The *out,out* to *out,in* Transition for 1,(*n*+2)-Diazabicyclo[*n*.3.1]alkanes

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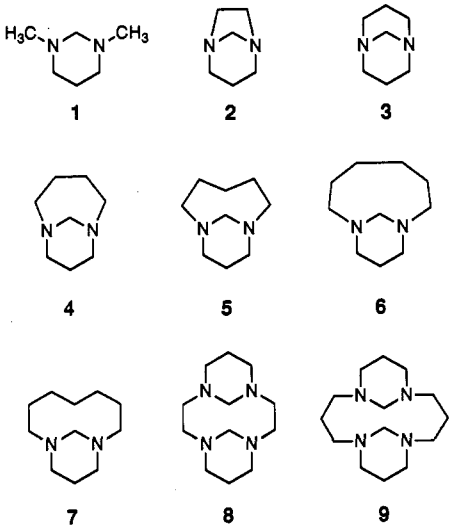
Abstract: Hexahydropyrimidines N,N-bridged by a chain of n methylene groups (1,(*n*+2)-diazabicyclo[*n*.3.1]alkanes) adopt *out,out* (axial,axial) structures for $n = 2$, 3, and 4. When $n = 5$, the photoelectron spectrum shows evidence of the presence of some of the *out,in* (axial,equatorial) isomer in the gas phase, although none can be found in solution. When $n = 6$, the compound is apparently entirely *out,in* in the gas phase but exists as a mixture of *out,out* and *out,in* conformers in solution. For $n = 7$, only the diamond lattice *out,in* isomer can be detected in solution. These experimental data are correlated with force field (MM2) calculations; multiple minimum search methods have been used to locate all low-energy conformations. Semiempirical calculations (MNDO, AM1, and PM3) have been carried out on model systems. Related tricyclic bis-aminals having 10- and 12-membered rings have also been studied. They adopt [2323] and [3333] conformations, respectively, each having *out,in* (equatorial,axial) bridged hexahydropyrimidine rings. For several of the compounds, dynamic NMR processes are observed, and possible mechanisms for these are discussed.

Introduction

Bicyclic structures can adopt only *out,out* structures when the rings are small (3- and 4-membered) or common-sized (5- and 6-membered). In larger systems, *out,in* and, eventually, *in,in* structures become possible and may be more stable.[1] Very little is known about the borderlines for these changes. While these isomers will be separated by high barriers for compounds with carbon bridgeheads,[2-4] for bridgehead diamines nitrogen inversion leads to easy equilibration of the isomers so that the thermodynamic preference can easily be discovered. It is known that bicyclo[3.3.3]undecanes have preferred *out,out* structures, although there is considerable flattening at the bridgehead atoms.[6-9] In bicyclo[4.4.4]tetradecanes,[9] an *out,in* conformation is preferred by *out*-6*H*-azabicyclo[4.4.4]tetradecane,[10] and the isoelectronic outside-protonated diamine 1,6-diazabicyclo[4.4.4]tetradecane,[11] while the free diamine adopts an *in,in* structure.[12] In this paper, we describe the properties of the 1,(*n*+2)-diazabicyclo[*n*.3.1]-alkanes **2**–**7** and discuss their preferred structures. The conformations of two related tricyclic bis-aminals **8** and **9** will also be discussed.



Simple *N,N'*-dialkylhexahydropyrimidines have been the subject of several conformational studies,[13-19] and the subject has

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(1) The *out/in* nomenclature was first used by Simmons and Park[2] and is simple and graphic. It is not entirely unambiguous or consistent, however,[3] since *out,out*- and *in,in*-isomers are, in reality, different conformers of the same configuration, whereas *out,out*- and *out,in*-isomers are different configurations. It is worth noting that the Cahn–Ingold–Prelog *R/S* nomenclature, in its extended form,[5] can handle all possibilities. When two of the bridges are the same, the *r/s* system is used, and this also works[5(b)] if all the bridges are the same. Thus *in*-NH-*out*-6*H*-1-azabicyclo-[4.4.4]tetradecane is the 1*s*,6*s*-isomer. However, the *out/in* designation is easier to use, and has been employed throughout the present manuscript.

(2) Simmons, H. E.; Park, C. H. *J. Am. Chem. Soc.* **1968**, *90*, 2429–2431. Simmons, H. E.; Park, C. H.; Uyeda, R. T.; Habibi, M. F. *Trans. N. Y. Acad. Sci., Ser. II* **1970**, *32*, 521–534.

(3) Haines and Karntiang reported the first examples of homeomorphic isomerization of compounds with CH bridgeheads: Haines, A. H.; Karntiang, P. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2577–2587.

(4) Saunders and Krause reported calculations on bicyclo[6.5.1]tetradecane and observation of homeomorphic isomerization between *out,out*↔*in,in* and *out,in*↔*in,out* isomers: Saunders, M.; Krause, N. *J. Am. Chem. Soc.* **1990**, *112*, 1791–1795.

(5) (a) Prelog, V.; Helmchen, G. *Angew. Chem., Int. Ed Engl.* **1982**, *21*, 567–583. (b) Prelog, V., personal communication to R. W. Alder.

(6) Wang, A. H.-J.; Missavage, R. J.; Bryn, S. R.; Paul, I. C. *J. Am. Chem. Soc.* **1972**, *94*, 7100–7104.

(7) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1975**, *97*, 4136–4137.

(8) Alder, R. W.; Goode, N. G.; King, T. W.; Mellor, J. M.; Miller, B. W. *J. Chem. Soc., Chem. Commun.* **1976**, 173–174.

(9) For a review of medium-ring bicyclic chemistry, see: Alder, R. W. *Tetrahedron* **1990**, *46*, 683–713.

(10) Alder, R. W.; Arrowsmith, R. J. *J. Chem. Res. (S)* **1980**, 163; *J. Chem. Res. (M)* **1980**, 2301–2313.

(11) Alder, R. W.; Orpen, A. G.; White, J. M., unpublished results.

(12) Alder, R. W.; Orpen, A. G.; Sessions, R. B. *J. Chem. Soc., Chem. Commun.* **1983**, 999–1000.

(13) Katritzky, A. R.; Patel, R. C.; Riddell, F. G. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 521–529, and references therein.

(14) Riddell, F. G. *J. Chem. Soc.(B)* **1967**, 560–561.

(15) Hutchins, R. O.; Kopp, L. D.; Eliel, E. L. *J. Am. Chem. Soc.* **1968**, *90*, 7174–7175.

(16) Farmer, R. F.; Hamer, J. *Tetrahedron* **1968**, *24*, 829–835.

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been reviewed.[20-22] Dynamic NMR has been used to measure nitrogen inversion[13] and ring inversion barriers and to determine the identities of low-energy conformations. Dynamic ^{1}H NMR of the aminal hydrogens can be used to monitor ring inversion, and when this is slow, ^{13}C NMR allows the identification of populated conformers and, in some cases, the determination of nitrogen inversion barriers.

In general, it is found that both diequatorial, (eq,eq), and equatorial,axial, (eq,ax) conformers are populated in simple *N,N'*-dialkylhexahydropyrimidines and there is more of the eq,ax conformer than would be expected on the basis of comparison with 1,3-dialkylcyclohexanes.[18,23] This difference has been attributed to the generalized anomeric effect,[15,24-26] whereby there is net stabilization due to lp–σ^* overlap when a lone pair (lp) is antiperiplanar to a C–X bond, where X is an electronegative element. In hexahydropyrimidines this is only possible in eq,ax and ax,ax conformations, but the latter is not significantly populated in simple monocyclic compounds due to severe 1,3-diaxial interactions between the *N*-alkyl groups.

There is therefore a substantial background to using the hexahydropyrimidine ring as a probe for the solution conformations of 1,(*n*+2)-diazabicyclo[*n*.3.1]alkanes. In addition, the ^{1}H chemical shifts of several of the nuclei in the hexahydropyrimidine ring are quite sensitive to the conformation.

The conformations of these molecules in the gas phase can be partially revealed by their photoelectron spectra. Nelsen and Buschek[27] found that 1,3-dimethylhexahydropyrimidine (**1**), which is largely eq,eq in solution, and 1,2,3-trimethylhexahydropyrimidine, which is largely eq,ax, gave very similar photoelectron spectra, with two peaks in the lone pair ionization region separated by 0.4 eV, whereas 1,5-diazabicyclo[3.2.1]octane (**2**) and 1,5-diazabicyclo[3.3.1]nonane (**3**) (which are assuredly ax,ax) gave two more widely separated peaks (separations 0.75[28] and 1.03 eV, respectively). It seems that photoelectron spectra can easily distinguish ax,ax from the other two conformations, although the latter are not clearly distinguished by this technique. The large splitting of the n_+ and n_- orbital energies for the ax,ax isomer is expected on theoretical grounds.[30] Thus photoelectron spectra can achieve the required distinction of *out,out* = ax,ax from *out,in* = eq,ax conformations for the 1,(*n*+2)-diazabicyclo[*n*.3.1]alkanes.

With all these experimental probes available, the 1,(*n*+2)-diazabicyclo[*n*.3.1]alkane series seems a good first choice for study of the *out,out/out,in/in,in* borderlines (see Figure 1). (From models, *in,in* = eq,eq structures only become likely as global minima for $n = 11$ and larger). As *n* increases, the number of conformations open to these compounds increases sharply, so that in order to provide a clear background for discussion of the experimental results, we have made a thorough study of compounds **3–7**, using the MM2 empirical force field. We also report some semiempirical MO calculations, using the MNDO, AM1, and PM3 methods. In/out isomerism in bicyclo[*n*.3.1]alkanes has been discussed theoretically before,[31] and two cases have been observed. Thus Sundberg and Smith[32] obtained both *in*- and *out*-CH isomers of a complex 1-azabicyclo[5.3.1]undecane fused to an indole. Recently *trans*-bicyclo[5.3.1]undecan-11-one (i.e., the *out,in*-isomer) was prepared,[33] but all attempts to effect equilibration with the known[34] *cis*(i.e., *out,out*)-isomer were unsuccessful, even though the bridgehead hydrogens are, in principle, enolizable.

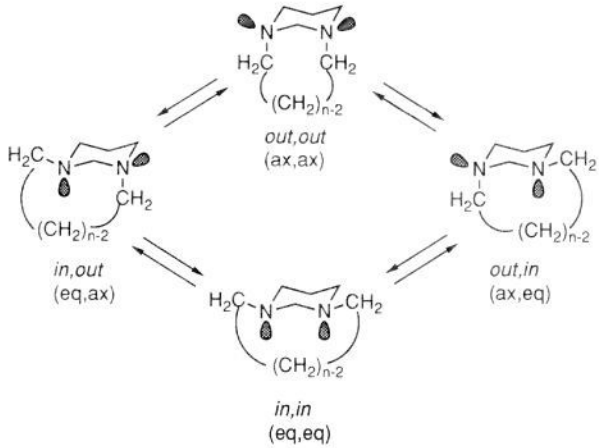


Figure 1. Conformational interconversion diagram for 1,(*n*+2)-diazabicyclo[*n*.3.1]alkane systems.

Results

Preparative Routes. The preparative routes used to make compounds **4–9** are shown diagrammatically in Scheme I. All of the compounds **4–9** were prepared by reaction of formaldehyde with the appropriate diamine or tetraamine. The diamines required for the preparation of **4–7** were prepared by reductive cleavage of a bicyclic aminal or amidine, using the diisobutylaluminum hydride (DIBAH) method of Yamamoto and Maruoka.[35] 1,5-Diazacyclononane and 1,5-diazacycloundecane were prepared from DBN and DBU, respectively, essentially as described.[35] 1,5-Diazacyclodecane was obtained from 1,5-diazabicyclo[4.4.0]decane hydrochloride salt,[36] itself prepared by condensation of 5-chloropentanal with 1,3-diaminopropane (this procedure has been described in brief;[37] full details are given in the Experimental Section). 1,5-Diazacyclododecane was obtained from the amidine 1,9-diazabicyclo[6.4.0]dodec-8-ene, which was prepared through reaction of 2-methoxy-1-azacyclooct-1-ene[38] with 3-bromopropylamine hydrobromide and base. It was noticed that both 1,8-diazabicyclo[6.3.1]dodecane (**6**) and 1,9-diazabicyclo[7.3.1]tridecane (**7**) were liquids but formed solid oligomers on standing, from which they could be recovered in fair to good yields by distillation. Full details of this interesting

(17) Ferguson, I. J.; Katritzky, A. R.; Read, D. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 818–820.
(18) Katritzky, A. R.; Baker, V. J.; Ferguson, I. J.; Patel, R. C. *J. Chem. Soc., Perkin Trans. 2* **1979**, 143–150. The value of $\Delta G°$ of 0.65 kcal/mol given in this paper for the free energy difference between the eq,eq and eq,ax appears to be in error; the correct figure is 0.54 kcal/mol.
(19) Katritzky, A. R.; Baker, V. J.; Brito-Palma, F. M. S.; Ferguson, I. J.; Angiolini, L. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1746–1751.
(20) Armarego, W. L. F. *Stereochemistry of Heterocyclic Compounds, Part 1*; Wiley-Interscience: New York, 1977; pp 180–183, and references therein.
(21) Riddell, F. G. *The Conformational Analysis of Heterocyclic Compounds*; Academic Press: New York, 1980, and references therein.
(22) Crabb, T. A.; Katritzky, A. R. *Adv. Het. Chem.* **1984**, *36*, 1–173.
(23) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley-Interscience: New York, 1965; pp 53–58.
(24) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *27*, 527–547.
(25) Szarek, W. A., Horton, D., Eds. *The Anomeric Effect: Origin and Consequences*; ACS Symposium Series, 87; American Chemical Society: Washington, DC, 1979.
(26) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983.
(27) Nelsen, S. F.; Buschek, J. M. *J. Am. Chem. Soc.* **1974**, *96*, 7930–7934.
(28) The relatively small peak separation observed in the case of the 1,5-diazabicyclo[3.2.1]octane is undoubtedly due to through-bond coupling[29] involving the two-carbon bridge which will oppose the splitting caused by the one-carbon bridge.[30]
(29) Heilbronner, E.; Muszkat, K. A. *J. Am. Chem. Soc.* **1970**, *92*, 3818–3821.
(30) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1–9.
(31) Mastryukov, V. S. *J. Mol. Struct.* **1983**, *96*, 361–367.
(32) Sundberg, R. J.; Smith, F. X. *J. Org. Chem.* **1975**, *40*, 2613–2621.
(33) Winkler, J. D.; Hey, J. P.; Willard, P. G. *J. Am. Chem. Soc.* **1986**, *108*, 6425–6427. Winkler, J. D.; Hong, B.-C.; Hey, J. P.; Willard, P. G. *J. Am. Chem. Soc.* **1991**, *113*, 8839–8846, and references therein.
(34) Warnoff,E.; Wong, C.; Tai, W. *J. Org. Chem.* **1967**, *32*, 2664–2669.
(35) Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 4186–4194.
(36) Peck, R. L.; Day, A. R. *J. Heterocycl. Chem.* **1969**, *6*, 181–185.
(37) Alder, R. W.; Eastment, P.; Moss, R. E.; Sessions, R. B.; Stringfellow, M. A. *Tetrahedron Lett.* **1982**, *23*, 4181–4184. 1,5-Diazacyclodecane was first prepared by: Mikolajewska, H.; Kotelko, A. *Acta Pol. Pharm.* **1966**, *23*, 425–431; *Chem. Abstr.* **1967**, *66*, 85776t.
(38) Benson, R. E.; Cairns, T. L. *J. Am. Chem. Soc.* **1948**, *70*, 2115–2118.

Scheme I. Preparative Routes for Compounds **4–9**

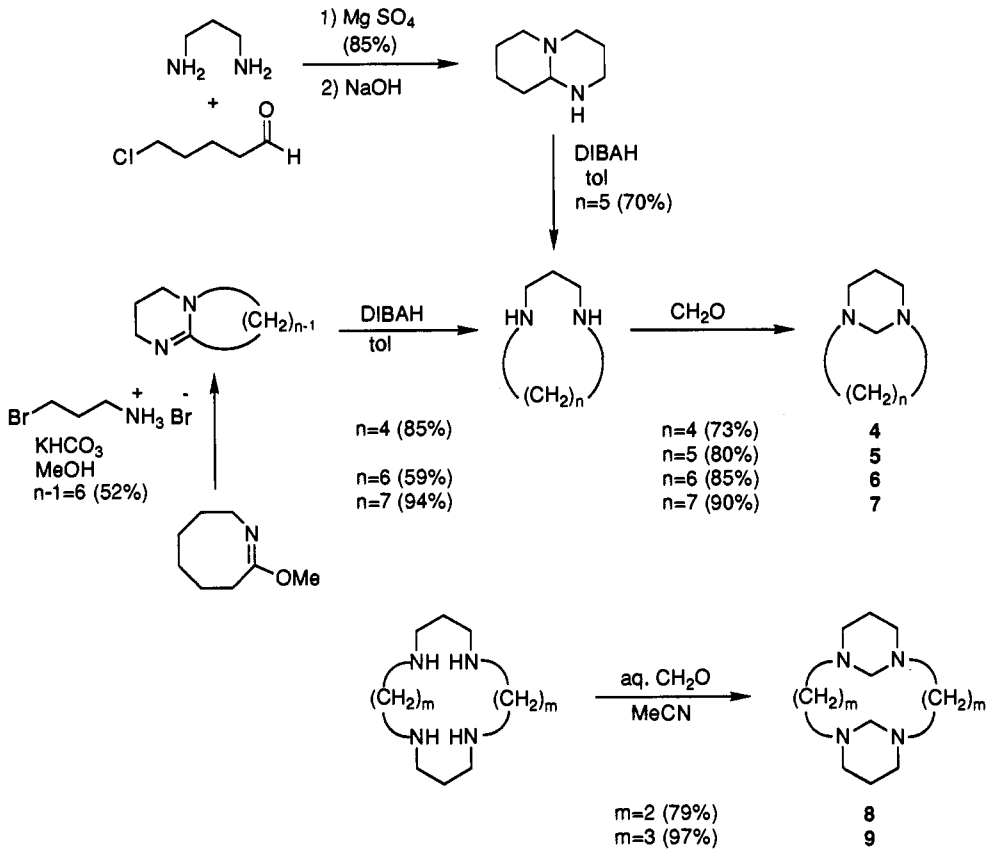
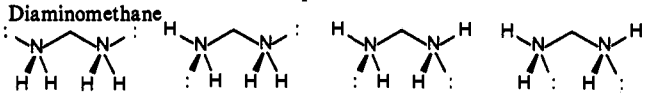


Table I. *Ab Initio* and Semiempirical Calculations for Diaminomethane



(A) C_{2h} (B) C_1 (C) C_2 (D) C_s

		calculated ΔH_f (kcal/mol); energies[a] relative to conformer (A) in parentheses			
conformer	lp-N-C-N-lp	RHF/4-21G[b]	MNDO	AM1	PM3
A	ap,ap		−2.74	−6.47	−1.22
		(0.00)	(0.00)	(0.00)	(0.00)
B	sc+,ap		−4.32	−4.86	−1.43
		(1.58)	(−1.57)	(1.60)	(−0.21)
C	sc+,sc+		−3.15	−1.71	0.19
		(2.38)	(−0.40)	(4.76)	(1.41)
D	sc+,sc−		−0.53	0.86	2.33
		(8.08)	(2.21)	(7.32)	(3.55)

[a] Relative potential energies for ab initio calculations; relative heats for semiempirical calculations. [b] From ref 46.

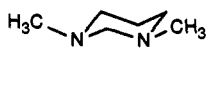
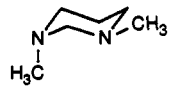
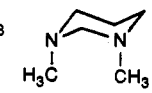
behavior are given in the Experimental Section. Compounds **8** and **9** have been briefly reported before;[39,40] full details of their preparation are given in the Experimental Section. The tetraamine needed for **9** was prepared according to literature methods.[41]

Semiempirical MO Calculations. Compounds **2–7** are too large for usefully high-level *ab initio* calculations with full geometry optimization to be practical, especially considering the large number of conformations that would require calculation; on the other hand, as will be discussed below, empirical force field (EFF) calculations had not been formally parametrized to account for the generalized anomeric effect in aminals. We hoped, therefore, that semiempirical MO calculations might prove useful in linking *ab initio* results on small model systems with the experimental results for **2–7**. Calculations on diaminomethane were performed using the MNDO, AM1, and MNDO-PM3 methods.[42,43] The relative energies of the possible conformations are shown in Table I.[44,45] It can be seen that both MNDO and PM3 give energetic ordering of the conformations at variance with published RHF/4-21G *ab initio* results,[46] whereas the agreement between AM1 and *ab initio* relative energies is encouraging. We therefore applied the semiempirical methods to *N,N'*-dimethylhexahydropyrimidine with some expectation of obtaining good modeling of experimental relative energies by AM1. However, the results were disappointing, as can be seen in Table II.

In defiance of experiment,[27] AM1 and PM3 calculations place

(39) Gabe, E. J.; Le Page, Y.; Prasad, L.; Weisman, G. R. *Acta Crystallogr.* **1982**, *B38*, 2752–2754.
(40) Gabe, E. J.; Le Page, Y.; Prasad, L.; Weisman, G. R. *Acta Crystallogr.* **1983**, *C39*, 275–278.
(41) Smith, W. L.; Raymond, K. N. *Inorg. Synth.* **1980**, *20*, 109–111.
(42) (a) MNDO: Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907–4917. (b) AM1: Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909. (c) MNDO-PM3: Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209–220; 221–264.
(43) All semiempirical MO calculations were carried out using AMPAC v. 1.0 (QCPE 506): Dewar Research Group; Stewart, J. J. P. *QCPE Bull.* **1986**, *6*, 24. The program was augmented with PM3 parameters and additional options by T. Clark (Erlangen) and P. A. Petillo (Wisconsin). All calculations employed the PRECISE option and Broyden-Fletcher-Goldfarb-Shanno (BFGS) geometry optimization. Use of the BFGS procedure in semiempirical SCF-MO calculations is discussed in the following papers: Cioslowski, J.; Kertesz, M. *QCPE Bull.* **1987**, *7*, 159–161, and references therein. Agrafiotis, D. K.; Rzepa H. S. *J. Chem. Res. (S)*, **1988**, 100–101, and references therein.
(44) After our calculations had been carried out, Aped *et al.* published MNDO results for diaminomethane.[45a] Our MNDO relative energies agree qualitatively with those reported, but there are some quantitative differences. We find the sc+,sc- (D) conformation (constrained to C_s) to be 3.78 kcal/mol above the MNDO global minimum, while they find the destabilization to be 4.22 kcal/mol. Differences in constraints and optimization procedures may account for other smaller inconsistencies. Comparison of semiempirical and *ab initio* calculations for methanediol and its protonated ion have also recently been reported.[45b]
(45) (a) Aped, P.; Schleifer, L.; Fuchs, B.; Wolfe, S. *J. Comput. Chem.* **1989**, *10*, 265–283. (b) Woods, R. J.; Szarek, W. A.; Smith, V. H. *J. Chem. Soc., Chem. Commun.* **1991**, 334–337.
(46) Schaefer, L.; Van Alsenoy, C.; Williams, J. O.; Scarsdale, J. N.; Geise, H. J. *J. Mol. Struct. (THEOCHEM)* **1981**, *12*, 349–361. For recent 3-21G results consistent with the 4-21G results, see ref 45a.

Table II. ΔH_f (kcal/mol) of 1,3-Dimethylhexahydropyrimidine and 1,3-Dimethylcyclohexane (in parentheses)

	 eq,eq	 eq,ax	 ax,ax
MM2[a]	1.11 (–44.57)	2.29 (–42.76)	7.87 (–39.23)
MNDO[b]	5.40 (–37.55)	4.11 (–36.44)	5.13 (–34.49)
AM1[b]	10.70 (–48.84)	6.50 (–47.39)	4.52 (–44.65)
PM3[b]	–7.25 (–42.70)	–9.91 (–41.60)	–11.03 (–40.47)

[a] Using the default parameters; dielectric constant = 1.5. [b] Calculations run with AMPAC using PRECISE option and BFGS optimization.

the ax,ax conformer of **1** as the global minimum and get eq,ax lower in energy than eq,eq. MNDO gets eq,ax as the global minimum, with ax,ax lower than eq,eq. In seeking the cause of the problem, we made comparable calculations on 1,3-dimethylcyclohexane (Table II). Here the agreement with MM2 is acceptable, with AM1 performing rather better than MNDO and PM3. Thus the failure of AM1 to correctly calculate the relative energies of the conformers of **1** must lie in the treatment of the amino nitrogen or the aminal unit,[46] despite the agreement between AM1 and RHF/4-21G calculated diaminomethane relative conformational energies. This agreement is most likely due to a fortuitous cancellation of errors in the AM1 calculations. The *ab initio* energies may also be suspect, since it is known that sp basis sets overestimate the flattening of amino nitrogen, possibly leading to an overestimation of the generalized anomeric effect.[47]

It is of interest to note that PM3 performed better than AM1 and MNDO for calculation of the geometries of the conformers of **1** (detailed in the supplementary materials). MNDO is known to flatten amino nitrogens excessively,[47b] and this occurs in the present case. AM1-calculated N–C–N angles are too large in diaminomethane (relative to *ab initio* results) and in **1** (relative to MM2 results). MNDO and AM1 both severely flatten the six-membered ring of the conformers of **1**. Comparisons with MM2-calculated geometries are justified since MM2 does a good job of reproducing X-ray structure bond lengths, angles, and torsion angles of crystalline hexahydropyrimidines (*vide infra*). The average deviations of torsion angles from MM2 torsion angles are 7.5° (14° = largest deviation) for MNDO, –6.1° (14° = largest deviation) for AM1, and 1.6° (4° = largest deviation) for PM3.

Empirical Force Field Calculations. We have used the well-established MM2 force field[48] throughout; input was accomplished graphically or by using the MMHELP program.[48c] The amine parameters of Profeta and Allinger[49] were used throughout for our aminal calculations. The results of calculations on *N,N'*-dimethylhexahydropyrimidine (**1**) using these (default) parameters have already been referred to (see Table II).[50] The parameters do not take specific account of the aminal anomeric effect. We made additional calculations using a V_2 (N–C–N–lp) torsional term = 1.0 kcal/mol, analogous to the corresponding O–C–O–lp term that has been used to model the anomeric effect in acetals.[51] MM2 uses a dipole interaction electrostatic treatment, with a default effective dielectric constant (DE) of 1.5 for the gas phase. In an attempt to model acetone/CF_2Cl_2 solution (see below), the bulk dielectric constant of acetone was taken as an estimate of DE. Use of this value had the effect of making the electrostatic contribution to the steric energies negligible. With both of these latter modifications incorporated (Table III), the eq,eq/eq,ax energy difference reproduces well an enthalpy difference of 0.71 kcal/mol calculated from the reported 1:9 isomer ratio at –150 °C in CF_2Cl_2/acetone-d_6,[18] assuming the major entropy difference to be due to the entropy of mixing (R ln 2 = 1.38 eu). Unfortunately, there are no experimental data for the eq,ax/ax,ax enthalpy difference which is of more interest here, so with the exception of **6**, where some V_2 = 1 calculations are reported, all subsequent calculations use the Allinger–Profeta default parameters. It should therefore be remembered in what follows that the steric energies of ax,ax (*out,out*) and, to a lesser extent, eq,ax (*out,in*) are probably being overestimated by these parameters. Aped *et al.*[45a] have recently reported a parametrization of the MM2 force field for aminals. However, on the basis of the reported results, it does not appear to reproduce experimental relative energies of dialkylhexahydropyrimidines.

Table III. MM2 Calculations for 1,3-Dimethylhexahydropyrimidine with Variation of Dielectric Constant and V_2 Torsion Term

		steric energies (kcal/mol) (strain energies)			ΔE (kcal/mol)	
DE[a]	V_2[b]	eq,eq	eq,ax	ax,ax	(eq,ax-eq,eq)	(ax,ax-eq,ax)
1.5	0	11.18 (1.72)	12.36 (2.90)	17.94 (8.48)	1.18	5.58
21	0	10.90 (1.44)	12.35 (2.89)	17.74 (8.28)	1.45	5.39
1.5	1	12.59 (3.13)	13.06 (3.60)	18.06 (8.60)	0.47	5.00
21	1	12.31 (2.85)	13.06 (3.60)	17.86 (8.40)	0.75	4.80

[a] Effective dielectric constant; 1.5 is default for the gas phase; 21 is for acetone solution. [b] V_2 term for N-C-N-lp (kcal/mol); minima at 0° and 180°.

The results of MM2 calculations on **3**–**7** and on the corresponding hydrocarbons are tabulated in Chart I; additional data are recorded in the supplementary material. We also report calculations on the related bis-aminals **8** and **9**, whose solid-state structures have been reported.[39,40] The number of conformations for these bicyclo[*n*.3.1]alkane systems increases rapidly as *n* increases, and we have therefore carried out conformational searches using MacroModel V2.5 BATCHMIN[52a] to try to ensure that all low-energy conformers have been located. The Monte Carlo multiple-minimum internal coordinate search method was employed.[52b,c] It has been pointed out that the minimum duplication rate (D_{min}), i.e., the smallest number of times any conformer is found during a search, is a useful measure of search convergence.[52b] After some trial and error, it was possible by careful choice of initial conditions to find all minima *at least* three times (usually more) in a single run, including those differing through nitrogen inversions. Our searches on the large members of the aminal series were computer-time limited, so we had to be satisfied with D_{min} of 3. While we cannot absolutely guarantee convergence, we are reasonably confident that we have not missed any important low-energy conformers. Some idea of the conformational complexity of the large systems can be gauged from the fact that 113 conformations for **7** were found within 19 kcal/mol of the global minimum. The MacroModel version of MM2 differs from the Allinger standard force field in its treatment of

(47) (a) Hehre, W. J.; Radom, L.; Schleyer. P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986; pp 175–181. See also refs 45a and 49a. (b) Nelsen, S. F.; Ippoliti, J. T.; Petillo. P. A. *J. Org. Chem.* **1990**, *55*, 3825–3833.

(48) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134. (b) MM2(77) Program: Allinger, N. L.; Yuh, Y. H. *QCPE* **1981**, *12*, 395. (c) Petillo, P. A.; Coolidge, M. B.; Weisman, G. R. *QCPE Bull.* **1985**, *5*, 68.

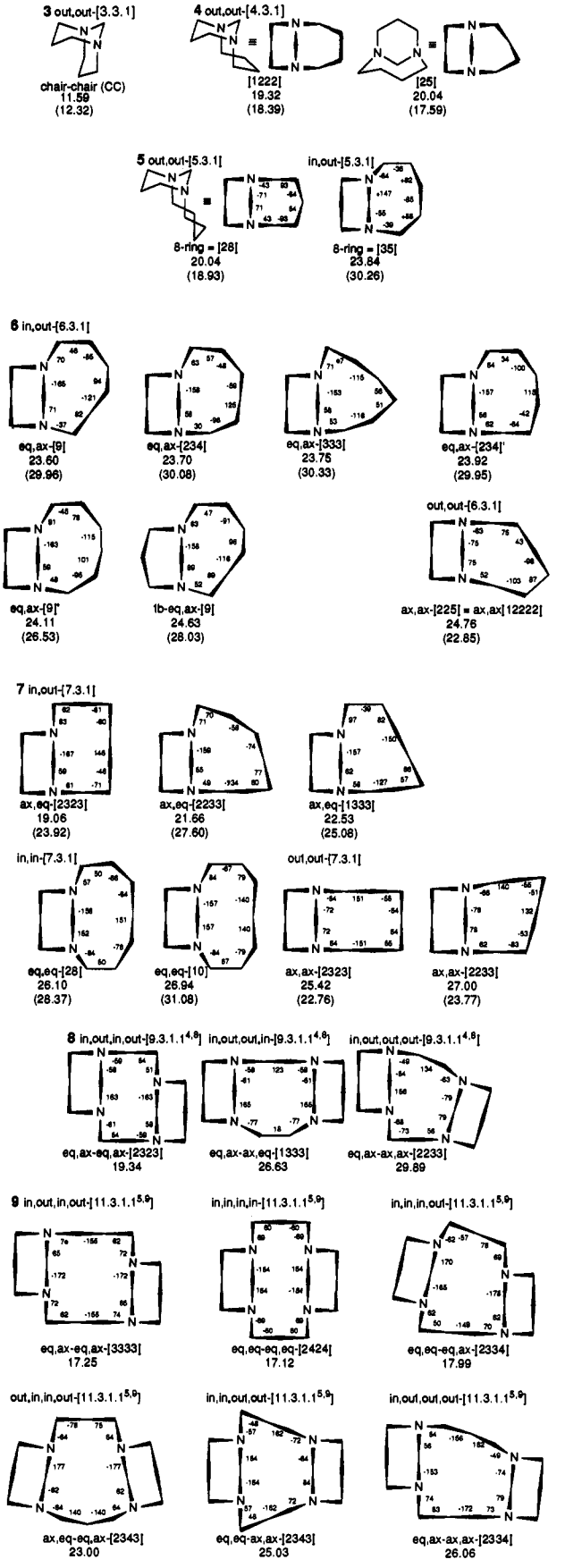
(49) (a) Profeta, S., Jr.; Allinger, N. L. *J. Am. Chem. Soc.* **1985**, *107*, 1907–1918. (b) The original QCPE distribution of MM2(77)[48b] contained an error in the amine parameters (Profeta, S., Jr. *QCPE Bull.* **1983**, *3*, 36). The error had been corrected in the implementation of MM2 used for the calculations described herein.

(50) Default MM2 results on **1** have also been reported by Carballiera *et al.*; steric energies are in agreement with those reported herein. Carballiera, L.; Mosquera, R. A.; Rios, M. A. *J. Mol. Struct.* **1988**, *176*, 89–105.

(51) Allinger, N. L.; Chang, S. H.-M.; Glaser, D. H.; Hoenig, H. *Isr. J. Chem.* **1980**, *20*, 51–56.

(52) (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467. (b) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386. (c) Saunders, M.; Houk, K. N.; Wu, Y.-D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419–1427.

Chart I. Selected Conformations of Compounds **3**–**9**[a]



[a] Structures shown are either expected to contribute appreciably to the equilibrium conformational mixture, or are involved in suggested dynamic processes. Numbers under each structure are the MM2-calculated strain energies, with strain energies for the corresponding alkanes in parentheses.

Table IV. Vertical Ionization Energies (eV)[a]

diamine	I_1	I_2	$\delta I = I_2 - I_1$
2	8.89	9.64	0.75
3	7.75	8.78	1.03
4	7.44	8.44	1.00
5[b]	7.42	8.56	1.14
6	8.00	8.00	0.00
c	7.40	8.50	1.10

[a] For all compounds except **6**, the assignment is $n_- > n_+$. [b] This compound also shows a band at 8.00 eV. [c] 1,6-Diazabicyclo[4.4.1]undecane.

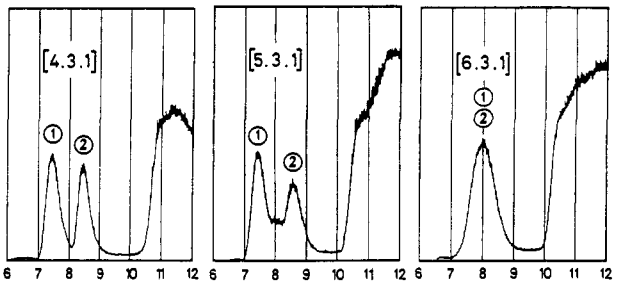


Figure 2. Photoelectron spectra for compounds **4**, **5**, and **6**.

electrostatic interactions (Coulomb electrostatics using point charges; DE = 1.0 for gas phase). All of the energies and geometrical data reported within the paper were obtained with standard MM2, although the additional data in the supplementary material are MacroModel values. In general, torsion angles do not differ by more than 2° and relative energies by more than 0.5 kcal/mol, although this sometimes results in two important conformations changing places energetically. Thus the eq,ax-eq,ax-[3333] conformation of **9**, which is the observed conformation in the solid state, is the global minimum obtained from MacroModel MM2 but is slightly less stable than the eq,eq-eq,eq-[2424] according to standard MM2. The relative energies of the lowest *in,in* and *out,out* for **7** also change rank between the two versions of MM2.

With one exception, all of the conformations shown have a chair hexahydropyrimidine ring; twist conformations were usually about 5 kcal/mol higher in energy than similar conformations with a chair six-membered ring. In Chart I, conformations are shown using either a perspective drawing or a Dale[53] diagram. The latter become increasingly preferable as *n* increases. Where appropriate, torsion angles are given around the large ring. The nomenclature of Dale[53] is used thoughout this paper to denote medium- and large-ring conformations.

Photoelectron Spectra. The lone pair ionization energies of the series **2**–**6** are given in Table IV, and the spectra of **4**–**6** are reproduced[54] in Figure 2. It can be seen that 1,6-diazabicyclo-[4.3.1]decane (**4**) shows two peaks with a separation almost the same as that of 1,5-diazabicyclo[3.3.1]nonane (**3**). Moreover, there is almost base line separation between the two peaks. Thus **4**, like **3**, must be completely *out,out* in the gas phase. Two main peaks are also seen in the spectrum of 1,7-diazabicyclo-[5.3.1]undecane (**5**), but there is clearly a smaller peak in between these at about 8.0 eV. The spectrum of 1,8-diazabicyclo[6.3.1]-dodecane (**6**) exhibits only one broad peak at 8.0 eV, with very little sign of small peaks corresponding to those seen for the smaller ring compounds. We suggest that **6** is almost completely *out,in* and that the peak seen at 8.0 eV in the spectrum of **5** is due to

(53) Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1115–1129. Dale, J. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley: New York, 1976; Vol. 9, pp 199–270. Dale's nomenclature utilizes [*abc*...] to represent ring conformation, where *a*, *b*, and *c* are each integers denoting the number of bonds between two true corners. A sequence of two gauche (synclinal) torsion angles of the same sign introduces a bend; the atom flanked by these torsion angles is referred to as a true corner. Thus, for example, the 10-membered ring of the ax,ax-[2323] conformation of compound **7** in Chart I has four true corners and four sides; it is a "rectangular" diamond-lattice [2323] conformation.

(54) Honegger, E.; Yang, Z.-Z.; Heilbronner, E.; Alder, R. W.; Moss, R. E.; Sessions, R. B. *J. Electron Spectrosc. Rel. Phenom.* **1985**, *36*, 297–304.

Table V. Selected ^{1}H NMR Chemical Shifts and Coupling Constants[a]

compd	δ N-CH_2-N ax	δ N-CH_2-N eq	δ N-C-CH_2-C-N ax	δ N-C-CH_2-C-N eq	J_{gem} (Hz) for N-CH_2-N	N-C-N angle[c] (deg)
2	4.02	3.27	1.88	1.10	−10.5	104.9
3	3.94	3.94	2.16	1.30		111.7
4	4.03	3.87	1.89	1.06	−14.4	113.8
5	3.80	4.23	2.32	0.91	−14.8	115.8
6	3.46	4.12	2.27	1.08	−13.2	108.9, 109.9, 116.9[d]
7	2.95	4.07	2.23	1.16	−11.8	111.8
8	2.90	5.45	2.26	1.17	−10.8	110.8
9	2.86[b]	3.87[b]			−11.2	110

[a] $CDCl_3$ solvent. [b] Temperature 2 °C; 90-MHz spectrum. [c] From MM2 calculations. [d] For the eq,ax-[333], eq,ax-[234], and ax,ax-[225] conformations, respectively.

the presence of some *out,in* isomer in the gas phase. It would appear that there is approximately 10–15% of this minor isomer present. We estimate that there cannot be more than 5–10% of the *out,out* isomer of **6** present in the gas phase.

^{1}H NMR Spectra. The proton spectra of **2–7** can be analyzed to obtain most of the chemical shifts and coupling constants in the hexahydropyrimidine ring and several of these spectral parameters are sensitive to the ring junction stereochemistry. These are listed in Table V.[55] The axial aminal hydrogen seems to be the simplest and clearest indicator. Its chemical shift is substantially affected by whether it is antiperiplanar to a lone pair. Unlike its equatorial partner, it is not also subject to variable amounts of steric compression from the $(CH_2)_n$ bridge. It should be noted that assignment of the aminal protons is made easy by the presence of a long-range W-plan coupling to the equatorial hydrogen. In compounds like **2** and **3**, which have the alkyl chain ax,ax (lone pairs *out,out*), the axial hydrogen appears at about 4 ppm, whereas in compounds **8** and **9**, where it is known from X-ray structural work[39,40] that the large ring is fused eq,ax to the hexahydropyrimidine ring, this proton absorbs below 3 ppm. On this criterion alone, **4** is *out,out* and **7** is *out,in*. Diamine **5** is at least largely *out,out*, but **6** looks likely to be a mixture.

The other proton whose chemical shift is potentially sensitive to the *out/in* structure is the equatorial hydrogen on the central carbon of the $(CH_2)_3$ bridge, which is found to be consistently upfield of its axial partner, the reverse of the usual order in cyclohexanes. Reversal of $\delta_{ae}(\beta)$ in six-membered heterocycles has been noted previously.[56] The equatorial proton has a W-plan arrangement with two (ax,ax) or one (eq,ax) lone pair and appears further upfield in ax,ax, (*out,out*) conformers. The magnitude of J_{gem} of methylene adjacent to nitrogen has been used as a conformational criterion in saturated 6-membered nitrogen heterocycles.[57] Of particular relevance here is the successful differentiation of eq,eq and ax,eq conformers of dialkylhexahydropyrimidines using the aminal J_{gem}.[58] The major factors that influence the magnitude of J_{gem} are the lp–N–C–H methylene torsional alignment and the N–C–N angle.[57] Listed in Table V are the measured J_{gem} values for the bicyclo[*n*.3.1]aminal series and N–C–N angles that have been extracted from MM2 results for appropriate representative conformations. The results suggest that J_{gem} can be used to differentiate ax,ax from ax,eq conformations. The measured values for eq,ax cases **7–9** are consistent with literature values for other eq,ax cases.[58] Theory predicts larger negative J_{gem} values for ax,ax conformers, as we observe for **4** and **5** and has been previously reported for the benzo analog of **3** (J_{gem} = −13 Hz).[59] The increase in J_{gem} (less negative values) with decreasing ring size through the ax,ax series (**5** through **2**) is a consequence of N–C–N angle compression.[57] The J_{gem} for **6** falls in between the values for **7–9** and **4–5**, consistent with a mixture of eq,ax and ax,ax conformers.

Table VI. ^{13}C Chemical Shifts[a]

compd	N-*C*-N	N-C-*C*-C-N	others
2	77.87	19.41	51.97, 54.25
3	69.46	22.88	50.53
4	66.26	21.45	30.59, 52.75, 54.77
5	61.22	12.94	25.64, 30.54, 50.43, 52.38
6	66.18	19.37	28.54, 28.77, 53.15, 53.44
7	69.69	20.92	22.96, 24.95, 25.46, 51.00, 54.07
8	69.07	20.37	49.52, 53.80
9	67.88	21.65	24.49, 49.46, 55.04

[a] In $CDCl_3$ solvent.

^{13}C NMR Spectra. The carbon NMR data for compounds **2–9** are listed in Table VI. We had initially hoped that the chemical shifts of the central carbon of the -$(CH_2)_3$- bridges would be diagnostic of conformation. However, as can be seen from the data in Table VI, these chemical shifts are almost the same for **7–9**, which are *out,in*, and **4**, which is *out,out (vide infra)*. The remarkable upfield shift for this carbon in **5** is not easily associated with any conformational effects (see Discussion section).

Dynamic NMR. Dynamic NMR studies of selected 1,(*n*+2)-diazabicyclo[*n*.3.1]alkanes were carried out in an attempt to detect and identify low-energy conformers directly. Two basic conformational processes, ring inversion and nitrogen inversion, must be slowed on the NMR time scale for this to be possible, Several dynamic NMR studies of *N,N'*-dialkylhexahydropyrimidines have shown that ring inversion ($\Delta G^{\ddagger} \approx 11$ kcal/mol) is a higher energy process than N-inversion ($\Delta G^{\ddagger}$ = 6–8 kcal/mol).[13,17-19] In the 1,(*n*+2)-diazabicyclo[*n*.3.1]alkanes, where both processes necessarily involve concomitant torsions in the (*n*+3)-membered rings, higher barriers might be expected.

Ring inversions in the 1,(*n*+2)-diazabicyclo[*n*.3.1]alkanes and related bis-aminals **8** and **9** were monitored by ^{1}H NMR, using geminal exchange of the aminal hydrogens (N–CH_2–N) as a probe. This mutual exchange was found to be in the slow exchange limit on the NMR time scale at ambient temperature for all members of the 1,(*n*+2)-diazabicyclo[*n*.3.1]alkane series and for **8**, i.e., each compound exhibited anisochronous proton resonances corresponding to diastereotopic geminal aminal hydrogens. High-temperature studies of **7** (90 MHz; pyridine-d_5) and **8** (90 MHz; Me_2SO-d_6) showed no dynamic broadening of the aminal AX subspectra up to temperatures of 100 °C and 170 °C, respectively. Estimated lower limits for $\Delta G^{\ddagger}$ of ring inversion in these systems are about 18 and 21 kcal/mol, respectively. In contrast, the 90-MHz ^{1}H NMR spectrum of bis-aminal **9** was severely dynamically broadened at room temperature, and the 360-MHz spectrum was somewhat broadened. A dynamic ^{1}H study carried out at 90 MHz showed that slow geminal (aminal) exchange was achieved by 2 °C (see Table V for shifts) and that the AX spectrum broadened and coalesced, giving a broad singlet at 66 °C. Using the coalescence temperature approximation for an AX mutual exchange[60] in conjunction with the measured slow exchange $\Delta\nu$ (90 Hz), coupling constant (11 Hz), and coalescence temperature ($T_c \approx 41$ °C) gives a calculated $\Delta G_c^{\ddagger}$ (314 K) = 15.1 kcal/mol.

Ring inversions in the 1,(*n*+2)-diazabicyclo[*n*.3.1]alkane series most logically interconvert *in,out* (equatorial,axial) and *out,in* (axial,equatorial) conformers.[4] Such inversions involve pushing the methylene of the one-membered bridge through the (*n*+3)-membered ring during a twist–boat,twist–boat interconversion of the six-membered hexahydropyrimidine ring. According to the experimental observations, this process is slow on the NMR time scale up through compound **7**. The result for bis-aminal **9**

(55) Nelsen *et al.* report data for the compounds **2** and **3**: Nelsen, S. F.; Hintz, P. J.; Landis, R. T. II *J. Am. Chem. Soc.* **1972**, *94*, 7105–7113.
(56) Lambert, J. B.; Goldstein, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 5689–5693.
(57) See ref 22, pp 17–25 and 123–128, and references therein.
(58) Crabb, T. A.; Newton, R. F. *Tetrahedron* **1970**, *26*, 701–713. Chivers, P. J.; Crabb, T. A. *Tetrahedron* **1970**, *26*, 3369–3387; 3389–3399. Riddell, F. G.; Williams, D. A. R. *Tetrahedron Lett.* **1971**, 2073–2074. Halls, P. J.; Jones, R. A. Y.; Katritzky, A. R.; Snarey, M.; Trepanier, D. L. *J. Chem. Soc. (B)* **1971**, 1320–1324.
(59) Shiotani, S.; Mitsuhashi, K. *Chem. Pharm. Bull.* **1966**, 14, 608–612.
(60) Kost, D.; Carlson, E. H.; Raban, M. *J. Chem. Soc., Chem. Commun.* **1971**, 656–657.

Table VII. Low-Temperature Dynamic ^{13}C NMR Spectra of **6**, **7**, **8**, and **9**, with Dynamic Broadening Indicated by Enclosure of Shift in Brackets

compd	T (°C)	N-*C*-N	N-C-*C*-C-N	C-*C*-N		other		
6 in $CDCl_3$[a]	+29	66.18	19.37	53.15	53.44	28.54	28.77	
	−12	65.21	17.87	52.95	53.21	28.15	28.67	
	−47	64.19	16.15	52.88	52.98	27.82	28.70	
	−67	63.74	15.41	52.89	52.89	27.69	28.74	
6 in CD_2Cl_2[b]	−62	64.53	{16.99}	52.71	52.91	27.91	28.56	
	−74	64.17	{16.43}	52.58	52.75	27.72	28.46	
	−80[c]	{63.81}	{15.90}	{52.41}	52.57	{27.50}	{28.31}	
	−90[c]	{63.46}	{15.17}[d]	{52.19}	52.36	{27.25}	{28.07}	
7 in Me_2CO-d_6[e]	+5	70.58	21.77	51.73	54.75	23.58[f]	25.52	26.03
	−26	70.24	21.32	{51.27}	54.83	22.68	{25.04}	{25.81}
	−50	69.97	20.96	{~51}	54.85	22.01	{24.77}	{25.71}
	−60[c]	69.87[g]	20.84	{g}	{54.8}	21.68	{~25 overlap}	
	−70[c]	69.72	20.65[h]	{45.4}	{53.8}	21.34[j]	{21.3}[j]	{22.9}
				{56.0}[i]	{56.0}[i]		{26.9}	{28.2}
	−80[c,k]	69.65	20.52	{45.05}	{53.72}	21.1[i]	{21.1}[j]	{22.66}
				{56.34}[j]	{55.98}[j]		{27.13}	{28.28}
8 in $CDCl_3$[a]	+35[c]	69.07	20.37	49.52	53.80			
	−45	68.32	19.77	{48.87}	53.53			
8 in CD_2Cl_2[a]	+35[c]	69.60	20.87	50.00	54.16			
	−73	68.65	20.19	{46.3}[g]	{53.96}			
				{53.2}[g]				
	−100[c]	68.56	20.09	{44.01}	{53.1}[j]			
				{54.3}[j]				
9 in $CDCl_3$[a]	+35[c]	67.88	21.56	49.46	55.04	24.49[m]		
	+20	67.68	21.45	{49.31}	54.97	24.28		
	−23	67.19	21.19	{~48}[g]	{54.81}	23.93		
				{~50}[g]				
	−35	67.13	21.16	{46.55}	{54.4}[g]	23.86		
				{51.07}	{55.2}[g]			
	−60	67.06	21.13	46.35	53.77	23.80		
				51.20	55.55			

[a] 22.50-MHz spectra. [b] 125.76-MHz spectra. [c] Approximate temperature. [d] Full width at half height = 45 Hz. [e] 68.08-MHz spectra. [f] C-5. [g] Coalescence. [h] Slight broadening, possibly anisotropic. [i] Overlapped pair. [j] Overlapped pair. [k] Anisotropic broadening of all lines. [l] Assignments may be reversed. [m] C-3 and C-11.

Table VIII. Coalescence Parameters and Free Energies of Activation from Dynamic ^{13}C NMR

compd	solvent	resonance[a] (δ)	$\Delta\nu$[b] (Hz)	T_c[c] (°C)	$\Delta G_c^{\ddagger}$ (kcal/mol)
7	Me_2CO-d_6	51.7	769	−55 ± 5	9.4 ± 0.3
8	CD_2Cl_2	50.0	231	−73 ± 3	9.1 ± 0.2
9	$CDCl_3$	49.5	110	−23 ± 3	11.8 ± 0.2
		55.0	40	−35 ± 3	11.7 ± 0.2

[a] C-*C*-N resonance. [b] Frequency difference from slow exchange spectrum. [c] Coalescence temperature.

suggests that the 1,11-diazabicyclo[9.3.1]alkane would be the crossover point at which ring inversion becomes a viable process on the NMR time scale. Ring inversions of *out,out* (axial,axial) conformers, which are the low-energy forms for the smaller members of the series, would produce *in,in* (equatorial,equatorial) conformers. Inspection of molecular models leads us to conclude that the high strain energies of the *in,in* conformers would preclude such ring inversions, at least up through **6**.

In view of the demonstrated slow ring inversions of members of the 1,(*n*+2)-diazabicyclo[*n*.3.1]alkane series on the NMR time scale at room temperature, a general conformational interconversion diagram may be formulated without regard for the conformational details of the (*n*+3)-membered ring, as shown in Figure 1. The three types of conformers (eq,ax and ax,eq are enantiomeric) are interconverted by two different nitrogen inversions (and the associated torsions). As stated above, eq,eq conformers are not expected to be significantly populated for the series under study, but they may not be so strained as to preclude inversion through eq,eq intermediates for larger members of the series. In cases where either eq,ax/ax,eq or a mixture of eq,ax/ax,eq and ax,ax is significantly populated, slowing of nitrogen inversions at low temperature should be observable by dynamic ^{13}C NMR. Such dynamic NMR studies of **6**–**9** have been carried out, and the results are recorded in Table VII. All four of these compounds exhibited dynamic broadening or decoalescence phenomena, and slow exchange spectra were obtained for all but **6**. A 22.50-MHz study of **6** showed no definitive dynamic broadening down to approximately −100 °C, but a large shift of the N-C-*C*-C-N resonance to higher field at low temperature. A 125.76-MHz study, however, showed dynamic broadening of several resonances at lower temperature, most notably that due to N-C-*C*-C-N. Slowing of nitrogen inversion should not result in broadening of that resonance if the **6** conformational mixture is dominated by either ax,ax or eq,ax/ax,eq. Although we were unable to obtain slow exchange spectra, the results are consistent with a conformational mixture of ax,ax and eq,ax/ax,eq, the relative populations of which vary to favor the former at lower temperature. Compounds **7**, **8**, and **9** all gave dynamic NMR spectra which unequivocally demonstrated the slowing of nitrogen inversions at low temperature and the predominance of eq,ax/ax,eq conformations. In each case, all of the proton-decoupled C-*C*-N singlets broadened as the temperature was lowered and in all but one case decoalesced and sharpened into two singlets of equal intensity, symmetrically displaced about the original fast-exchange resonance positions. The observations are consistent with a mutual dynamic exchange process. The slow exchange limit was not achieved by −100 °C at 22.50 MHz for one of the C-*C*-N resonances of **8**, but it was clearly on its way to decoalecence. In **7**, two C-*C*-C resonances (C-3,C-7 and C-4,C-6) underwent broadening and decoalescence as well. In none of the three cases did either aminal N-*C*-N or N-C-*C*-C-N carbons undergo dynamic broadening. In the cases of **8** and **9**, the slow exchange spectra were indicative of conformations having two-fold symmetry, i.e., the resonances of the two hexahydropyrimidine rings were degenerate in each case. Coalescence parameters and derived free energies of activation at coalescence for the observed mutual exchanges (nitrogen inversions) are given in Table VIII. Both **7** and **8** exhibit nitrogen inversion barriers that are on the order of 2 kcal/mol higher than those of simple *N,N'*-dialkylhexahydropyrimidines, while **9** exhibits a barrier almost 5 kcal/

mol higher. Conformational assignments and proposed interconversion pathways will be detailed in the discussion of individual compounds below.

Discussion

1,6-Diazabicyclo[4.3.1]decane (4). The force field calculations on **4** clearly favor ax,ax (*out,out*) conformations (see Chart I and supplementary material); the lowest energy *out,in* conformation was 12.9 kcal/mol higher in energy. This is clearly in accord with the PE spectrum, which closely resembles those of **2** and **3**. Ax,ax conformations are clearly favored in solution, too, as shown by the strong deshielding (δ 4.03) of the axial aminal proton (Table V). Although MM2 predicts **4** to be a mixture of ax,ax conformers, barriers to interconversions of 7-membered ring conformations are low, and no experimental evidence for this is available.

1,7-Diazabicyclo[5.3.1]undecane (5). Unlike its next higher homologue **6**, **5** is predicted to be conformationally very simple by MM2 calculations. MM2 predicts a strong (3.8 kcal/mol) preference for an ax,ax (*out,out*) structure for **5** over the eq,ax (*in,out*) structure (Chart I), the preferred conformation having a [26] or boat–chair 8-membered ring; there is then another large energy gap to the next ax,ax structure. Nevertheless, the presence of an ionization at 8.0 eV in the PE spectrum seems clear evidence for some (10–15%) of the compound being in an ax,eq (*out,in*) structure in the gas phase. One possible reason for the failure of MM2 to make the *out,in* structure more competitive is that this structure requires substantial flattening at the nitrogen atom where the 5-carbon bridge is equatorial to the six-membered ring (one C-N-C angle is calculated to be 119° and the average is over 113.5°). It is known that MM2 overestimates the energy cost of this flattening, partly at least because of its inclusion of explicit lone pairs.[47b] We have recalculated the two lowest energy structures for **5** with the recent MM3 program, which does not include explicit lone pairs on nitrogen atoms.[61] The energy difference between the *out,out* and *out,in* structures is then reduced to 2.46 kcal/mol, and one N-C-N angle is 122°. In solution, on the other hand, the NMR evidence points to an *out,out* conformation strongly predominating. *Out,out* conformations should be more strongly solvated through better interactions of solvent with the lone pairs. Thus the axial aminal proton is still at low field (δ 3.80) as in **2**, **3**, and **4**. There is, however, one feature of the ^{13}C NMR of **5** which is most surprising. The central carbon of the trimethylene bridge, N-C-*C*-C-N, resonates at 12.94 ppm, 6.5 ppm upfield of the corresponding carbon in any other compound in the series. We can offer no convincing explanation for this; such an upfield shift might result from strong steric compression, but this is definitely not present in the predicted global minimum. We have considered the possibility that **5** oligomerizes, as described for **6** and **7** (see Experimental Section), but we see no evidence for this, nor can we suggest dimer or trimer structures which would be expected to cause this remarkable upfield shift.

1,8-Diazabicyclo[6.3.1]dodecane (6). The conformational situation for **6** is more complex than for other members of the aminal series that we have studied. The photoelectron spectrum of **6** is indicative of predominance of *out,in* (eq,ax) conformers in the gas phase. Only a broad peak at approximately 8.0 eV was observed (Table IV), consistent with the small splitting expected[27] for eq,ax lone pairs. The results of MM2 calculations on **6** (Scheme I) are in agreement with this conclusion. Use of default MM2 amine parameters and a dielectric constant appropriate for the gas phase (1.5) gave five low-steric-energy eq,ax (*out,in*) conformers within 0.5 kcal/mol of one another: one [333], two [234], and two [9] conformers. The lowest *out,out* conformer, ax,ax-[225], was over 1.4 kcal/mol above the lowest eq,ax conformer and 0.4 kcal/mol above an *out,in* conformer having a twist–boat 6-membered ring (tb-eq,ax-[9]). Inclusion of a 2-fold torsional term (V_2 = 1.0 kcal/mol for N-C-N-lp) in the calculations brought ax,ax-[225] below tb-eq,ax-[9] but also stabilized eq,ax-[9] to the global minimum 1.6 kcal/mol below ax,ax-[225]. Entropy of mixing should also contribute to the dominance of *out,in* conformations in the gas phase.

The solution conformational situation for **6** is more ambiguous. The NMR data for **6** in $CDCl_3$ and CD_2Cl_2 are most logically interpreted in terms of significant population of *out,out* in solution. The ^1H chemical shift of the axial aminal hydrogen of **6** falls almost at the midpoint between the characteristic shifts exhibited by *out,out* compound **4** and *out,in* compound **7** (Table V). (The evidence for dominance of *out,in*-**7** will be presented below.) Likewise, the aminal J_{gem} of **6** is consistent with a mixture of *out,in* and *out,out* conformers. Dynamic ^{13}C NMR experiments on **6** (Table VII) showed dynamic broadening of several resonances at low temperature. Although the slow exchange limit was not achieved, some useful interpretation is still possible. Based upon our results with **7** and the bis-aminals (*vide infra*), we assign the broadening in **6** to slowing of nitrogen inversions (and the concomitant torsions), although we cannot rigorously exclude slowing of 9-membered ring torsional interconversions. Broadening of the N-*C*-N and 6-membered ring N-C-*C*-C-N resonances requires that the process being slowed interconverts at least two conformational diastereomers. Enantiomerization of a single type of eq,ax conformer (as observed for **7** (see below)) or of an averaged eq,ax conformational set is excluded. The chemical shift of the N-C-*C*-C-N is strongly temperature dependent (Table VII), suggesting that significant conformational biasing occurs as a function of temperature.

Overall, we believe that the experimental data are most consistent with an *out,in*/*out,out* mixture that is biased toward *out,out* at low temperatures. However, this interpretation is clearly at odds with the MM2 results. The inconsistency may be a consequence of solvation: we expect that specific solvation effects (hydrogen bonding and dipole orientation) should favor *out,out* conformers, which have more sterically accessible lone pairs. MM2 (MacroModel) calculations employing a method for modeling solvation by water[62] narrowed the gap between eq,ax conformers and ax,ax-[225] somewhat but are still inconsistent with our interpretation of the experimental results, especially when the entropy factor is taken into account.

1,9-Diazabicyclo[7.3.1]tridecane (7). Compound **7**, unlike **6**, should be conformationally simple. A diamond-lattice type *out,in* conformation, eq,ax-[2323], is computed (MM2) to be the global minimum for **7**, 2.60 kcal/mol more stable than any other conformation. The lowest energy *out,out* and *in,in* conformers have very similar energies (6–7 kcal/mol above the global minimum; Chart I). The predominance of the [2323] conformation in solution is supported by the 400-MHz ^1H NMR spectrum of **7** at room temperature. Experimental multiplicities and vicinal coupling constants agree well with time-averaged coupling constants calculated[63] on the basis of MM2-optimized [2323] enantiomers in fast exchange (see Experimental Section). The relative high-field shift of H-5(c) (δ 1.37) and low-field shift of H-5(t) (δ 2.33) (see Figure 3) provide further support for the conformational assignment. The environments of each of these two protons should be invariant with enantiomerization according to Figure 3, H-5(t) remaining intraannular and transannular to a nitrogen lone pair and H-5(c) remaining extraannular. The transannular "steric compression" of H-5(t) with a lone pair across the [2323] 10-membered ring results in deshielding of H-5(t) and shielding of its geminal partner, H-5(c). This effect has also

(61) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551–8566. For MM3 on amines, see: Schmitz, L. R.; Allinger, N. L. *J. Am. Chem. Soc.* **1990**, *112*, 8307–8315.

(62) Hasel, W.; Hendrickson, T. F.; Still, W. C. *Tetrahedron Comput. Methodol.* **1988**, *1*, 103–116.

(63) All vicinal coupling constants reported compared favorably with values calculated using the MM2 optimized torsion angles and the coupling constant equation of Haasnoot *et al.*: Haasnoot, C. A. G.; deLeeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792. Program 3JHH: Petillo, P. A. (after Jaime, C.; Osawa, E.) *QCPE Bull.* **1987**, 7, 50.

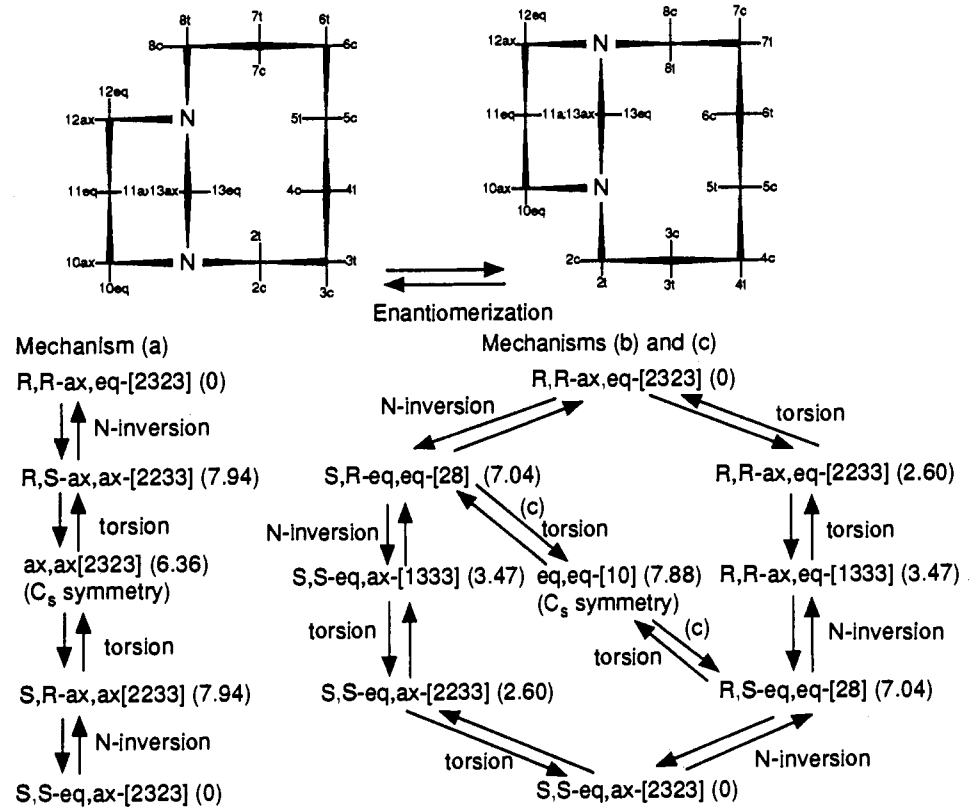


Figure 3. Conformational enantiomerization of **7** and possible interconversion pathways. Hydrogen atoms on the $(CH_2)_7$ bridge are labeled as cis or trans to the lone pair on N-1 in the left-hand formula (see text). Numbers in parentheses in mechanisms a–c are the energies of intermediates relative to the eq,ax-[2323] conformation (see Chart I for Dale diagrams of the intermediate conformations).

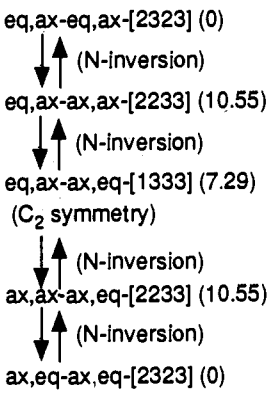


Figure 4. Topomerization scheme for **8**. Numbers in parentheses are the energies of intermediates relative to the eq,ax-eq,ax-[2323] conformation.

been observed in **8**, which is unequivocally [2323] (*vide infra*), and in some other similar cases.[64]

Dynamic NMR results also provide strong evidence for the predominance of *out,in* isomers in solution. The room temperature ^1H and ^{13}C NMR spectra of **7** are indicative of time-averaged C_s symmetry. (Ring inversions are slow on the ^1H NMR timescale, as discussed in a previous section). Cooling of a $(D_3C)_2CO$ solution of **7** resulted in dynamic broadening and decoalescence of four of the seven carbon resonances, giving an 11-line spectrum (no symmetry) at approximately −80 °C. The C-5, C-11, and C-13 resonances did not decoalesce. These results are consistent with the slowing of interconversion of enantiomeric *out,in* conformers, ax,eq-[2323] and eq,ax-[2323], as shown in Figure 3. The process effects mutual exchange of four pairs of resonances: C-4/C-6, C-3/C-7, C-2/C-8, and C-10/C-12. Two nitrogen inversions must be on the conformational pathway, and either ax,ax or eq,eq conformers are potential intermediates. In analogy with conformational interconversions in cyclododecane,[53] three possible interconversion mechanisms are shown in Figure 3. The two nitrogen inversions are necessarily coupled with torsional motions, accomplishing "corner movements". Thus, the nitrogen inversion barrier for this system, no doubt the rate-determining conformational barrier, is expected to be higher than those found for monocyclic hexahydropyrimidines. Indeed, a ΔG_c^* of 9.4 ± 0.3 kcal/mol is calculated from the decoalescence of the 51.73 ppm resonance (Table VIII).

Mechanisms a, proceeding via the C_s-symmetric ax,ax-[2323] conformation, and c, proceeding via the C_s-symmetric eq,eq-[10] conformation, are relatively straightforward. Mechanism b, which utilizes the lowest energy series of intermediates, is most unusual in that enantiomers are interconverted without the system ever passing through an intermediate or transition state with a plane of symmetry or other S_n symmetry element. Instead, there are two enantiomeric pathways. We are not aware of any previous discussion of this type of possibility. Unfortunately, we see no simple way to distinguish experimentally between these mechanisms.

1,4,8,11-Tetraazatricyclo[9.3.1.1^{4,8}]hexadecane (8). The low-temperature dynamic ^{13}C NMR results for **8** are consistent with predominance of the eq,ax-eq,ax-[2323] conformation (C_i symmetry) that is found in the solid state by X-ray.[39] In agreement, MM2 calculations show this conformation to be the global minimum by over 6 kcal/mol. Topomerization by sequential N-inversions leads to exchange averaging of C-2,9 with C-3,10 and C-5,12 with C-7,14 at room temperature. The barrier for the process (Table VIII) is similar to that measured for bicyclic aminal **7**. A topomerization sequence consistent with the MM2 results is shown in Figure 4. Alternative pathways seem ruled out by the high energies of the intermediates which would be involved: ax,ax-ax,ax-[2323] (C_{2h}) is 16 kcal/mol above the global energy minimum, and the eq,eq-eq,ax-[28] intermediate

(64) Alder, R. W.; Eastment, P.; Hext, N. M.; Moss, R. E.; Orpen, A. G.; White, J. M. *J. Chem. Soc., Chem. Commun.* **1988**, 1528–1530. See also: Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *J. Org. Chem.* **1980**, *45*, 3259–3265. Konnecke, A.; Skarzewski, J.; Mlachawski, *J. Monatsh. Chem.* **1982**, *113*, 761–765.

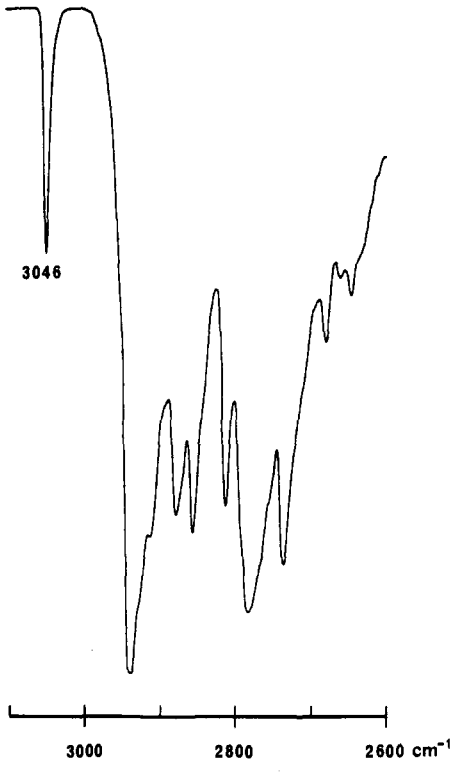


Figure 5. Infrared spectrum (KBr) of the C–H stretching region of **8**.

required for a mechanism like b for **7** in Figure 3 is 12.9 kcal/mol above the global minimum, while the barrier for the topomerization is only about 9 kcal/mol. As previously discussed, ^{1}H NMR shows that ring inversions are slow on the NMR time scale, even up to relatively high temperature.

In the eq,ax-eq,ax-[2323] conformation, each of the two symmetry-related aminal units has one hydrogen (equatorial to the 6-membered ring and intraannular to the 10-membered ring) that is sterically compressed into a transannular nitrogen lone pair. X-ray[39] and MM2 give this N···H—C compression distance as 2.26 and 2.4 Å, respectively. (The X-ray[39] and MM2-calculated geometries agree remarkably well.) Since the environments of the aminal hydrogens are independent of the topomerization of Figure 4, this compression should be reflected in the room-temperature ^{1}H NMR and IR spectra of **8**. Indeed, as shown in Table V, the eq-aminal protons of **8** resonate at remarkably low field (δ 5.45). That this deshielding effect is at least partly due to true C–H compression, as opposed to dominant nitrogen magnetic anisotropy, is indicated by IR results. As shown in Figure 5, the IR spectrum of **8** (KBr) exhibits an isolated, sharp band at 3046 cm^{-1}. In CCl_4 solution this band occurs at 3038 cm^{-1} and is somewhat broader. Our assignment of this band to aminal C–H stretching (presumably an asymmetric stretch[65]) was confirmed by the absence of the band in the IR of the corresponding N–CD_2–N compound (**8**-15,15,16,16-d_4). Increased C–H stretching frequencies have been observed in several cases of C—H···H—C steric compression, albeit at somewhat lower frequency (2991 cm^{-1}).[65-67] Of particular relevance is the fact that cyclodecanol exhibits such a band.[65] To our knowledge, **8** provides the first dramatic example of a C–H stretching frequency increase as the result of C—H···N compression.

1,5,9,13-Tetraazatricyclo[11.3.1.1^{5,9}]octadecane (9). As in the case of compound **8**, the low-temperature dynamic ^{13}C NMR results for **9** conclusively establish predominance of a single type of conformer having two equivalent eq,ax-hexahydropyrimidine rings. All of the solution data point to the chiral eq,ax-eq,ax-[3333] conformer (C_2 symmetry) and its enantiomer, which rapidly interconvert (enantiomerization) at room temperature on the ^{13}C NMR time scale. X-ray diffraction has established that **9** assumes this [3333] conformation in the solid state.[40] MM2 gives eq,eq-eq,eq-[2424] as the global minimum, 0.13 kcal/mol lower in steric energy than eq,ax-eq,ax-[3333] (see Scheme II). It must be remembered, however that such MM2 calculations using the unmodified Allinger–Profeta amine parameters overestimate ΔE_s(eq,ax-eq,eq) for the dialkylhexahydropyrimidines by approximately 0.7 kcal/mol (*vide supra*, Table III). When this correction is applied to bis-aminal **9**, the eq,ax-eq,ax-[3333] conformer is favored over the eq,eq-eq,eq-[2424] conformation by ΔE_s of about 1.3 kcal/mol. In addition, the [2424] conformation has two pairs of nitrogen lone pairs 1.94 Å apart across the ring, and we know that MM2 underestimates the repulsive interaction between such lone pairs. Thus 1,6-diazabicyclo[4.4.4]tetradecane is calculated to have an N···N distance of 2.64 Å, whereas the experimental distance is 2.81 Å.[12] Entropy effects should also favor the [3333] conformation. Therefore the eq,eq-eq,eq-[2424] is likely somewhat higher in energy, although it may still be a viable intermediate in conformational interconversions (see below).

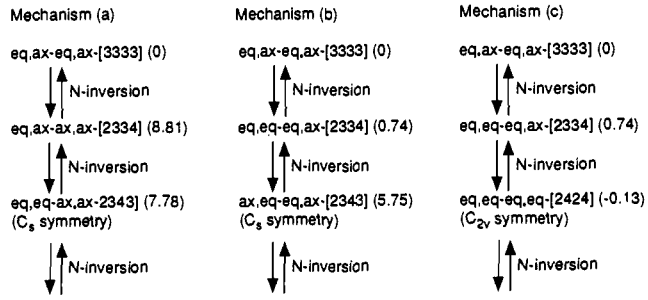


Figure 6. Enantiomerization scheme for **9**. One half of each pathway is shown, i.e., as far as the C_s or C_{2v} intermediate. Numbers in parentheses are the energies of intermediates relative to the eq,ax-eq,ax-[3333] conformation.

Three possible enantiomerization pathways involving sequential corner-moving nitrogen inversions are shown in Figure 6; we see no way of easily distinguishing between them. The measured $\Delta G^{\ddagger}$ for the process (Table VIII) is almost 3 kcal/mol higher than the $\Delta G^{\ddagger}$ for topomerization of **8**. While the magnitude of the barrier in **9** is somewhat surprising, the relative order is consistent with the relative torsional corner movement barriers in [3333]-cyclododecane and [2323]-cyclodecane.[53] As discussed in the Dynamic NMR section, **9** also undergoes a higher barrier (15 kcal/mol) conformational process involving net inversion of all three rings.

In the eq,ax-eq,ax-[3333] conformation of **9**, one face of the central [3333] 12-membered ring has four intraannular hydrogens, two of which are opposing equatorial aminal hydrogens. The other face has two opposing intraannular hydrogens and two opposing nitrogen lone pairs. The IR spectrum of **9** was examined to see if intraannular H···H compressions (closest approaches 2.0–2.1 Å[40]) led to any observable high-frequency bands. Indeed, a sharp band at 2990 (KBr) or 2982 cm^{-1} (CCl_4) was present in the IR spectrum of **9** but absent in the IR spectrum of **9**-17,17,18,18-d_4. Thus, the band is assigned to an aminal C–H stretch, and its relatively high frequency is tentatively ascribed to steric compression. No such compression band was observed in the IR spectrum of cyclododecanol.[65]

Conclusions

The borderline for changeover from *out,out* to *out,in* structures for a homologous series of bicyclic molecules has been defined for the first time for the case of 1,(n+2)-diazabicyclo[n.3.1]-alkanes. The borderline is at compound **5** in the gas phase but

(65) Kivelson, D.; Winstein, S.; Bruck, P.; Hansen, R. L. *J. Am. Chem. Soc.* **1961**, *83*, 2938–2944.
(66) Lenior, D.; Frank, R. M. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 318–319, and references therein.
(67) Doyle, M.; Hafter, R.; Parker, W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 364–372.

at compound **6** in solution (in $CDCl_3$); this solvent effect is reasonably attributed to better solvation of *out* lone pairs.

Experimental Section

Starting Materials and General Procedures. Starting materials were used as obtained from commercial sources unless otherwise specified below. Melting points were obtained on a Reichert hot stage or Hoover-Thomas capillary apparatus and are uncorrected. Kugelrohr distillations were performed on a Büchi GKR-50 or Aldrich apparatus. ^1H and ^{13}C NMR spectra were recorded on JEOL FX200, JNM-GX270 or 400 (at Bristol), JEOL FX90Q, and Bruker AM-360 spectrometers (at New Hampshire). Photoelectron spectra were obtained at Basel with a $\pi/2$ 5-cm-radius Turner-type spectrometer, using He (1α) radiation as described earlier;[68] the spectra of **4**, **5**, and **6** have been reported in a data bank.[54]

1,5-Diazacyclononane. The procedure used closely follows that of Yamamoto and Maruoka.[35] 1,5-Diazabicyclo[4.3.0]non-5-ene (5.0 g) (DBN, from Aldrich) was treated with diisobutylaluminum hydride (DIBAH, 102 mL of a 25% solution in toluene, 4 equiv) and the reaction mixture was refluxed overnight under a nitrogen atmosphere. Sodium fluoride (27.0 g) and water (9 mL) were added slowly with cooling and vigorous stirring. Stirring was continued for 30 min. The reaction mixture was then filtered, and the solids were washed with Et_2O (2 × 75 mL). The combined organic solutions were dried, and the solvent was removed to yield 4.4 g (85%) of a colorless oil which could be used satisfactorily without further purification: ^{13}C NMR (50 MHz, D_2O solution of bishydrochloride) δ_c 45.4 (2C), 43.8 (2C), 22.4 (2C), 22.0 (1C). The bisperchlorate salt was prepared and recrystallized from ethanol, mp 219–222 °C dec. Anal. Calcd for $C_7H_{18}Cl_2N_2O_8$: C, 25.5; H, 5.5; N, 8.5. Found: C, 25.73; H, 5.73; N, 8.77.

1,6-Diazabicyclo[4.3.1]decane (4). 1,5-Diazacyclononane (2 g) was dissolved in toluene (60 mL). Formaldehyde (1.27 mL of 37% aqueous solution) was added and the reaction mixture refluxed for 2 h under a Dean-Stark water trap. Removal of the solvent and distillation of the product (Kugelrohr, 100 °C, 19 mmHg) gave a colorless oil (1.6 g, 73%): ^1H NMR (200 MHz, $CDCl_3$) δ 4.06–3.83 (m, 2H), 3.29–2.69 (m, 8H), 1.99–1.69 (m, 5H), 1.10–0.93 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_c 66.3 (1C), 54.8 (2C), 52.6 (2C), 30.6 (2C), 21.4 (1C). Treatment of the diamine with 1.1 equiv of iodomethane in Et_2O gave the monoquaternary iodide which was recrystallized from EtOH/Et_2O: ^1H NMR (200 MHz, D_2O) δ 4.6 (d, 1H), 4.1 (d, 1H), 3.6–2.9 (m, 8H), 2.9 (s, 3H), 2.2–1.7 (m, 6H); ^{13}C NMR (50 MHz, D_2O) δ_c 78.2, 63.2, 62.8, 52.8, 52.5, 47.1, 28.4, 23.5, 19.1. Anal. Calcd for $C_9H_{19}IN_2$: C, 38.3; H, 6.8; N, 9.9. Found: C, 38.1; H, 7.1; N, 10.1.

1,5-Diazabicyclo[4.4.0]decane hydrochloride salt.[37] 5-Chloropentanal (6.4 g) (prepared by DIBAH reduction of 5-chlorovaleronitrile) and anhydrous $MgSO_4$ (20 g) were added to a solution of 1,3-diaminopropane (3.6 g) in CH_2Cl_2 (100 mL), and the mixture was stirred vigorously overnight. Filtration, washing of the residues with CH_2Cl_2, and removal of the solvent gave a yellow crystalline solid which was washed with Et_2O to remove excess aldehyde. The yield of material suitable for reductive cleavage was 7.3 g (85%). Recrystallization from ethanol gave colorless needles, mp 169–172 °C dec (lit.[36] mp 172.5–175 °C): ^{13}C NMR (50 MHz, $CDCl_3$) δ_c 77.7 (1C), 53.2 (2C), 42.9 (1C), 23.0 (1C), 22.9 (1C), and 22.2 (1C). Anal. Calcd for $C_8H_{17}ClN_2$: C, 54.4; H, 9.7; N, 15.8. Found: C, 54.0; H, 9.9; N, 15.7.

1,5-Diazacyclodecane.[37] 1,5-Diazabicyclo[4.4.0]decane was obtained from its hydrochloride salt (6 g) by extraction from 2 M NaOH solution with CH_2Cl_2. The oil (4.4 g) was treated with DIBAH (79 mL of a 25% solution in toluene, 4 equiv), and the reaction mixture refluxed overnight under nitrogen. Workup as described above for 1,5-diazacyclononane produced a light yellow oil (3.1 g, 70%): ^1H NMR (200 MHz, $CDCl_3$) δ 2.95 (t, 4H), 2.7 (t, 4H), 2.55 (br s, 2H, N*H*), 1.9–1.5 (m, 8H); ^{13}C NMR (50 MHz, D_2O solution of the dihydrobromide) δ_c 43.8 (2C), 41.9 (2C), 21.5 (2C), 21.1, (1C), 20.2 (1C).

1,7-Diazabicyclo[5.3.1]undecane (5). 1,5-Diazacyclodecane (1.0 g), formaldehyde (0.6 mL of 37% aqueous solution, 1 equiv), and toluene (60 mL) were refluxed together for 1 h under a Dean–Stark trap. Removal of the solvent and distillation (Kugelrohr, 170 °C, 18 mmHg) produced a colorless oil (0.87 g, 80%): ^1H NMR (200 MHz, $CDCl_3$) δ 4.22 (d, 1H), 3.81 (d, 1H), 3.31–2.89 (m, 8H), 2.44–2.16 (m, 1H), 2.01–1.92 (m, 2H), 1.76–1.46 (m, 4H), 0.94–0.87 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_c 61.2 (1C), 52.4 (2C), 50.4 (2C), 30.5 (1C), 25.6 (2C), 12.9 (1C). The monomethyl iodide derivative was prepared as described for 1,6-diazabicyclo[4.3.1]decane, mp 201–204 °C dec: ^1H NMR (200 MHz, $CDCl_3$) δ 4.8 (d, 1H), 4.5 (d, 1H), 4.1–2.7 (m, 8H), 3.15 (s, 3H), 2.4–1.4 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_c 73.7, 61.1, 57.9, 51.3, 48.1, 46.8, 28.4, 24.0, 21.2, 15.8. Anal. Calcd for $C_{10}H_{21}IN_2$: C, 40.5; H, 7.1; N, 9.5. Found C, 40.3; H, 7.1; N, 9.6.

1,5-Diazacycloundecane. The reduction of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) with DIBAH was carried out by a modification of the procedure of Yamamoto and Marouka.[35] DBU (7.46 g, 49.0 mmol) was maintained at 0 °C in a 500-mL flame-dried 3-neck flask under nitrogen as 300 mL of 1.0 M DIBAH in toluene (300 mmol) was carefully added in 30-mL aliquots via syringe. The solution was then heated to reflux for 36 h. The reaction mixture was cooled to 0 °C, 50 mL of toluene was added to the solution, and 20 mL of 10% aqueous NaOH was added dropwise cautiously. The solution was then allowed to warm to room temperature, and 10% aqueous NaOH was added until the white precipitate appeared granular. The reaction mixture was filtered, and the solids were thoroughly washed with CH_2Cl_2. The combined filtrates were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to yield a yellow oil. This was purified by Kugelrohr distillation (50 °C, 0.20 mmHg) to yield 4.50 g (59%) of clear liquid product: ^1H NMR (90 MHz, $CDCl_3$) δ 1.6 (m, 10H), 2.5–3.0 (m, 10H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ_c 50.59, 48.64, 27.38, 25.82 (lit.[35] ^{13}C NMR (9 resonances) is in error); IR ($CHCl_3$) 3290, 2940, 2870, 2520, 1458, 1145, 1130 cm^{-1}; MS *m/z* (relative intensity) 168(1.9), 156(15), 127(4.4), 112(16), 98(22), 84(22), 70(56). Anal. Calcd for $C_9H_{20}N_2$: C, 69.18; H, 12.90; N, 17.93. Found: C, 69.13; H, 13.19; N, 17.11.

1,8-Diazabicyclo[6.3.1]dodecane (6). 1,5-Diazacycloundecane (1.34 g, 8.61 mmol) was dissolved in 300 mL of MeCN in a 500-mL 3-neck flask under nitrogen. A 1.00-mL portion of 40% aqueous CH_2O was added, and the solution was stirred for 20 h. MeCN was evaporated under reduced pressure, the resulting white solid was dissolved in CH_2Cl_2, and the solution was dried over Na_2SO_4 and filtered. CH_2Cl_2 was evaporated under reduced pressure to yield a white waxy solid (mp 64–66 °C). Kugelrohr distillation of the solid (75 °C, 0.005 mmHg) gave 1.15 g of clear liquid product (85% yield): ^1H NMR (250 MHz, $CDCl_3$) δ 1.08 (dm, J = 13.3 Hz, 1H, H-10(eq)), 1.43–2.0 (m, 8H, H-3,4,5,6), 2.27 (dtt, J = –13.3 (*gem*), 13.3 (*ap*), 5.7 Hz (*sc*), 1H, H-10(ax)), 2.70 (ddd, J = –12.5 (*gem*), 7.0, 2.4 Hz, 2H, H-2,7), 2.86–3.08 (m, 6H, H-9,11 (4H) and H-2,7 (2H)), 3.46 (d, J = –13.2 Hz (*gem*), 1H, H-12(ax aminal)), 4.12 (dt, J = –13.2 (*gem*), 1.9 Hz (*W-plan*), 1H, H-12(eq)); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ_c 66.20, 53.46, 53.20, 28.81, 28.55, 19.38. This liquid product undergoes an apparent reversible oligomerization upon standing, resulting in a waxy solid (mp 76–78.5 °C) that was insoluble in acetone, Et_2O, and MeOH at room temperature; it dissolved in warm MeOH but decomposed according to ^1H NMR (MeOH-d_4). A small amount of this solid could be dissolved in $CDCl_3$ very slowly at room temperature, giving a ^1H NMR identical to that of the liquid prior to solidification. The solid could be repeatedly Kugelrohr distilled to give the desired liquid, $CHCl_3$-soluble product, which resolidified slowly upon standing. The reported NMR experiments utilized freshly distilled samples. Due to the relative rapidity of the solidification process, reported IR and mass spectra are no doubt due to mixtures of the desired product and the oligomerization products. However, the mass spectra clearly indicated the presence of the desired bicyclic compound: IR ($CHCl_3$) 2935, 2865, 1445, 1355, 1025 cm^{-1}, (KBr) 2935, 2855, 2810, 2735, 1475 cm^{-1}; MS *m/z* (relative intensity) 168(96), 124(68), 96(62), 70(88) [low intensity (<2) peaks at *m/z* 270, 243, 213, 198, 183 were also present]; HRMS *m/z* calcd for $C_{10}H_{20}N_2$ (M^+) 168.162 65, found 168.165 06.

1,9-Diazabicyclo[6.4.0]dodec-8-ene. To a stirred solution of 2-methoxy-1-azacyclooct-1-ene (prepared from 2-azacyclooctanone (Aldrich) according to the method of Bensen,[38] 2.54 g, 0.0180 mol) in MeOH (50 mL) was added 3-bromopropylamine hydrobromide (4.06 g, 0.0185 mol) followed by $KHCO_3$ (5 g). The resulting mixture was stirred at room temperature for 2 days, the solids were filtered off, and the MeOH was removed under reduced pressure. The resulting oil was dissolved in water (10 mL), adjusted to pH 9 by the addition of concentrated HCl dropwise, and extracted with Et_2O (2 × 60 mL, Et_2O layer discarded), and then a solution of NaOH (10 g) in water (10 mL) was added to the aqueous layer. This was then extracted with Et_2O (3 × 50 mL), the Et_2O extracts were combined, dried (Na_2SO_4), and filtered through Celite, and the solvent was removed under reduced pressure. The resultant opaque oil was Kugelrohr distilled (100 °C, 2 mmHg) to give the amidine 1,9-diazabicyclo[6.4.0]dodec-8-ene as a clear oil (1.58 g, 52%): ^1H NMR (270 MHz, CD_3CN) δ 3.6–2.8 (m, 6H), 2.6–2.3 (m, 2H), 2.0–1.2 (m, 8H); ^{13}C NMR (67.9 MHz, CD_3CN) δ_c 161.6, 49.6, 46.0, 43.5, 33.4,

(68) Alder, R. W.; Arrowsmith, R. J.; Casson, A.; Sessions, R. B.; Heilbronner, E.; Kovač, B.; Huber, H.; Taagepera, M. *J. Am. Chem. Soc.* **1981**, *103*, 6137–6142.

31.4, 28.8, 26.6, 25.0, 22.2; IR 1615 cm^{-1}(strong); HRMS *m/z* calcd for $C_{10}H_{18}N_2$ (M^+) 166.147, found 166.1461.

1,5-Diazacyclododecane. 1,9-Diazabicyclo[6.4.0]dodec-8-ene (0.620 g, 3.73 mmol) stirred under nitrogen was treated with a solution of DIBAH (25% in toluene, 12 mL; 5 equiv), and the resulting solution was stirred for 12 h. Sodium fluoride (5 g) was added, and the slurry was stirred vigorously. Water (2 mL) was added cautiously, stirring was continued for 1 h, the resulting suspension was filtered through a bed of Celite, and the solids were washed with $CHCl_3$ (40 mL). The organic extracts were combined, solvents were removed under reduced pressure, and the resulting clear oil was distilled on the Kugelrohr (100 °C, 1 mmHg) to give 1,5-diazacyclododecane (0.590 g, 94%): ^1H NMR (270 MHz, $CDCl_3$) δ 2.96 (br s, 2H, N*H*), 2.77–2.73 (m, 4 H) 2.6–2.235 (m, 4H), 1.64–1.25 (m, 12 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ_c 51.29, 48.34, 28.46, 25.93, 25.17, 23.27; IR 3400, 3240 cm^{-1} (NH); HRMS *m/z* calcd for $C_{10}H_{22}N_2$ (M^+) 170.1783, found 170.1790.

1,9-Diazabicyclo[7.3.1]tridecane (7). Formaldehyde solution (39% aqueous, 0.25 mL, 1 equiv) was added to a stirred solution of 1,5-diazacyclododecane (0.59 g) in toluene (60 mL), and the resulting mixture was stirred rapidly and refluxed (nitrogen atmosphere) under a Dean–Stark water trap for 1.5 h. The resulting solution was dried ($MgSO_4$) and then filtered, and the solvents were removed under reduced pressure to give a pale yellow oil. Kugelrohr distillation (100 °C, 1 mmHg) gave 1,9-diazabicyclo[7.3.1]tridecane (0.57 g, 90%): IR (neat) 3050 cm^{-1} (C–H weak); ^1H NMR (400 MHz, $CDCl_3$; protons on the $(CH_2)_7$ bridge are labeled cis (c) or trans (t) to the (out) lone pair on N-1, protons in the six-membered ring are labeled axial (ax) or equatorial (eq), see Figure 3; *J* values were calculated using the equation of Haasnoot *et al.*[59]) δ 1.19 (dm, *J* = –12.9 Hz (*gem*), 1H, H-11(eq)), 1.37 (dtt, *J* = –12.8 (*gem*), 6.4 (*vic*), 6.4 Hz (*vic*), 1H, H-5(c)), 1.43–1.66 (m, 6H; H-4 + H-6(c + t) and probably H-3(t) + H-7(t)), 1.66–1.78 (m, 2H, probably H-3(c) + H-7(c)), 2.24 (dtt, *J* = –12.9 (*gem*), 12.9 (*app*), 5.0 Hz (*sc*), 1H, H-11(ax)), 2.33 (m, 1H, H-5(t)), 2.41 (ddd, *J* = 12.7 (*gem*), 5.7 (*vic*), 3.2 Hz (*vic*), 2H, H-2(c) + H-8(c)), 2.60 (ddd, *J* = –12.7 (*gem*), 12.7 (app), 3.6 Hz (sc), 2H, H-10(ax) + H- 12(ax)), 2.86 (dm, *J* = –12.7 Hz (*gem*), 2H, H-10(eq) + H-12(eq)), 2.92 (ddd, *J* = –12.7 (*gem*), 10.1 (*vic*), 2.8 Hz (*vic*), 2H, H-2(t) + H-8(t)), 2.99 (d, *J* = –11.8 Hz (*gem*), 1H, H-13(ax)), 4.17 (dt, *J* = –11.8 (*gem*), 2.1 Hz (*W-plan*), 1H, H-13(eq)); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ_c 69.69, 54.07, 51.00, 25.46, 24.95, 22.96, 20.91; HRMS *m/z* calcd for $C_{11}H_{22}N_2$ 182.1783, found 182.1785. The diamine, which is an oil, forms a solid insoluble oligomer or polymer on standing, but heating at 280 °C under a vacuum releases the diamine which is distilled off with *ca.* 10% loss.

1,4,8,11-Tetraazatricyclo[9.3.1.1^{4,8}]hexadecane (8).[39] 1,4,8,11-Tetraazacyclotetradecane (cyclam, Strem Chemical) (0.795 g, 3.97 mmol) and MeCN (300 mL) were stirred under nitrogen at room temperature as 37% aqueous formaldehyde (1.0 mL) was added to the heterogeneous mixture in one portion. The cyclam immediately started to dissolve. The reaction mixture was stirred at room temperature for 24 h. Solvent was then removed from the solution under reduced pressure to yield crude crystalline product. Sublimation (50 μmHg, 70 °C) gave 0.707 g (79%) of pure **8**, mp 106–108 °C: ^1H NMR (270 MHz, $CDCl_3$) δ 1.17 (dtt, *J* = –13.4, (*gem*), 3.3 (*sc*), 1.6 Hz (*sc*), 2H, H-6,13(eq)), 2.26 (dtt, *J* = –13.4 (*gem*), 12.6 (*app*), 5.1 Hz (*sc*), 2H, H-6,13(ax)), 2.38 (*AA'XX'*, 4H, H-2,3,9,10(eq)), 2.63 (ddd, *J* = –12.6 (*gem*), 12.5 (*app*), 3.5 Hz (*sc*); 4H; H-5,7,12,14(ax)), 2.84 (dddd, *J* = –12.6 (*gem*), 5.2 (*sc*), 1.5 (*sc*), 2.2 Hz (*W-plan*), 4H, H-5,7,12,14(eq)), 2.90 (d, *J* = –10.8 Hz (*gem*), 2H, H-15,16(ax) (aminal)), 3.15 (*AA'XX'*, 4H, H-2,3,9,10(ax)), 5.45 (dt, *J* = –10.8 (*gem*), 2.2 Hz (*W-plan*), 2H, H-15,16(eq) (aminal)); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ_c 20.37(t), 49.52(t), 53.80(t), 69.07(t); IR (KBr) 3046 (sh), 2940, 2875, 2855, 2803, 2785, 2730, 2680, 2650 (w) cm^{-1}; MS *m/z* (relative intensity) 224 (M^+, 48). Anal. Calcd for $C_{12}H_{24}N_4$: C, 64.24; H, 10.78; N, 24.97. Found: C, 64.26; H, 10.92; N, 25.14.

1,5,9,13-Tetraazatricyclo[11.3.1.1^{5,9}]octadecane (9).[40] 1,5,9,13-Tetraazacyclohexadecane (173.3 mg, 0.7587 mmol, prepared according to the method of Smith and Raymond[41]) was suspended in 150 mL of CH_3CN. A 200-μL portion of 37% aqueous formaldehyde solution was added, and the resulting solution was stirred 8 h. The solvent was evaporated under reduced pressure to yield white crystalline material which was sublimed at 52 °C (0.1 mmHg) to yield 184.7 mg (97%) of white crystalline **9**, mp 78–80 °C: IR (KBr) 2990, 2938, 2924, 2871, 2852, 2794, 2770, 2736, 2682, 2656 (w) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.26 (br m, 2H), 1.55 (p, 8H), 2.29–3.60 (2 br m, 16H), 3.83 (br m, 2H); ^1H NMR (360 MHz, $CDCl_3$) δ 1.1–1.3 (br m, 2H), 1.35–1.7 (br m, 4H), 1.9–3.3 (br m, 20H), 3.3–4.0 (br m, 2H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ_c 21.65(t), 24.49(t), 49.46(t), 55.04(t), 67.88(t). Anal. Calcd for $C_{14}H_{28}N_4$: C, 66.62; H, 11.18; N, 22.20. Found: C, 66.63; H, 11.42; N, 22.14.

1,4,8,11-Tetraazatricyclo[9.3.1.1^{4,8}]hexadecane-15,15,16,16-d_4 (8-d_4). A 1.07 M aqueous formaldehyde-d_2 solution was prepared by mixing 47.9 mg (1.50 mmol) of paraformaldehyde-d_2 with 1.4 mL of D_2O and refluxing the mixture for 2 h until all paraformaldehyde-d_2 was dissolved. This solution was transferred into a suspension of 1,4,8,11-tetraazacyclotetradecane (cyclam) (44.6 mg, 0.233 mmol) in 59 mL of CH_3CN. The resulting mixture was stirred for 10 h at room temperature under nitrogen. The solvent was evaporated under reduced pressure to give a white crystalline solid which was sublimed at 75 °C (0.01 mmHg) to yield 40.0 mg (78.6%) of white crystalline product, mp 105.5–107.5 °C: ^1H NMR (60 MHz, $CDCl_3$) δ 0.98–1.25 (m, 4H), 2.32–3.24 (m, 16H) (the proton NMR spectrum matched a spectrum of authentic **8** except for resonances absent at 5.45 and 2.90 ppm); IR (KBr) 2940, 2875, 2855, 2785, 2730, 2680, 2650, 2350, 2260, 2140, and 2022 cm^{-1}; MS *m/z* (relative intensity) 229 (M + 1, 10), 228 (M^+, 51), 227 (M – 1, 6.8). Anal. Calcd for $C_{12}H_{20}N_4D_4$: C, 63.13; N, 24.54. Found: C, 63.11; N, 24.34.

1,5,9,13-Tetraazatricyclo[11.3.1.1^{5,9}]octadecane-17,17,18,18-d_4 (9-d_4). A 0.947 M aqueous formaldehyde-d_2 solution was prepared by mixing 45.6 mg (1.42 mmol) of paraformaldehyde-d_2 with 1.5 mL of D_2O and refluxing the mixture for 2 h until all paraformaldehyde-d_2 was dissolved. This solution was transferred into a suspension of 1,5,9,13-tetraazacyclohexadecane (49.5 mg, 0.27 mmol) in 55 mL of CH_3CN. The resulting mixture was stirred for 12 h at room temperature under nitrogen. The solvent was evaporated under reduced pressure to give a white crystalline solid which was sublimed at 70 °C (0.015 mmHg) to yield 50.0 mg (89.9%) of pure product, mp 79–80.5 °C: ^1H NMR (60 MHz, $CDCl_3$) δ 1.13 (p, 8H), 2.29–3.13 (br m, 16H) (this proton NMR spectrum matched a spectrum of authentic **9** except for resonances absent at 3.8 and 3.1 ppm); IR (KBr) 2945, 2935, 2925, 2870, 2845, 2785, 2760, 2735, 2685, 2655, 2220, 2190, 2150, and 2015 cm^{-1}; MS *m/z* (relative intensity) 257 (M + 1, 23), 256 (M^+, 84), 255 (M – 1, 11), 254 (M – 2, 9.0). Anal. Calcd for $C_{14}H_{24}N_4D_4$: C. 65.59; N, 21.85. Found: C, 65.76; N, 21.61.

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Supplementary Material Available: Geometrical data associated with the semiempirical calculations reported in Tables I and II; listings of energies and conformations found by the BATCHMIN multiple minima search program for compounds **1–9** (10 pages). Ordering information is given on any current masthead page.