaction mixture to quench excess borane. Sodium hydroxide (30 mL of 3 M aqueous solution) was added, followed by 15 mL of 30% aqueous H_2O_2, keeping the temperature in the range of 30−35 °C by means of an ice bath. The reaction mixture was stirred for 3 h, then the solvent was removed by rotary evaporation. A solution of the residue in 300 mL of $CHCl_3$ was washed with water (3 × 150 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was dried under vacuum, yielding 22 g (66%) of crude product, which could be used in the next step without further purification. For the purpose of characterization, the product was recrystallized from EtOH/CH_2Cl_2, mp 201.5−202.5 °C; R_f 0.24 (silica gel, ethyl acetate/hexane (1:1, v/v)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 8 Hz, 4 H), 7.59 (d, J = 8 Hz, 2 H), 7.33 (d, J = 8 Hz, 4 H), 7.31 (d, J = 8 Hz, 2 H), 3.72 (m, 2 H), 3.47 (m, 4 H), 3.20 (m, 6 H), 2.72 (dt, J = 5, 14 Hz, 2 H), 2.43 (s, 6 H), 2.43 (s, 3 H), 2.34 (m, 1 H), 2.18 (m, 1 H), 1.98 (m, 2 H), 1.83 (m, 2 H). ^{13}C NMR (75 MHz, $CDC1_3$): δ 143.8, 143.5, 135.5, 133.6, 129.8, 127.3, 127.0, 60.8, 47.3, 47.1, 44.2, 37.0, 27.0, 21.5. IR ($CDCl_3$): 3530 cm^{-1}.

3-Chloromethyl-1,5,9-tris(4-methylbenzenesulfonyl)-1,5,9-triazacyclododecane (21). Triphenylphosphine (0.7 g, 2.7 mmol) was added slowly to a solution of 1.33 g (2 mmol) of **20** and CCl_4 (0.6 mL) in 5 mL of anhydrous DMF, which was cooled by means of an ice bath. The reaction mixture was stirred overnight at room temperature. The solvent was removed by rotary evaporation, and the reaction product was isolated by flash chromatography (ethyl acetate/hexane (1:1, v/v)) and recrystallized from EtOH/CH_2Cl_2, yielding 0.85 g (64%) of solid, mp 156−157 °C; R_f 0.45 (silica gel, ethyl acetate/hexane (1:1, v/v)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 8 Hz, 4 H), 7.60 (d, J = 8 Hz, 2 H), 7.33 (d, J = 8 Hz, 4 H), 7.31 (d, J = 8 Hz, 2 H), 3.61 (d, J = 5 Hz, 2 H), 3.47 (m, 4 H), 3.20 (m, 6 H), 2.72 (dt, J = 5, 14 Hz, 2 H), 2.41 (m, 10 H), 2.03 (m, 2 H), 1.78 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.8, 143.7, 135.3, 133.4, 129.8, 129.7, 127.4, 127.1, 48.0, 46.7, 44.7, 37.0, 26.3, 21.5. IR ($CDCl_3$): 975 cm^{-1}.

3-Chloromethyl-1,5,9-triazacyclododecane (22). A solution of 1.37 g (2 mmol) of **21** in 2 mL of 98% H_2SO_4 was kept at 100 °C for 54 h under nitrogen. The solution was cooled in an ice bath, and 10 mL of absolute ethanol was added slowly by means of an addition funnel, followed by 20 mL of anhydrous ether. The precipitate was collected by filtration and dried under nitrogen. It was dissolved in the minimum volume of water, and the pH was adjusted to >13 with 10 M aqueous NaOH. This solution was extracted with chloroform (3 × 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated by rotary evaporation. The crude product was used in the next step without purification. A sample of this oil was completely dried in vacuo. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.4 (br s, 3 H), 3.51 (d, J = 5 Hz, 2 H), 2.95 (m, 6 H), 2.6 (m, 6 H), 2.4 (m, 1 H), 1.9 (m, 2 H), 1.7 (m, 2 H). MS *m*/*z* (rel intens): 221 (M + 2, 2.5), 220 (M + l, 1.3), 219 (M$^+$, 6.9), 184 (19.9), 70 (100).

1,5,9-Triazabicyclo[9.1.1]tridecane (23). The crude 3-chloromethyl-1,5,9-triazacyclododecane (**22**) product obtained from 1.37 g (2 mmol) of **21**, 400 mL of anhydrous 2-propanol and 0.3 g (2 mmol) of K_2CO_3 was heated under reflux for 10 h. The solvent was removed by rotary evaporation. A mixture of the residue and 5 M aqueous NaOH solution was extracted with $CHCl_3$. The $CHCl_3$ extract was dried with $MgSO_4$ and concentrated by rotary evaporation. The crude product was distilled in vacuo from powdered KOH, yielding 0.22 g (58%), bp 110−130 °C (0.1 mm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.28 (m, 2 H), 2.98 (m, 2 H), 2.86 (t, J = 5 Hz, 2 H), 2.76 (d, J = 3 Hz, 2 H), 2.62 (m, 4 H), 2.63 (m, 2 H), 2.61 (m, 2 H), 2.44 (t, J = 6 Hz, 2 H), 2.15 (tt, J = 3, 7 Hz, 1 H), 1.61 (p, J = 5 Hz, 2 H), 1.38 (J = 6 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 57.5, 57.1, 52.0, 49.8, 49.0, 48.4, 32.8, 29.3, 25.2. IR (neat): 3600−3000, 2920, 2790, 1640, 1420−1500, 1350, 1290, 1200, 1135, 1040, 1010, 900 cm^{-1}. MS *m*/*z* (rel intens): 184 (M + l, 1), 183 (M$^+$, 2), 182 (M − 1, 3), 84 (100), 70 (85), 58 (58), 44 (66). Anal. Calcd for $C_{10}H_{21}N_3$: C, 65.53; H, 11.55; N, 22.92. Found: C, 64.85; H, 11.72; N, 22.85.

Bis(2-cyanoethyl)amine (26).[23] A mixture of 53.1 g (1.3 mol) of acrylonitrile and 100 g of 29% aqueous ammonium hydroxide was stirred vigorously in an open Erlenmeyer flask at room temperature. After 1 h a homogeneous solution was obtained. Stirring was continued overnight. Solid NaCl was added, causing separation of two layers. The product was extracted with chloroform, and the chloroform solution was dried over $MgSO_4$ and then concentrated in vacuo. Fractional distillation of the residual oil gave 42.5 g (53%) of the product as a colorless oil, bp 140−155 °C (0.5 mm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (t, J = 7 Hz, 4 H), 2.50 (t, J = 7 Hz, 4 H), 1.5 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 118.4, 44.4, 18.8. IR (film): 3330 (s), 2920 (s), 2850 (s), 2240 (s), 1440 (s), 1415 (s), 1360 (m), 1130 (s), 750 (br, m) cm^{-1}.

Bis(2-cyanoethyl)benzylamine (27). A mixture of 13 g (106 mmol) of bis(cyanoethyl)amine (**26**), 12.7 g (0.1 mol) of benzyl chloride, 9.25 g (0.11 mol) of $NaHCO_3$, and 20 mL of water was heated under reflux for 6 h. The reaction mixture was partitioned between chloroform and saturated aqueous NaCl solution. The chloroform layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was fractionally distilled, yielding 15.4 g (68%) of a colorless oil, bp 186−187 °C (0.5 mm) (lit.[22b] 190 °C, 0.05 mm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.8 (m, 5 H), 4.18 (s, 2 H), 3.35 (t, J = 7 Hz, 4 H), 2.93 (t, J = 7 Hz, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 128.3, 127.4, 118.4, 57.7, 49.1, 16.4. IR (film): 3070 (w), 3050 (m), 3020 (s), 2930 (s), 2830 (s), 2240 (s), 1595 (m), 1575 (w), 1485 (s), 1445 (s), 1415 (s), 1360 (br m), 1250 (br m), 1125 (s), 1070 (s), 1020 (s), 960 (s), 730 (s), 690 (s) cm^{-1}.

Bis(3-aminopropyl)benzylamine (28). A mixture of 14.5 g (68 mmol) of **27**, 3 g of Raney nickel and 55 mL of 1.5 M aqueous NaOH solution in 95% EtOH was placed in a glass Parr reaction bottle and shaken under 40 psi of hydrogen. (***Caution:*** explosion hazard; air must be completely replaced by hydrogen in the Parr apparatus before reaction is begun.) The catalytic hydrogenation was carried out for 40 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. Fractional distillation of the residue gave 12.2 g (81%) of a colorless oil, bp 151−155 °C (0.5 mm) (lit.[22b] 110 °C, 0.05 mm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (m, 5 H), 3.89 (s, 2 H), 3.06 (t, J = 7 Hz, 4 H), 2.82 (t, J = 7 Hz, 4 H), 1.97 (p, J = 7 Hz, 4 H), 1.35 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 128.3, 127.7, 126.3, 58.3, 50.9, 40.0, 30.6. IR (film): 3360 (br, m), 3270 (br, m), 3070 (w), 3050 (w), 3020 (m), 2920 (br, s), 2850 (s), 2800 (s), 1600 (s), 1485 (s), 1450 (s), 1360 (m), 1110 (br, m), 1070 (m), 1020 (m), 730 (m), 690 (m) cm^{-1}.

***N,N′*-Bis(4-methylbenzenesulfonyl)bis(3-aminopropyl)benzylamine (29) and 29-HCl.** A solution of 20 g (0.11 mol) of tosyl chloride in 50 mL of CH_2Cl_2 was added dropwise with vigorous stirring over 2 h to a solution of 11.1 g (0.05 mol) of **28** and 4.4 g (0.11 mol) of NaOH in 30 mL of water. The reaction mixture was stirred for 1 h, and the organic layer was separated, washed with an equal volume of saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. Attempts to crystallize the crude oily product were not successful. TLC analysis showed only one spot. All remaining solvent was removed under vacuum, yielding 25 g (95%) of the product, which was used without further purification (silica gel, ethyl acetate/hexane (1:1, v/v)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J = 8 Hz, 4 H), 7.28 (d, J = 8 Hz, 4 H), 7.20 (m, 5 H), 5.80 (br s, 2 H), 3.43 (s, 2 H), 2.92 (t, J = 6 Hz, 4 H), 2.42 (s, 6 H), 1.64 (p, J = 6 Hz, 4 H), 1.27 (m, 2 H), 0.89 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1, 136.9, 129.6, 129.0, 128.4, 127.3, 127.0, 58.6, 51.8, 42.2, 25.9, 21.4. IR (film): 3280, 3050, 3020, 2940, 2850, 2810, 1595, 1490, 1450, 1320, 1150, 1085, 810, 730, 690, 660 cm^{-1}. The HCl salt was prepared by washing a solution of 16.9 g of the product in 150 mL of CH_2Cl_2 with a mixture of 50 mL of 2 N aqueous HCl and 100 mL of saturated aqueous NaCl solution. The organic layer was separated and washed with saturated aqueous NaCl solution (3 × 100 mL), then concentrated to minimum volume by boiling. Ethyl acetate (50 mL) was added to induce the formation of a precipitate, which was collected by vacuum filtration and dried at room temperature (1 mm), yielding 9.65 g (54%) of **29**·HCl as an off-white solid, mp 150−152 °C. A sample for microanalysis was prepared by recrystallization from CH_2Cl_2/ethyl acetate and dried at 78 °C (1 mm, 20 h), mp 160−161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.06 (br s, 1H), 7.74 (d, J = 8 Hz, 4H), 7.57 (m, 2 H), 7.39 (m, 3 H), 7.25 (d, J = 8 Hz, 4 H), 6.78 (t, 2 H), 4.21 (d, 2 H), 3.20 (m, 4 H), 2.94 (m, 4 H), 2.38 (s, 6 H), 2.15 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 136.5, 131.3, 130.1, 129.7, 129.4, 128.3, 127.1, 57.3, 50.1, 40.2, 23.6, 21.5. IR (KBr): 3154 (br), 2928, 2873, 2620 (br), 1597, 1441, 1335, 1323, 1162, 1093, 813, 694, 659 cm^{-1}. Anal. Calcd for $C_{27}H_{36}N_3S_2O_4Cl$: C, 57.28; H, 6.41; N, 7.42; S, 11.32; Cl, 6.26. Found: C, 57.34; H, 6.43; N, 7.39; S, 11.33; Cl, 6.41.

9-Benzyl-3-methylene-1,5-bis(4-methylbenzenesulfonyl)-1,5,9-triazacyclododecane (30). NaH (3.6 g, 0.15 mol) was added under N_2 to a solution of 26.5 g (0.05 mol) of **29** in 500 mL of anhydrous DMF. The mixture was held at 80−100 °C for 1 h then transferred through a glass fiber filter under N_2 by means of a cannula to a 2-L three-necked, round-bottomed flask equipped with a rubber septum and a thermometer. An additional 500 mL of anhydrous DMF was used to ensure complete transfer. A solution of 6.25 g (0.05 mol) of 3-chloro-2-chloromethyl-1-propene (**18**) in 50 mL of anhydrous DMF was added to the 100 °C solution over 9 h by means of a syringe pump. Heating was continued for an additional 12 h. The solvent was removed completely by rotary evaporation using a boiling water bath. A solution of the residue in 150 mL of $CHCl_3$ was washed with water (3 × 100 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The product was isolated and purified in the same way as that described for **10**, yielding 16 g (55%) of solid, mp 156−158 °C (ethyl acetate/hexane); R_f 0.58 (silica gel, ethyl acetate/hexane (1:1, v/v)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 8 Hz, 4 H), 7.51 (d, J = 8 Hz, 4 H), 7.4 (m, 5 H), 5.43 (s, 2 H), 4.04 (s, 4 H), 3.59 (s, 4 H), 3.32 (t, J = 7 Hz, 4 H), 2.63 (s, 6 H), 2.56 (t, J = 6 Hz, 4 H), 1.85 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 139.3, 138.3, 135.5, 129.7, 128.7, 128.1, 127.2, 126.9, 116.2, 59.0, 51.0, 49.5, 44.0, 24.4, 21.5. IR ($CDCl_3$): 3020, 2940, 2920, 2850, 2800, 1600, 1490, 1450, 1330, 1150, 1080 cm^{-1}. Anal. Calcd for $C_{31}H_{39}N_3S_2O_4$: C, 64.00; H, 6.76; N, 7.22; S, 11.02. Found: C, 63.91; H, 6.65; N, 7.13; S, 11.04.

3-Methylene-1,5-bis(4-methylbenzenesulfonyl)-1,5,9-triazacyclododecane (31) and 31-HCl. A solution of 11.6 g (20 mmol) of thoroughly dried **30** in 100 mL of anhydrous 1,2-dichloroethane (distilled from P_2O_5 under N_2) was cooled by means of an ice bath, and then 2.86 g (20 mmol) of α-chloroethyl chloroformate (ACE-Cl) was added. Stirring was continued at 0 °C for 15 min; the reaction mixture was then heated under reflux for 50 min. The solvent was removed in vacuo, and 100 mL of methanol was added to the residue. The resulting solution was heated under reflux for 30 min. Methanol was again removed in vacuo, the residue was dissolved in 100 mL of chloroform, and the chloroform solution was washed with 1 M aqueous NaOH solution. The chloroform solution was filtered through silica gel, washing with CH_2Cl_2 to elute the byproduct, benzyl chloride. The silica gel was washed with methanol, and this methanol eluate was concentrated in vacuo to yield 7.7 g (78%) of product **31**, mp 143−145 °C; R_f 0.21 (silica gel, ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 8 Hz, 4 H), 7.32 (d, J = 8 Hz, 4 H), 4.98 (s, 2 H), 3.80 (s, 4 H), 3.17 (t, J = 6 Hz, 4 H), 2.60 (t, J = 6 Hz, 4 H), 2.43 (s, 6 H), 1.65 (p, J = 6 Hz, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 135.1, 137.8, 129.5, 127.1, 114.9, 51.5, 44.0, 42.8, 27.7, 21.3. IR ($CDCl_3$): 3340, 3060, 3030, 2980, 2950, 2920, 2860, 2820, 1660, 1650, 1600, 1490, 1450, 1330, 1160, 1090, 1040, 940, 915, 815, 730, 685, 655 cm^{-1}. The HCl salt was formed by stirring a mixture of 1.75 g of the product, 50 mL of CH_2Cl_2, 6 mL of 2 N aqueous HCl, and 25 mL of saturated aqueous NaCl solution for 15 min. The organic layer was separated and washed with saturated aqueous NaCl solution (3 × 25 mL) and then concentrated in vacuo. The residue was dissolved in a minimum volume of warm methanol, then 20 mL of ethyl acetate/

hexane (1:1, v/v) was added slowly to induce precipitation. After the mixture stood at 0 °C overnight, the white solid (**31**·HCl) was collected by vacuum filtration, washed with hexane, and dried at 78 °C (1 mm, 16 h), yielding 1.44 g, mp 185−186 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.29 (s, 2 H), 7.69 (d, J = 8 Hz, 4 H), 7.45 (d, J = 8 Hz, 4 H), 5.31 (s, 2 H), 3.70 (s, 4 H), 3.15 (m, 4 H), 2.96 (m, 4 H), 2.40 (s, 6 H), 1.82 (m, 4 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 143.7, 140.7, 134.6, 130.0, 127.2, 118.0, 51.5, 47.0, 22.1, 21.0. IR (KBr): 3341 (br, m), 2957, 2767, 2654 (br, m), 1598, 1449, 1341, 1158, 1089, 995, 887, 816, 727, 689, 657 cm^{-1}. Anal. Calcd for $C_{24}H_{34}N_8S_2O_4Cl$: C, 54.58; H, 6.49; N, 7.96; S, 12.14; Cl, 6.71. Found: C, 54.58; H, 6.44; N, 7.91; S, 12.13; Cl, 6.58.

9-Benzyl-3-hydroxymethyl-1,5-bis(4-methylbenzenesulfonyl)-1,5,9-triazacyclododecane (32). A solution of thexylborane in THF (1.0 M, 75 mL, 0.075 mol), prepared by adding 6.32 g (75 mmol) of 2,3-dimethyl-2-butene to 75 mL of 1.0 M BH_3·THF solution in an ice bath and stirring for 1 h under N_2, was added slowly to a solution of 14.6 g (25 mmol) of **30** in 200 mL of anhydrous THF at room temperature. The reaction mixture was stirred at room temperature for 4 h and heated under reflux for 1 h. Ethanol (10 mL) was added cautiously to the cooled reaction mixture to quench the excess borane; 25 mL of 3 M aqueous NaOH solution and 10 mL of 30% aqueous H_2O_2 solution were then added, controlling the temperature in the range of 30−35 °C by means of a water bath. The reaction mixture was stirred for 3 h at room temperature. The solvent was removed completely by rotary evaporation. A solution of the residue in 200 mL of $CHCl_3$ was washed with dilute aqueous NaOH solution (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was dried under vacuum. The crude product was used in the next step without further purification. A sample of the product was purified by flash chromatography and dried under vacuum to give a glassy solid; R_f 0.38 (silica gel, ethyl acetate/hexane (1:1, v/v)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J = 8 Hz, 4 H), 7.32 (d, J = 8 Hz, 4 H), 7.2 (m, 5 H), 3.75 (m, 2 H), 3.48 (m, 4 H), 3.42 (s, 2 H), 3.3 (m, 4 H), 3.1 (m, 2 H), 2.5 (m, 2 H), 2.44 (s, 6 H), 2.2 (m, 1 H), 1.9 (m, 2 H), 1.5 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 138.8, 135.5, 129.8, 128.9, 128.3, 127.2, 60.7, 58.3, 49.8, 47.3, 44.2, 36.0, 24.1, 21.5. IR ($CDCl_3$): 3530, 3050, 3020, 2950, 2920, 1595, 1490, 1450, 1330, 1150, 1080, 720, 650 cm^{-1}.

9-Benzyl-3-chloromethyl-1,5-bis(4-methylbenzenesulfonyl)-1,5,9-triazacyclododecane (33). The procedure was the same as that used for synthesis of **21**. The product could not be crystallized but was obtained as a glassy solid, mp 59−70 °C; R_f 0.57 (silica gel, ethyl acetate/hexane (1:1, v/v)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 8 Hz, 2 H), 7.32 (d, J = 8 Hz, 2 H), 7.2 (m, 5 H), 3.58 (d, J = 6 Hz, 2 H), 3.4 (m, 4 H), 3.36 (s, 2 H), 3.3 (m, 4 H), 2.9 (m, 4 H), 2.43 (s, 6 H), 2.2 (m, 1 H), 1.6 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 138.8, 135.3, 129.8, 129.0, 128.3, 127.1, 58.6, 49.7, 48.0, 44.4, 44.2, 36.3, 23.0, 21.4. IR ($CDCl_3$): 3050, 3020, 2950, 2920, 2860, 2800, 1595, 1490, 1445, 1330, 1150, 1105, 1080, 935, 900, 810, 720, 650 cm^{-1}.

3-Chloromethyl-1,5-bis(4-methylbenzenesulfonyl)-1,5,9-triazacyclododecane (34). A mixture of 0.25 g (0.4 mmol) of **33**, 0.25 g of 5% Pd/C and 100 mL of 2-propanol was stirred for 7 d under H_2. The catalyst was removed by filtration, and the filtrate was concentrated to dryness by rotary evaporation. The residue was purified by flash chromatography (silica gel, ethyl acetate/ethanol), yielding 80 mg (25%) of a solid, mp 82−84 °C; R_f 0.48 (silica gel, ethyl acetate/methanol (9:1, v/v)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 8 Hz, 4 H), 7.33 (d, J = 8 Hz, 4 H), 3.56 (d, J = 5 Hz, 2 H), 3.27 (m, 4 H), 3.13 (m, 4 H), 2.67 (m, 2 H), 2.48 (m, 2 H), 2.44 (s, 6 H), 1.81 (m, 2 H), 1.43 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 135.1, 129.7, 127.3, 48.8, 45.1, 44.4, 44.2, 35.5, 26.6, 21.5. IR ($CDCl_3$): 3330, 3050, 3020, 2940, 2905, 2860, 2810, 1605, 1490, 1450, 1330, 1150, 1080, 1020, 950, 900, 810, 720, 705, 650 cm^{-1}. MS m/z (rel intens): 338 (2.9), 337 (6.8), 336 (30), 293 (30), 267 (30), 155 (30), 91 (100).

5,9-Bis(4-methylbenzenesulfonyl)-13-oxa-1,5,9-triazatricyclo-[5.5.1^{1,7}.1^{7,12}]tetradecane (36). A mixture of 0.39 g (0.8 mmol) of **31**, 0.17 g (1 mmol) of *m*-chloroperoxybenzoic acid, 0.14 g (0.9 mmol) of K_2CO_3, and 5 mL of CH_2Cl_2 was stirred for 65 h at room temperature. The reaction mixture was basified by addition of 3 M aqueous NaOH solution and then extracted with chloroform. The chloroform layer was dried over $MgSO_4$ and concentrated in vacuo. The product (82 mg, 20%) was isolated by flash chromatography (ethyl acetate/hexane) and recrystallized from acetonitrile, mp 234−235 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, J = 8 Hz, 2 H), 7.54 (d, J = 8 Hz, 2 H), 7.25 (d, J = 8 Hz, 2 H), 7.21 (d, J = 8 Hz, 2 H), 3.76 (d, J = 13 Hz, 1 H), 3.62 (m, 1 H), 3.50 (d, J = 13 Hz, 1 H), 3.4 (m, 1 H), 3.18 (m, 1 H), 2.92 (m, 2 H), 2.85 (m, 2 H), 2.50 (d, J = 13 Hz, 1 H), 2.44 (d, J = 13 Hz, 1 H), 2.37 (s, 3 H), 2.34 (s, 3 H), 1.85 (m, 1 H), 1.75 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 143.3, 136.5, 135.9, 129.8, 129.7, 126.8, 87.6, 63.9, 53.6, 53.1, 52.5, 50.3, 44.7, 34.6, 34.4, 25.6, 21.5. IR ($CDCl_3$): 3040 (w), 3020 (w), 2920 (s), 2860 (m), 1600 (m), 1490 (m), 1470 (m), 1450 (s), 1440 (s), 1330 (s), 1160 (s), 1090 (s), 980 (m), 950 (m), 930 (m), 920 (m), 900 (m), 810 (m), 750 (m), 730 (s), 660 (s) cm^{-1}; MS m/z (rel intens): 505 (M^+, 2.6), 506 (0.7), 507 (0.3), 350 (30). Anal. Calcd for $C_{24}H_{31}N_3O_5S_2$: C, 57.01; H, 6.18; N, 8.31; S, 12.68. Found: C, 56.64; H, 6.16; N, 8.26; S, 12.01.

Aminomercuration of 31. A mixture of 60 mL of cold ethyl acetate, 1.48 g (3 mmol) of **31** and 1 g (3.6 mmol) of mercuric acetate was stirred for 90 min at 10−20 °C, and then 0.34 g (9 mmol) of $NaBH_4$ was added, followed by 50 mL of 2 M aqueous NaOH solution added 20 min later. Stirring was continued at room temperature for 12 h. Metallic mercury was removed by decantation, the layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined ethyl acetate solutions were washed with 2 M aqueous NaOH solution and dried over $MgSO_4$. Residual solvent was removed in vacuo, and the product was purified by flash chromatography (ethyl acetate/hexane). Three components were isolated, compound **38** (15%, R_f 0.46, silica, ethyl acetate/hexane (1:1, v/v)), **37** (53%, R_f 0.6), and **31**·BH_3 (8%, R_f 0.75), giving the following spectroscopic data. **5,9-Bis(4-methylbenzenesulfonyl)-7-methyl-1,5,9-triazabicyclo[5.5.0]-dodecane (38):** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 8 Hz, 4 H), 7.33 (d, J = 8 Hz, 4 H), 3.36 (d, J = 15 Hz, 2 H), 3.17 (d, J = 15 Hz, 2 H), 3.05 (m, 4 H), 2.96 (m, 4 H), 2.43 (s, 6 H), 1.89 (m, 2 H), 1.68 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 134.9, 129.7, 127.2, 59.7, 58.8, 49.7, 49.3, 29.0, 22.8, 21.5. MS m/z (rel intens): 336 (72), 181 (100), 91 (39). IR ($CDCl_3$): 3050 (w), 3020 (w), 2940 (m), 2910 (m), 2850 (m), 1595 (w), 1490 (m), 1450 (m), 1330 (s), 1150 (s), 1080 (s), 990 (m), 900 (m), 810 (m), 740 (m), 720 (m), 650 (m) cm^{-1}. **5,9-Bis(4-methylbenzenesulfonyl)-7-hydroxymethyl-1,5,9-triazabicyclo[5.5.l]tridecane (37):** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 8 Hz, 4 H), 7.32 (d, J = 8 Hz, 4 H), 3.61 (s, 2 H), 3.58 (d, J = 15 Hz, 2 H), 3.29 (dd, J = 8, 15 Hz, 2 H), 3.13 (dd, J = 6, 15 Hz, 2 H), 3.04 (b, 4 H), 2.85 (dd, J = 8, 15 Hz, 2 H), 2.43 (s, 6 H), 1.94 (m, 2 H), 1.80 (m, 1 H), 1.60 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 134.4, 129.8, 127.3, 65.3, 63.5, 55.2, 50.7, 50.1, 29.2, 21.5. MS m/z (rel intens): 476 (12), 352 (19), 334 (6), 321 (58), 197 (21), 166 (18), 91 (100). IR ($CDCl_3$): 3520 (br. m), 3050 (w), 3020 (w), 2940 (s), 2850 (m), 1595 (m), 1490 (w), 1460 (m), 1330 (s), 970 (s), 910 (m), 810 (m), 750 (m), 730 (m), 680 (m), 660 (m) cm^{-1}. **3-Methylene-1,5-bis(4-methylbenzenesulfonyl)-1,5,9-triazacyclododecane−BH_3 complex (31·BH_3):** mp 196−198 °C (toluene/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J = 8 Hz, 4 H), 7.36 (d, J = 8 Hz, 4 H), 5.33 (s, 2 H), 3.80 (d, J = 16 Hz, 2 H), 3.65 (d, J = 16 Hz, 2 H), 3.08 (m, 6 H), 2.95 (m, 2 H), 2.45 (s, 6 H), 2.04 (m, 2 H), 1.94 (m, 2 H), 1.2−1.7(br, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.3, 133.0, 129.9, 127.6, 141.2, 118.7, 53.1, 50.9, 48.3, 23.5, 21.5. MS m/z (rel intens): 503 (0.4), 348 (10), 306 (7), 91 (100). IR (KBr): 3240 (s), 3070 (w), 3050 (w), 2960 (w), 2910 (m), 2860 (m), 2350 (s), 2300 (m), 2260 (w), 1600 (m), 1490 (m), 1450 (m), 1330 (s), 1150 (s), 1080 (s), 1010 (m), 910 (s), 810 (s), 720 (s), 680 (s), 650 (s) cm^{-1}. Anal.

Calcd for $C_{24}H_{36}BN_3O_4S_2$: C, 57.02; H, 7.18; N, 8.31. Found: C, 57.16; H, 7.31; N, 8.16.

7-Methyl-1,5,9-triazabicyclo[5.5.0]dodecane (39). A solution of 3.17 g (6.4 mmol) of **38** in 10 mL of 98% H_2SO_4 was heated at 100 °C for 54 h under N_2. The resulting solution was cooled in an ice bath, and 10 mL of absolute ethanol was added slowly from an addition funnel, followed by 50 mL of anhydrous ether. The precipitate was collected by filtration and dried under nitrogen. It was dissolved in the minimum amount of water, and the pH of this solution was adjusted to >13 by addition of 10 M aqueous NaOH solution. This solution was extracted with chloroform (5 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated by rotary evaporation. The residue was thoroughly dried under vacuum overnight. The resulting yellow oil was distilled from powdered KOH to afford 0.56 g (46%) of the product as a colorless liquid, bp 100 °C (0.3 mm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.7−2.8 (m, 4 H), 2.64 (d, J = 14 Hz, 2 H), 2.58−2.68 (m, 2 H), 2.45−2.54 (m, 2 H), 2.30 (d, J = 14 Hz, 2 H), 1.59 (m, 2 H), 1.54 (m, 2 H), 1.29 (m, 2 H), 0.73 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 61.1, 60.6, 50.3, 32.2, 22.3. IR (film): 2000−3700 (br, s), 2920 (br, m), 2840 (br, w), 1550 (br, m), 1460 (m), 1400 (m), 1300 (br, w), 1200 (w), 1170 (w), 805 (m) cm^{-1}. MS m/z (rel intens): 184 (M+1, 1), 183 (M^+, 8), 168 (12), 140 (27), 125 (33), 97 (46), 84 (74), 70 (100), 43 (55). Anal. Calcd for $C_{10}H_{27}N_3$: C, 65.53; H, 11.55; N, 22.92. Found: C, 65.51; H, 11.75; N, 22.87.

Measurement of pK_a Values by Potentiometric Titration. Solutions of the freshly distilled triamine in deionized, distilled water (0.1 M or 5.0 mM amine concentration) were titrated with 1.00 M aqueous HCl solution under nitrogen at 25 ± 0.1 °C in a jacketed glass vessel. Water from a constant-temperature bath was circulated through the glass jacket, and the temperature of the titration solution was measured by means of a thermocouple. A Corning model 150 pH/ion meter with a semi-micro rugged bulb glass electrode was used to measure pH values. The pH meter was calibrated at two points by means of Mallinckrodt buffers (pH 4.01 and 10.00, 25 °C). Thermodynamic pK_a values were calculated from the titration curves, considering the activities of all ions in the system.[34] Data from the titrations of triamines **6**, **12**, **13**, **15**, **16**, **23**, and **39** and equations for pK_a calculations are included in the Supporting Information.

Crystallography. HI salts of triamines **12** and **16** were crystallized by gradually cooling solutions in a mixture of toluene and chloroform. Crystal data for **12**·HI: $N_3C_{12}H_{24}I$, M = 339.1, F(000) = 688, orthorhomic, a = 13.867(11) Å, b = 13.898(13) Å, c = 15.506(12) Å, U = 2988.4 Å^3, d_c = 1.51 gcm^{-3}, d_m = 1.49 gcm^{-3}, Z = 8, 1 = 0.7107 Å, μ = 21.5 cm^{-1}, spacegroup $Pbc2_1$, (nonstandard setting of No. 29). Crystal data for **16**·HI: $N_3C_{14}H_{28}I$, M = 375.1, F(000) = 760, monoclinic, a = 8.145(9) Å, b = 13.984(12) Å, c = 15.698(14) Å, β = 110.0(1)°, U = 1680.2 Å^3, d_c = 1.49 gcm^{-3}, d_m = 1.43 gcm^{-3}, Z = 4, 1 = 0.7107 Å, μ = 19.4 cm^{-1}, spacegroup $P2_1/c$. Crystals of approximate size 0.3 × 0.4 × 0.3 mm (**12**·HI) and 0.3 mm × 0.3 mm × 0.3 mm (**16**·HI) were set up to rotate about a axes on a Stoe Stadi2 diffractometer, and data were collected via variable width ω scan. Background counts were for 20 s, and a scan rate of 0.333°/s was applied to a width of (1.5 + sin μ/tan θ). For **12**·HI, 2370 independent reflections were measured of which 1329 with $I > 2\sigma(I)$ were used in subsequent refinement. For **16**·HI, 2869 independent reflections were measured of which 1812 with $I > 3\sigma(I)$ were used in subsequent refinement. Empirical absorption corrections were applied to both crystals.[35] The structures were determined by the heavy atom method. In both structures hydrogen atoms were included in calculated positions, although the methyl hydrogen atoms were refined as rigid groups. In **16**·HI, all non-hydrogen atoms were given anisotropic thermal parameters. In **12**·HI, only the iodine atoms were so refined. Both structures were given a weighting scheme in the form $w = 1/[\sigma_2(F) + 0.003F^2]$. In **16**·HI, the final R value was 0.073 (R_w = 0.073). In **12**·HI, the structure was refined with coordinates (x,y,z) and ($-x,-y,-z$) and the set with the lowest R value was chosen (R 0.084, R_w 0.086). Calculations for both structures were carried out using Shelx76[36] and some of our own programs on an Amdahl 5870 computer at the University of Reading. In the final cycles of refinement, no shift/error ratio was greater than 0.1σ. In the final difference Fourier maps, the maximum and minimum peaks were 1.32, −1.23 e/Å^3 in **16**·HI and 1.52, −0.75 e/Å^3 in **12**·HI. The largest peaks were ca. 1.0 Å from the iodide ions. Positional parameters, bond lengths and angles, hydrogen atom positions, and thermal parameters are given in the Supporting Information.

Computational Chemistry. Calculations were carried out on an Amdahl 5870 computer at the University of Reading. For molecular mechanics, we used the MM2 (1987) program[37] which incorporates a treatment of hydrogen bonds that has been described.[38] All parameters in the force field were taken from the program. Quantum mechanical calculations were carried out with Gaussian98.[39]

Dynamic NMR studies. All spectra were acquired with a Nicolet 300 MHz ^{1}H NMR spectrometer (75.5 MHz for ^{13}C). Temperatures were stabilized within ±1 °C before data acquisition. Curve fitting was performed by the complete bandshape (CBS) method using the iterative GENXCH program[40] for two-site exchange simulation. The activation free energy was calculated from exchange rates at various temperatures by means of the Arrhenius equation, using a value of 4.575 cal/mol.[41] Stack-plots of VT ^{1}H NMR data for **16**·HI and ^{13}C NMR data for **13**·HI are included in the Supporting Information.

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Supporting Information Available: Tables of atomic coordinates, bond lengths and angles, and anisotropic and isotropic thermal parameters for **12**·HI and **16**·HI, stack-plots of VT NMR data for **13**·HI (^{13}C) and **16**·HI (^{1}H), potentiometric titration data for triamines **6**, **12**, **13**, **15**, **16**, **23**, and **39**, and equations for thermodynamic pK_a calculations (PDF). X-ray crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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