The Effect of Neighboring 1- and 2-Adamantyl Group Substitution on the Conformations and Stereodynamics of *N*-Methylpiperidine. Dynamic NMR Spectroscopy and Molecular Mechanics Calculations[1]

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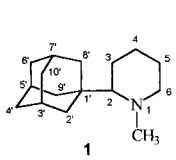
When a 1-adamantyl or a 2-adamantyl substituent is introduced at the 2-position in *N*-methylpiperidine, four different chair conformations are possible. Experimental observation using dynamic NMR spectroscopy and molecular mechanics calculations agree that the chair conformation with an equatorial adamantyl group and an axial methyl group is by far the most stable, but in both cases a minor population of a second conformation is demonstrated and characterized. Interaction between adamantyl and methyl groups is much more conformation-determining than any preference for equatorial over axial location which predominates in simpler 2-substituted *N*-methylpiperidines.

Introduction

The conformational behavior of piperidine derivatives has attracted particular attention in recent years because such heterocycles are present in many molecules of important medicinal interest.[2] In this work we have used NMR spectroscopy and molecular mechanics calculations to study 2-(1-adamantyl)-1-methylpiperidine **1** and 2-(2-adamantyl)-1-methylpiperidine **2**, which exhibit interesting antiviral properties[3] and in which the bulky substituents are formally tertiary and secondary alkyl groups, respectively. In a previous work, we reported the effect of a spiroadamantane structure on the stereodynamics of *N*-methylpiperidine.[4]



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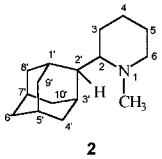

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There are three dynamic processes for compounds **1** and **2** that might produce temperature-dependent NMR spectra, viz. ring and nitrogen inversion and rotation about C1′−C2 or C2′−C2 bond. Scheme 1 is a conformational square for the compounds **1** and **2** showing how the conformations **A**−**D** can be interconverted by successive ring and nitrogen inversion processes.

Rotation of the adamantyl group in compound **1** leads to three identical conformers because of the C_{3v} symmetry of the 1-adamantyl group, but positions 2′, 8′, and 9′ are different when this rotation is slow on the NMR time scale. Rotation of the 2-adamantyl group in compound **2** in contrast interconverts three nonequivalent staggered conformations. There are no studies of 1-adamantyl or 2-adamantylcyclohexanes that afford an indication of the size of these groups.

We now report molecular mechanics calculations which suggest that for both compounds **1** and **2** several of conformations **A**−**D** are likely to be populated and Dynamic NMR results showing directly from low-temperature spectra that two conformations are populated for each compound. We will show that calculations agree quite well with experiment as to what these populated conformations are, and this will be confirmed by studies of the protonation of the piperidines.[5] In this last experiment, rapid irreversible protonation of either piperidine **1** or **2** (with trifluoroacetic acid) leads to a mixture of stereoisomeric salts, the population ratio of which reflects the population ratio of the free piperidine conformations before addition of the acid. The new conformational diagram is shown in Scheme 2, with passage from the left to the right representing dissociation/reassociation of a proton. This is slow even at room temperature, so two sets of signals are seen, one corresponding to the stereoisomer of the left-hand side and the other to the stereoisomer of the right-hand side, and

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(1) Part of the experimental work presented in this paper was run during a stay of Dr. A. Kolocouris at UCL.

(2) For reviews, see: (a) Crabb, T. A.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1984**, *36*, 3. (b) Delpuech, J.-J. In *Cyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takeuchi, Y., Eds.; VCH Publishers: New York, 1992.

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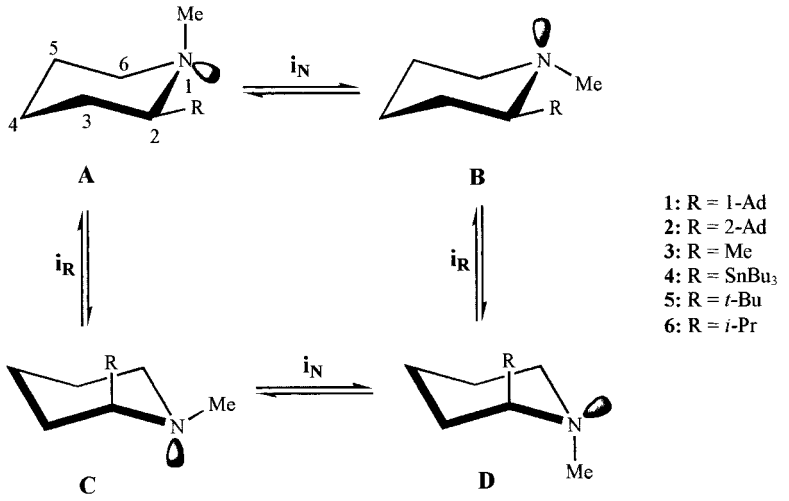
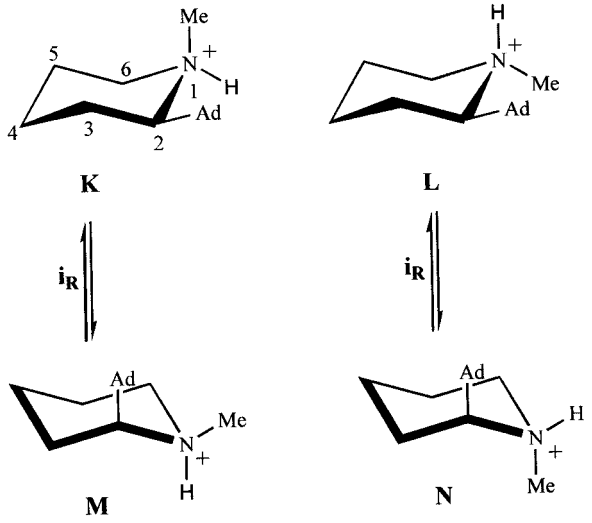
Scheme 1



Scheme 2



their relative abundance reflects the relative abundance of free piperidines that existed before the protonation experiment.

The conformational equilibrium in 2-substituted-*N*-methylpiperidines has already been experimentally measured and discussed for the 2-methyl[5] and the 2-tributylstannyl[6a] substituents, compounds **3** and **4**, respectively (Scheme 1). In both cases, the two conformations **A** and **D** were not considered in detail, but rather the 2-fold equilibrium detected and measured in Dynamic NMR studies was rationalized in terms of an equilibrium between the two structures **B** and **C**, with the assumption that the conformations **A** and **D** with axial *N*-methyl groups spontaneously revert by nitrogen inversion to **B** and **C**, respectively. Clearly, all four conformations should be considered for both these molecules, so we report MM3 calculations of their conformational energies in Table 2 along with the equilibria observed experimentally.

For the tributylstannyl compound **4**, two sets of signals of relative intensity 55:45 were observed in the NMR spectrum at low temperatures. The major set has been attributed[6a] to the diequatorial conformation **B** flattened at nitrogen to give a "half-chair" conformation (which we presume resembles cyclohexanone). While the substituents are both equatorial, the arguments for the nonchair conformation are unconvincing. They are based on the three-bond C−C−C−Sn coupling constants, using results for trimethylstannylcyclohexanes[6b] as models. There is a dramatic nitrogen substituent effect on the 1-bond C−Sn coupling constant (380−400[6b] in cyclohexanes compared with 139−214 Hz in compound **4**[6a]). The three-bond coupling constants observed for piperidine **4**, which are intermediate between axial and equatorial stannylcyclohexane model values, were however interpreted as representing intermediate (i.e. "half-chair") conformations, without considering the likelihood of a comparable nitrogen substituent effect on the magnitude of the three-bond coupling constants. We interpret the $^3J_{Sn-C}$ values for piperidine **4** in terms of a major diequatorial conformation, **B**, and a minor component with an axial $SnBu_3$ conformation which, following our calculations is some combination of **C** and **D**, interconverting easily by a nitrogen inversion process without the substituents crossing.

Results

Calculations. Molecular mechanics calculations will be discussed first as they illustrate the range of conformational possibilities. For compounds **1** and **2**, the MM3[7] and MM+[8] force fields were used. Quantum mechanical methods may not be any more useful indicators[9] for such conformational equilibria. Molecular dynamics and grid scan search analysis were used to find all possible conformational minima.[10] Nonchair conformations were located and found to be more, often much more, than 3 kcal mol^{-1} less stable than the preferred conformation, and therefore will not be mentioned further. We have also carried out MM3 calculations for compounds **3** and **4** and for 2-*tert*-butyl, **5**, and 2-isopropyl, **6**, derivatives of *N*-methylpiperidine as simpler

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Table 1. MM3 and MM+ Calculations Results for the Low-Energy Conformations A−D of 2-(1-Adamantyl)-1-methylpiperidine 1 and 2-(2-Adamantyl)-1-methylpiperidine 2

compound	rel energy (kcal mol^{-1})		conformation	% calcd popln[a] (T = 298 K)	
1	MM+	MM3	description	MM+	MM3
A	0.00	0.00	Ad (eq), *N*-Me (ax)	85.2	82.8
B	1.11	1.23	Ad (eq), *N*-Me (eq)	13.0	10.4
C	7.24	5.48	Ad (ax), *N*-Me (eq)		
D	2.29	1.48	Ad (ax), *N*-Me (ax)	1.8	6.8
compound **2**	MM+	MM3	conformation description	MM+	MM3
A	0.00	0.00	Ad (eq), *N*-Me (ax)	83.5	46.6
B	3.04	3.91	Ad (eq), *N*-Me (eq)		
C	4.29	3.97	Ad (ax), *N*-Me (eq)		
D	0.96	0.08	Ad (ax), *N*-Me (ax)	15.5	53.4

[a] Calculated populations of less than 1% are ignored.

models for **1** and **2.** Detailed results for compounds **1** and **2** are shown in Table 1, while results for **1** to **6** are summarized in Table 2.

Three conformational minima, **A**, **B**, and **D**, are predicted to be populated for compound **1**. Conformation **A** with the 1-adamantyl group equatorial and *N*-Me group axial were calculated to be the most stable by more than 1.1 kcal mol^{-1} by both methods. Conformation **B** with both groups equatorial is the next most stable, more likely than conformation **D** with both groups in the axial orientation. Table 1 also shows the population of each conformer calculated from equation $\Delta G° = -RT \ln K_{eq,}$ broadly 80−85% of conformation **A** with up to 10% and 5% or so each of conformations **B** and **D**, respectively.

The dihedral drive option in the MM3 program allowed us to calculate barriers to rotation around the C1′−C2 bond, i.e., to rotation of the adamantyl group, in compound **1**. The barrier is different in the four confomations **A**−**D**, namely, 8.7, 9.4, 6.0, and 6.0 kcal mol^{-1}, respectively, and these results will be discussed below.

Two conformations of the piperidine ring in compound **2**, namely, **A** and **D** were calculated to be populated, the other possible chair conformations being more than 3 kcal mol^{-1} higher in energy. Conformation **A** with the 2-adamantyl group equatorial and *N*-Me group axial is a little more stable than conformation **D** which strikingly has both substituents axial. Calculated relative populations of each conformation are shown in Table 1 and at room temperature are close to 3:1 for **A**:**D**.

For compound **2** there are three staggered conformations for the exocyclic C2−2-adamantyl bond, but calculations for each of **A**−**D** suggest that the one with hydrogen atoms at opposite ends of the bond *anti* to each other is by far the most stable. This was confirmed experimentally by a coupling constant of 11 Hz between these hydrogens.

The main conclusions of the calculations for compounds **3** to **6**, summarized in Table 2, will be useful in the discussion later.

Dynamic NMR Study. In the proton NMR spectrum of compound **1** at room temperature, the C2 proton appears at 2.19 ppm as a doublet of doublets, J = 3.1, 11.4 Hz (Figure 1), which suggests the predominance of a conformation in which that proton is axial and the adamantyl group is equatorial. The C6 axial proton is only 0.53 ppm upfield of equatorial and therefore cannot be antiperiplanar to an adjacent axial lone pair, i.e., the *N*-methyl group is axial. These together suggest that conformation **A** predominates (Scheme 1).

The ^{1}H and ^{13}C NMR spectra of both compounds **1** and **2** in $CHCl_2F/CHClF_2/CD_2Cl_2$ ~45:45:10 solution are temperature dependent, showing broadening and splitting of signals as the sample temperature is lowered. Because of poor resolution of spectra, peak overlap, not all minor peaks were observed. The processes involved were more clearly observed in the variable temperature ^{13}C NMR spectra due to their better dispersion. The carbon peaks were assigned by using literature data,[11] DEPT and 2D COSY and HMQC spectra, while the dynamic broadening behavior of some peaks was also helpful. Assignments on this basis will not be justified in detail (Table 3).

In the variable temperature carbon-13 NMR spectra of compound **1**, the signals of carbons 6, 4, 3, and 1′ and *N*-Me are significantly broadened at temperatures between 295 and 213 K, but broadening is less marked for the signals of carbons 2 and 5. Decoalescence was observed for the former resonances at about 243 K, with clear sharpening again below 193 K. At this temperature the *N*-methyl carbon signal of a minor conformer could seen at 46.5 ppm, indicating an equatorial orientation of the *N*-Me group, identified from its correlation with the *N*-Me proton peak at 2.42 ppm in the 2D HMQC spectrum. Peak integration gave a 97.5:2.5 major/minor population ratio, ΔG^0_{193} = 1.40 kcal mol^{-1}. Of the two conformations **B** and **C** which have an equatorial group, **C** with an axial adamantyl group is excluded following the calculations, so the minor isomer is the diequatorial conformation **B**.

A second process affecting only the adamantyl signals causes the signals for carbons 2′, 8′, and 9′ to broaden progressively below about 198 K with decoalescence at about 183 K, and at 153 K three peaks of equal intensity were observed. There is a less important broadening effect at 4′,6′,10′-C and 3′,5′,7′-C peaks in the same temperature region, and at 153 K these peaks appeared as 2:1 doublets, presumably triplets with accidental equivalence of two signals. No other change was observed on lowering the temperature to 145 K. At the coalescence temperature T_c = 183 K for 2′,8′, and 9′ carbons the barrier for the process involved, rotation of the adamantyl group, was calculated to be 7.6 kcal mol^{-1}. Corresponding changes were seen in the proton NMR signals of the adamantyl group but they were not suitable for simple analysis.

The ^{1}H NMR spectrum of the piperidine part of **1** shows some evidence of a minor conformer as the temperature is lowered to 173 K, but due to peak overlap only the *N*-methyl resonances of major and minor conformations were suitable for assignment and population measurement. The two *N*-methyl peaks were confirmed to be in exchange from a correlation with the same sign as the diagonal (negative sign) in the ^{1}H 2D EXSY spectrum (Figure 1). The major/minor population was measured by peak integration to be 95.6:4.4 at 173 K, ΔG^0_{173} = 1.06 kcal mol^{-1}, cf. the ^{13}C spectrum value, ΔG^0_{193} = 1.40 kcal mol^{-1}.

According to the dynamic NMR theory for a biased equilibrium,[12] at the temperature of maximum broaden-

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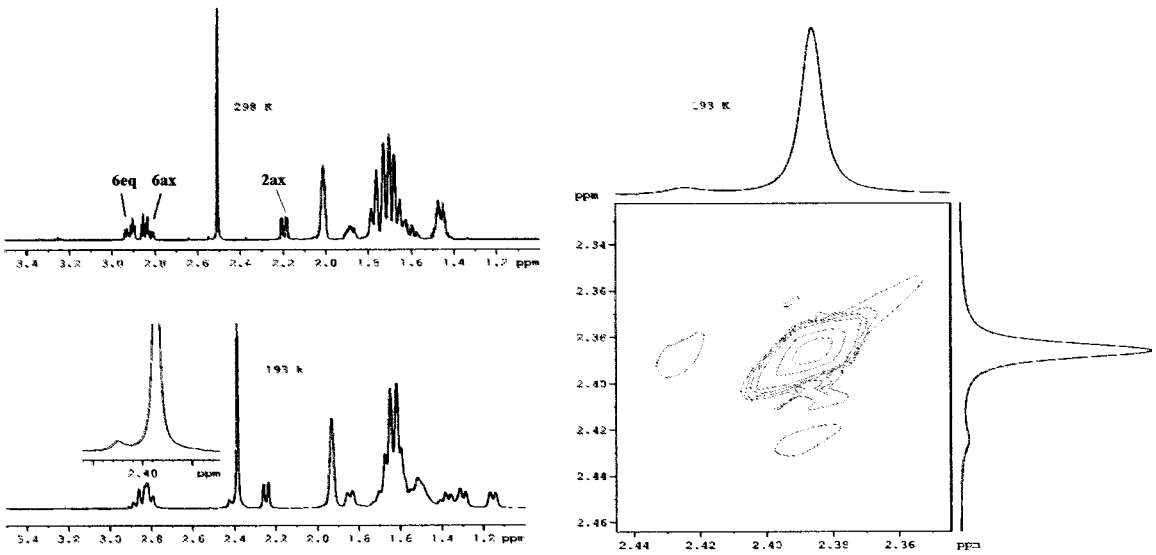

Figure 1. ^{1}H NMR spectra of 2-(1-adamanty)-1-methylpiperidine **1** in a $CHCl_2F/CHClF_2/CD_2Cl_2$ ~45:45:10 solution (500 MHz) at 298 and 193 K when a *N*-Me signal of a minor isomer (4.4%) was identified. In the right-hand part of the the figure is shown part of the ^{1}H 2D EXSY spectrum at 193 K showing the exchange peak between the two *N*-Me signals of major **A** and minor **B** conformation.

Table 2. MM3-Calculated Relative Energies (kcal mol^{-1}) for the Low-Energy Conformations A−D of the 2-Substituted 1-Methylpiperidines 1−6. The Experimental Values Show Only Those Conformations Detected by NMR Spectroscopy

		conformation				
		A	**B**	**C**	**D**	
compd	R	C−R (eq) *N*-Me (ax)	C−R (eq) *N*-Me (eq)	C−R (ax) *N*-Me (eq)	C−R (ax) *N*-Me (ax)	exptl[ref]
	H	2.38	0.00	0.00	2.38	0.00 (**B**+**C**), 2.41 (**A**+**D**)[18]
3	Me	2.30	0.00	1.61	2.66	0.00 (**B**), 1.70 (**A**+**C**)[5]
4	$SnBu_3$	1.05	0.00	0.14	0.43	0.00 (**B**), 0.08 (**C**+**D**)[6a]
2	2-Ad	0.00	3.91	3.97	0.08	0.00 (**A**), 1.21 (**D**)[a]
6	*i*-Pr	0.00	3.12	3.37	0.10	*b*
1	1-Ad	0.00	1.23	5.48	1.48	0.00 (**A**), 1.40 (**B**)[a]
5	*t*-Bu	0.00	0.62	5.22	1.49	*b*

[a] This work. [b] No experimental evidence.

Table 3. Carbon-13 Chemical Shifts (major peaks) of Compounds 1 and 2 in ~45:45:10 $CHCl_2F/CHClF_2/CD_2Cl_2$ Solution at 295 K and at Low Temperatures (100 MHz)

	chemical shifts			
	compound **1**		compound **2**	
carbons	295 K	153 K	295 K	183 K
2	71.9	69.4	60.2	58.7
3	25.2	25.9	25.8	25.7
4	18.7	16.2	21.2	20.0
5	19.9	18.6	20.0	18.4
6	56.1	57.6	55.6	55.6
1′	37.7	35.3	30.1	28.5
2′	40.8	42.7[a]	46.3	45.3
3′	30.0	27.9[c]	28.9	27.2
4′	38.3	36.2[b]	33.0[d]	31.5[d]
5′	30.0	27.9[c]	29.5[e]	28.0[e]
6′	38.3	36.4[b]	39.4	38.0
7′	30.0	28.4[c]	29.1[e]	27.7[e]
8′	40.8	35.8[a]	40.1	38.6
9′	40.8	38.6[a]	32.9[d]	31.4[d]
10′	38.3	36.4[b]	40.7	39.1
N-Me	40.2	35.1	35.2	31.8

[a−e] The chemical shifts marked with the same letter can be interchanged.

ing the major form converts to the minor with a rate constant $k = 2\pi\omega^*$, where ω^* (Hz) represents the maximum broadening of the major line and equals $p\Delta\nu$, where p is the population of the minor form and $\Delta\nu$ is the peak separation. Thus, for the *N*-Me carbon peaks $T_c = 203$ K, $\Delta\nu = 20.4$ Hz (100 MHz), $p = 4.4\%$ at 173 K, and $k = 58.9$ s^{-1}. From this the free energy of activation $\Delta G^{\#}$ for the major to minor interconversion is 10.1 kcal mol^{-1} at 203 K.

For compound **2** at room temperature, the signal of the C2 proton at 2.86 ppm is a doublet of doublets of doublets showing two large couplings of about 11.1 and 9.4 Hz and one small coupling of 3.1 Hz (Figure 2). The signal of the adamantyl H2′ (broad doublet at 1.63 ppm, $J = 11.1$ Hz) confirms the *anti* conformation around the C2−C2′ bond. The 9.4 Hz coupling shows that one conformation predominates with the C2 proton axial (so the adamantyl group is equatorial). As with **1**, the relative shift of the two C6 protons, less than 0.2 ppm, suggests that the nitrogen lone pair is not antiperiplanar to either, i.e., that the lone pair is equatorial, so the *N*-methyl group is axial. Conformation **A** thus appears to predominate for compound **2** as well as for **1**.

Assignments for the carbon-13 NMR spectrum for compound **2** are shown in Table 3. Below about 233 K, peaks, most noticeably for carbons 2, 2′, 8′, *N*-Me, 1′, 3′, 3, 4, and 5, begin to broaden with a maximum at about 213 K. At 183 K peaks are sharp, and signals for a minor

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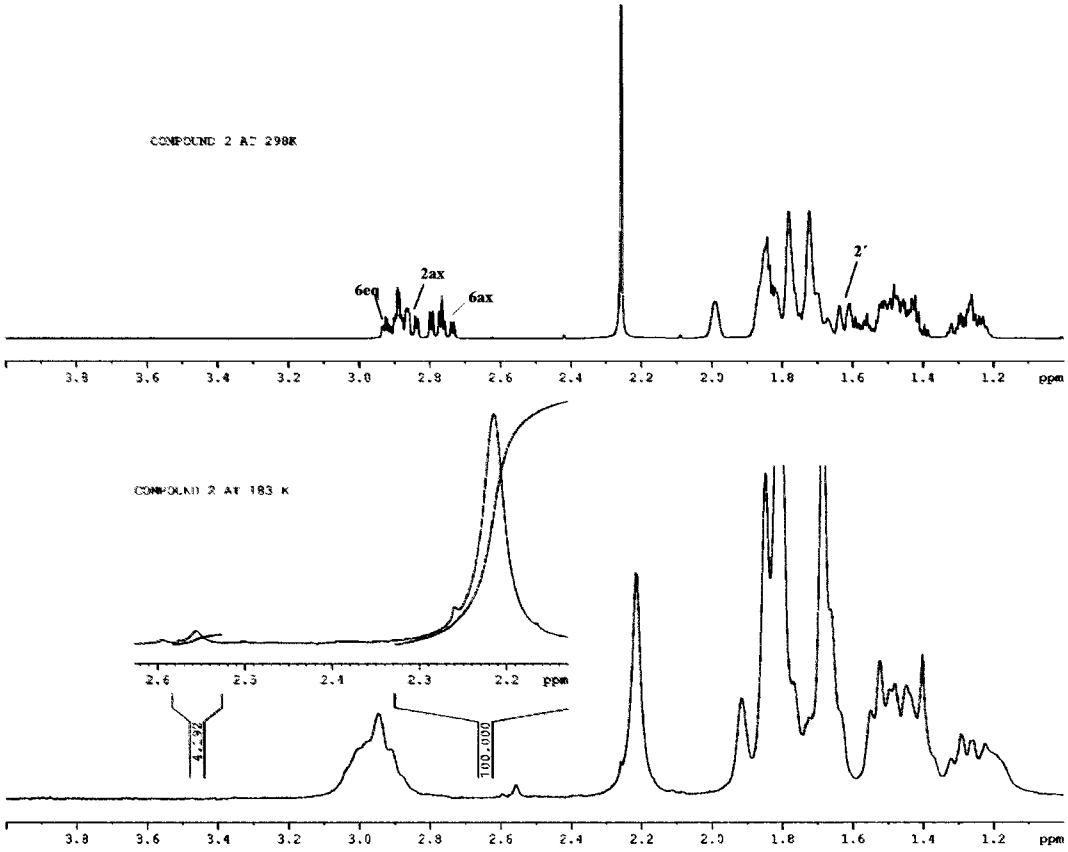


Figure 2. ^{1}H NMR spectra of 2-(2-adamanty)-1-methylpiperidine **2** in $CHCl_2F/CHClF_2/CD_2Cl_2$ ~45:45:10 solution (500 MHz) at 298 and 183 K when a *N*-Me signal of a minor isomer (4.0%) was identified.

isomer are observed with about 3.4% relative population, $\Delta G^0_{183} = 1.21$ kcal mol^{-1}.

The ^{1}H NMR spectrum for compound **2** also shows broadening of the spectrum on cooling, with decoalescence at about 213 K. From the two *N*-methyl peaks at 183 K, the population ratio is 96.0:4.0 corresponding to a 1.15 kcal mol^{-1} energy difference between conformations. The barrier for major to minor interconversion for the biased equilibrium was calculated as above to be 10.9 kcal mol^{-1} at the maximum broadening temperature (T_c = 213 K).

No additional process was observed at lower temperatures in either the proton or carbon-13 NMR of compound **2**, which fits with a single populated conformation for the exocyclic bond, in which the C2 and C2′ protons are *anti*.

Protonation Studies. When compound **1** was protonated at room temperature by addition of a drop of trifluoroacetic acid to the NMR tube, two sets of signals for **1**$^+$**H** were seen, with relative intensity 94.2:5.8, which corresponds to $\Delta G^0_{298} = 1.65$ kcal mol^{-1} for the free amine if protonation is rapid and irreversible (Figure 3). Protonation in a solution precooled to 195 K led to the peak ratio 96.0:4.0. In the proton NMR spectrum, the major salt isomer showed C2H as a doublet (J = 12.6 Hz) of triplets (J = 2.2 Hz). This indicates that the C2 proton is axial, showing a large coupling to axial C3H. The small triplet splitting is due to coupling to equatorial C3H and to the proton on nitrogen which must therefore be equatorial, hence the N^+-methyl group is axial. The major isomer for the salt and for the free amine are thus as in conformations **K** and **A**, respectively, with the *N*-methyl group axial and the 1-adamantyl group equatorial (Schemes 1 and 2). Other aspects of the spectrum fit this assignment.

The minor isomer signal for the salt **1**$^+$**H** undoubtedly reflects a *trans* arrangement of adamantyl and methyl groups and has interesting couplings. The C2H appears as a doublet of doublets of doublets with coupling constants 2.6, 5.7, and 8.5 Hz. The latter two coupling constants are oddly intermediate between those of about 2−4 Hz expected for an equatorial proton and those of 10−12 Hz expected for an axial proton. We believe that the spectrum observed represents a fairly evenly balanced equilibrium, fast on the NMR time scale, between the two chair conformations of the *trans* configuration of the salt **1**$^+$**H**, the diequatorial **L**, and the diaxial **N** (Scheme 2). In fact, as the temperature is lowered, the minor signal of the salt does broaden compared to the major signal, this being particularly evident in the ^{13}C NMR spectrum, but even at 193 K, the lowest temperature at which solution spectra of the salt could be obtained, splitting of the minor signal was not observed. Molecular mechanics calculations for the salt (Table 4) suggest that there should be about 8% of the *trans* configuration of the salt in the diequatorial conformation, which should exist at about six times as much diaxial as diequatorial, a suggestion that fits reasonably with the interpretation of the spectral behavior that we have offered.

An alternative explanation is that twist boat conformations might be populated, but these are calculated to be markedly higher in energy than conformations **L** and **N**. The minor isomer undoubtedly arises from protonation

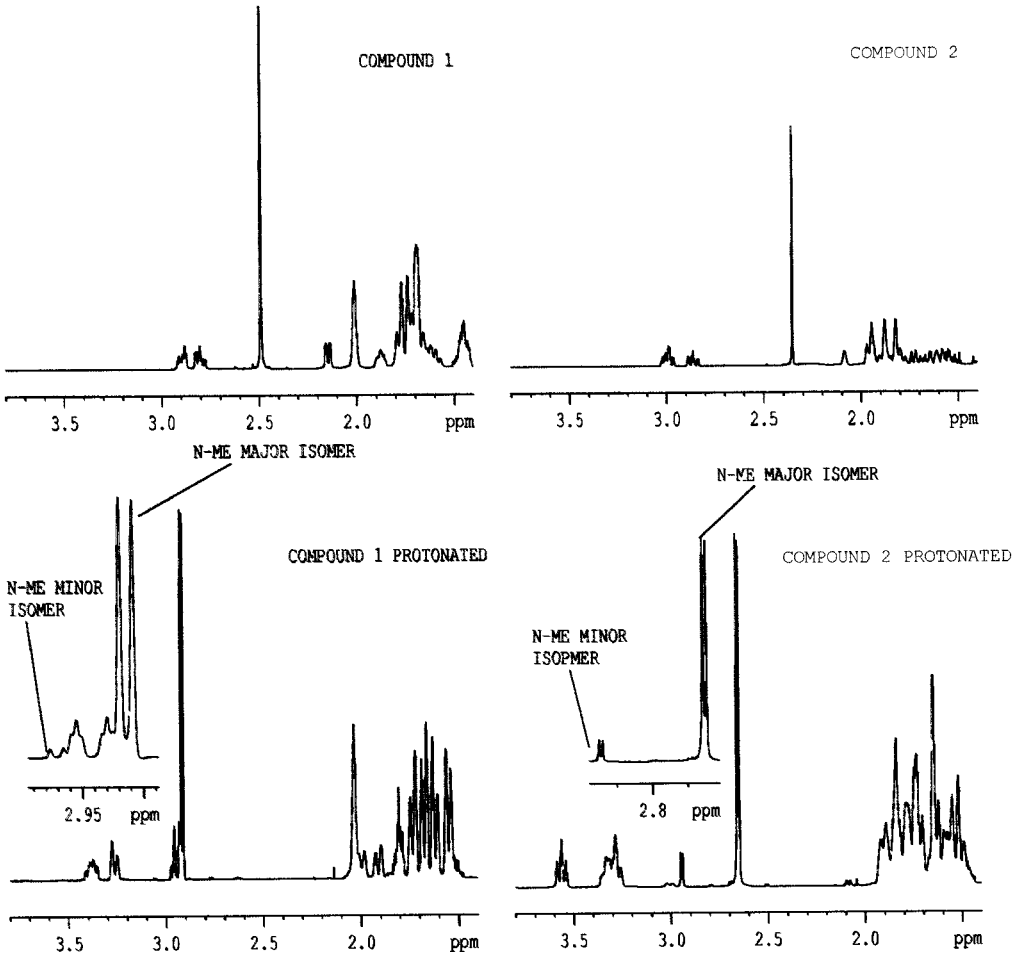


Figure 3. Proton NMR spectra (500 MHz) of compounds **1** and **2** in a $CHCl_2F/CHClF_2/CD_2Cl_2$ ~45:~45:~10 solution before and after adding a drop of trifluoroacetic acid at ambient temperature.

Table 4. MM3 and MM+ Calculations Results for the Low-Energy Conformations K−N of Protonated 2-(1-Adamantyl)-1-methylpiperidine 1 and 2-(2-Adamantyl)-1-methylpiperidine 2

compound	rel energy (kcal mol^{-1})		conformation	% calcd popln[a] (T = 298 K)	
1$^+$**H**	MM+	MM3	description	MM+	MM3
K	0.00	0.00	Ad (eq), *N*-Me (ax)	92.1	91.6
L	1.59	1.50	Ad (eq), *N*-Me (eq)	6.3	7.3
M	6.58	5.16	Ad (ax), *N*-Me (eq)	-	-
N	2.39	2.62	Ad (ax), *N*-Me (ax)	1.6	1.1

compound			conformation		
2$^+$**H**	MM+	MM3	description	MM+	MM3
K	0.00	0.00	Ad (eq), *N*-Me (ax)	85.3	87.8
L	3.30	3.73	Ad (eq), *N*-Me (eq)	-	-
M	4.02	2.36	Ad (ax), *N*-Me (eq)	-	-
N	1.04	1.17	Ad (ax), *N*-Me (ax)	14.7	12.2

[a] Calculated populations of less than 1% are ignored.

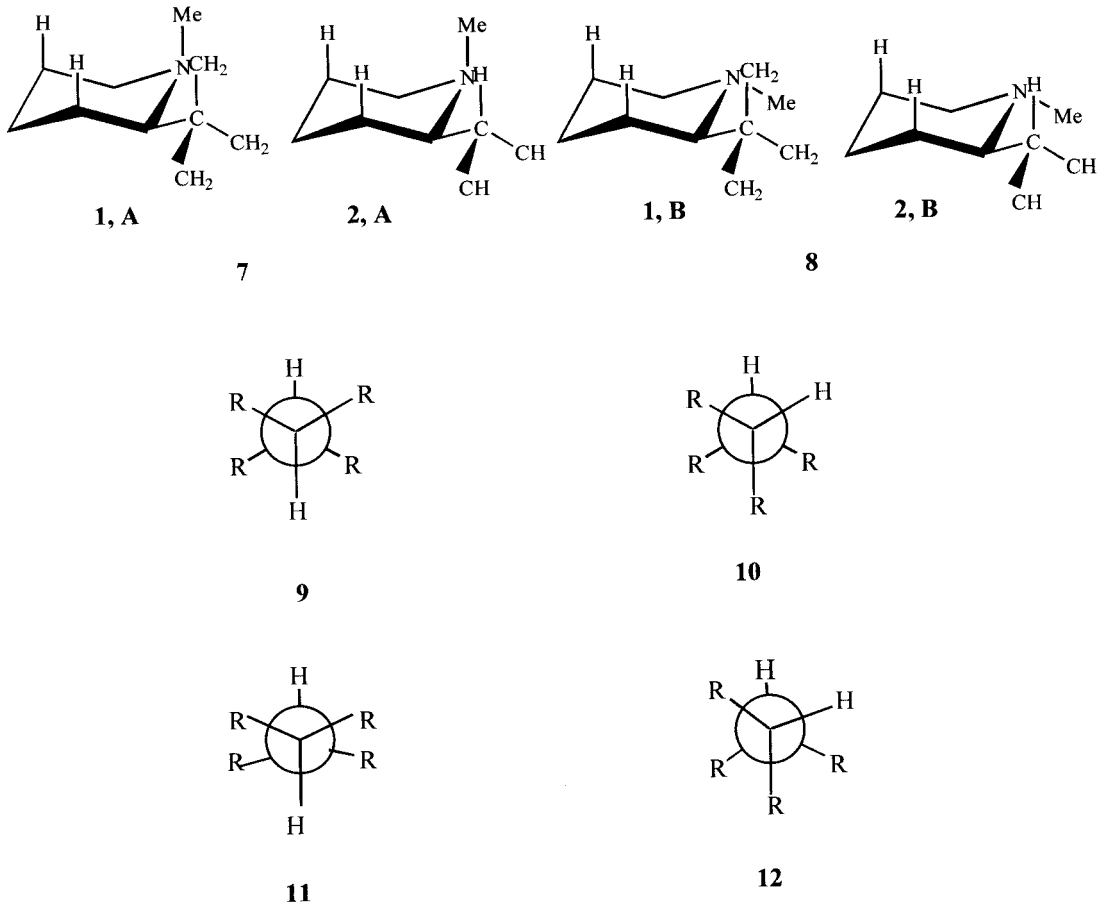
of the *trans* configuration of the free amine, and we conclude from the calculations that there is likely to be slightly more of the diequatorial form **L** than of the diaxial form **N**, both of which may result from protonation of conformations **B** or **D** followed by ring inversion if necessary. Thus, the minor isomer of the free amine **1** at room temperature is either **B** or **D**, and the earlier NMR evidence has excluded **D**.

When compound **2** was protonated at room temperature, two sets of NMR signals were observed in the proportion 90.2:9.8, "ΔG^0_{298}", see above = 1.32 kcal mol^{-1} both in the proton and in the carbon-13 NMR spectrum (Figure 3).

In the spectrum of the major salt isomer, the two C6 protons have very similar chemical shifts but the C2 proton signal at 3.57 ppm is an apparent triplet of triplets with couplings of about 2.5 and 11.6 Hz. This C2 proton must thus be axial with large couplings with the axial C3 proton and the C2′ proton of the secondary adamantyl group, located *anti* as discussed above. The two small couplings are with the C3 and the N^+H equatorial protons, so the N^+-methyl group is axial. The predominant conformations of the salt **2**$^+$**H** and of the piperidine **2** are as in conformations **K** of Scheme 2 and **A** of Scheme 1, respectively.

The minor C2 proton signal for **2**$^+$**H**, in contrast, is a doublet (J = 11.5 Hz) of broad multiplets, the large coupling being with the adjacent adamantyl proton. The C2 proton is therefore equatorial. Whether the N^+H proton is axial or equatorial cannot be determined from its own broad appearance, from its small coupling to equatorial C2H, nor from its coupling to the minor axial C6 proton signal which is obscured by the major signal. Since the C2-proton is equatorial and calculations predict that diaxial conformation **N** is much more stable than diequatorial **L** (Scheme 2), we conclude that the minor conformations for **2**$^+$**H** and thus for **2** itself are **N** and **D**,

Scheme 3[a]



[a] Only significant hydrogen atoms and part of the adamantyl groups are shown.

respectively, with both the *N*-methyl and 2-adamantyl groups axial!

Discussion

Much of the interest in this present report is in the adamantyl−methyl interaction in the various conformations. Such interaction of substituents at adjacent ring positions in a six-membered ring can lead to stark modifications of the chair−chair equilibrium, and this is particularly likely when one of the substituents is very large. The energy advantage in the substituents' being as distant from each other as possible may then overwhelm the ring's preference for equatorial substitution. An extreme example of this is *trans*-1,2-di-*tert*-butylcyclohexane for which both the diaxially substituted chair conformation and a twist boat are more stable than the classic diequatorially substituted chair conformation.[13]

When viewed along an exocyclic bond, a 1-adamantyl group substituent resembles a *tert*-butyl group in many ways, but notably, its rigidity reduces its ability to distort to accommodate strain. Similarly, a 2-adamantyl group may be viewed as a rigid isopropyl group. Piperidines with substituents on nitrogen and on carbon atom 2 have a particular interest since nitrogen inversion (which interconverts the configuration at nitrogen) provides access to four chair conformations (see Scheme 1) rather than the two that would obtain for a 1,2-disubstituted cyclohexane. In addition, substituent interactions are accentuated due to the short carbon−nitrogen bond, about 146 pm compared to 154 pm for the carbon−carbon bond.

In each of compounds **1** and **2**, the striking feature, by NMR observation and calculation, is that the conformation preferred is **A** with an equatorial adamantyl group and an axial *N*-methyl group, rather than **B** with both substituents equatorial. In both **A** and **B**, the two substituents are *gauche* to each other along a C−N bond in the ring, see diagrams **7** and **8** (Scheme 3), yet the conformation **A** (= **7**) with an axial *N*-methyl group (and thus its parallel 1,3-interactions with axial hydrogen atoms) is nonetheless more stable than conformation **B** (= **8**) with the equatorial methyl group.

This tendency has already been noted by Eliel and coworkers[5] when comparing the equilibrium measured in compound **3** with that for 2-methylpiperidine. The *cis* conformation of **3** with one of the methyl groups axial is *more stable than expected* relative to the *trans* conformation with both groups equatorial, although the latter is still the more populated. For compounds **1** and **2** with the larger adamantyl substituent, the *cis* conformation **A** is actually, not just relatively, more stable than the *trans* diequatorial conformation **B**, and for compound **2**, the latter conformation is so destabilized that the minor populated conformation is the *trans* diaxial conformation **D**. The tributylstannyl group is smaller than a methyl group as a single substituent on cyclohexane but the

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experimentally determined[6a] 55:45 ratio for **B**:**C**+**D** in compound **4** makes it appear *larger*, when interactions with an *N*-methyl group along an N−C bond are the conformational feature.

Since the two substituents are mutually *gauche* both in **A** and **B**, the increasing preference for the *N*-methyl axial conformation **A** over conformation **B** as the C2 substituent increases in size needs an explanation. The C2−N1 bond in the piperidine ring is tetrasubstituted, and a comparison with a well-studied acyclic series of compounds is illuminating.

1,1,2,2-Tetrasubstituted ethanes might be expected to adopt the *anti* conformation, like **9**, with two *gauche* interactions rather than the *gauche* conformation **10** with three *gauche* interactions or its enantiomer. However, even when the four substituents are simple methyl groups, i.e., in 2,3-dimethylbutane, the two conformations are about equal in energy,[14] whereas for larger substituents only the *gauche* conformation **10** and its enantiomer are populated.[15] This happens because of opening up of bond angles R−C−R, which in conformation **9** forces *vicinal* substituents R together with no possibility of relief by rotation, see **11**. With bond angle opening in conformation **10**, *gauche* substituents are moved apart and steric interaction may be further eased by rotation about the central bond, see structure **12**. This well-established explanation in the acyclic case also fits the 2-adamantyl-*N*-methylpiperidines as conformations **B** and **A** clearly resemble the acyclic conformations **9** and **10**, respectively, both in structure and relative stability.

For compound **1**, calculations confirm that the bond angle opening at C1′−C2−C3 and CH_3−N−C6 is greater in **A** than **B** (114° and 111° vs 110° and 107°), although the ring system limits rotation about the N−C2 bond. Conformations **1**,**C** and **1**,**D** are of high energy but **1**,**D** with the two groups axial is more stable than **1**,**C** with a methyl/adamantyl *gauche* interaction.

When the substituents are symmetrical and *gauche* to each other as in **1**, rotation of both groups about the *exocyclic* bonds in the same sense reduces their mutual interaction.[16] In conformation **A**, the *exocyclic* bonds to adamantyl and methyl are calculated to be skewed 16.3° and 5.5° away from perfect staggering, while the values in **B** are 20.6°and 5.9°, respectively.

A contrasting example of a 1,1,2,2-tetrasubstituted bond is provided by the exocyclic bond to the 2-adamantyl substituent in compound **2**. Bond angle opening is resisted by the adamantyl structure, and only *anti* conformers of the exocyclic bond are populated. In conformations **B** and **C**, the *N*-methyl group clashes with an adamantyl CH group, whereas in conformations **A** and **D** it confronts a methine hydrogen. Thus, the rotational characteristics of the 2-adamantyl group (smaller than 1-adamantyl) reinforce the preference for conformation **A** for compound **2** and change the preferred minor conformation from **B**, which is found for compound **1**, to **D**, for compound **2**.

Table 2 shows MM3 calculations of conformations of compounds **5** and **6**, analogues of **1** and **2**, with less rigid *tert*-butyl and isopropyl group substituents instead of 1-adamantyl and 2-adamantyl, respectively. The relative amounts of the stable conformations for compounds **2** and **6** are very similar, but for the 2-*tert*-butyl compound **5**, the diequatorial conformation **B** is much closer in energy (0.62 kcal mol^{-1}) to the preferred conformation **A** than in the 1-adamantyl compound **1** (1.23 kcal mol^{-1}), suggesting that the *tert*-butyl group is better able to distort to accommodate compression from the *N*-methyl group than is the 1-adamantyl group, which agrees well with previous experience.[17]

Table 5. *N*-Methylpiperidine ^{13}C and ^{1}H (500 MHz) Chemical Shifts of Compound 1 in ~45:45:10 $CHCl_2F$/$CHClF_2$/CD_2Cl_2 Solution at 193 K When the Major and Minor Conformers A and B Are in Slow Exchange

	^{13}C		^{1}H	
position	major	minor	major	minor
N-CH_3	35.4	46.3	2.4	2.43
2	70.1	71.1	2.1	*a*
3	26.0	19.1	1.8(eq), 1.4(ax)	*a*
4	16.7	20.0	1.6(eq), 1.3(ax)	*a*
5	18.8	18.4	1.7(eq), 1.1(ax)	*a*
6	57.9	48.1	2.79(eq+ax)	*a*

[a] Not resolved.

Since the conformations of **1** and **2** that are detectably populated are different, **A** and **B** for **1**, but **A** and **D** for **2**, the dynamic processes seen in the NMR are different. For compound **1**, chair−chair interconversion may have a high barrier (that of *N*-methylpiperidine[18] being 11.8 kcal mol^{-1}) but conformations linked by ring inversion are not populated. The populated conformations **A** and **B** of **1** are related by nitrogen inversion, so this is the first process observed, with a barrier of 10.1 kcal mol^{-1}. This is a high-demand nitrogen inversion barrier since the methyl and 1-adamantyl groups have to pass, eclipsing each other along the C2−N1 bond.[19]

For compound **1**, the second process, seen only in the adamantyl group signals, is rotation around the C1′−C2 bond, i.e., adamantyl group rotation. The barrier of 7.6 kcal mol^{-1} was measured from the spectrum of the major conformation **A** and can be compared with MM3-calculated values of 8.7, 9.4, 6.0, and 6.0 kcal mol^{-1} for the four conformations **A**−**D**. The experimental value and that calculated for conformation **A** agree within acceptable limits, particularly since MM3-calculated enthalpies of activation for rotation are expected to be slightly lower than experimental free energies of activation.[20] The low 6.0 kcal mol^{-1} calculated barriers for conformations **C** and **D** reflect the strain felt by an axial adamantyl group, even in its rotational ground state, for the ring−adamantyl bond is far from perfectly staggered.

From DNMR experiments on compound **2**, one process was identified with a barrier of 10.9 kcal mol^{-1} at 213 K, higher than for any process in compound **1**. That the major conformation is **A** with the 2-adamantyl substituent equatorial and *N*-Me group axial while the minor isomer **D** has both substituents axial has been justified above. The interconversion of these conformations re-

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Table 6. *N*-Methylpiperidine ^{13}C and ^{1}H (500 MHz) Chemical Shifts of Protonated Compounds 1 and 2 in ~45:45:10 $CHCl_2F/CHClF_2/CD_2Cl_2$ Solution at 193 K. Peaks Due to Major and Minor Isomers Are Shown

	compound **1**				compound **2**			
	^{13}C		^{1}H		^{13}C		^{1}H	
position	major	minor	major	minor	major	minor	major	minor
N-Me	36.0	45.2	2.77	2.98	32.4	41.5	2.77	3.08
2	73.7	76.2	2.96	2.68	64.4	64.1	3.67	3.52
3	23.4	19.1	1.99(eq), 1.51(ax)	*b*	22.4	19.5[a]	1.96(eq), 1.41(ax)	*b*
4	18.6	17.3	1.80(eq), 1.70(ax)	*b*	21.3	18.3[a]	2.01(eq), 1.35(ax)	*b*
5	18.5	16.0	1.70(eq), 1.59(ax)	*b*	18.3	17.1[a]	1.86 (eq+ax)	*b*
6	58.4	50.6	3.39(eq), 3.28(ax)	*b*	56.4	49.3	3.41 (eq+ax)	3.49(eq), 2.82(ax)

[a] The chemical shifts of these carbons can be interchanged. [b] Not resolved.

quires both ring and nitrogen inversion, but separate signals will be seen when either process is slow, so that the experimental barrier is higher for **2** than for **1**, which suggests that for **2** ring inversion is the determining process. The 10.9 kcal mol^{-1} barrier is smaller than that of *N*-methylpiperidine, 11.8 kcal/mol,[18] which suggests that distortion to find the most stable ground state conformation for adjacent adamantyl and methyl substituents reduces the subsequent distortions to interconvert chair conformations.

Nitrogen inversion in **2**,**D** should have a lower barrier than for **1**, since it does not involve substituents passing. If nitrogen inversion is still fast at 180 K, the signal assigned to **2**,**D** may represent an equilibrium of that conformation with **2**,**C**.

Experimental Section

The assignments of ^{1}H and ^{13}C signals (see Table 3) were achieved by the combined use of DEPT, 2D COSY, and HMQC experiments. Many peaks due to minor conformers were identified using HMQC and ^{1}H and ^{13}C 2D EXSY spectra. In Table 5 are shown the ^{1}H and ^{13}C chemical shifts of *N*-methylpiperidine nuclei for major and minor conformers **1**,**A** and **1**,**B** and in Table 6 those of protonated forms. The samples for low-temperature experiments were prepared by connecting the NMR tubes containing compound **1** or **2** dissolved in CD_2Cl_2 to a vacuum line and condensing therein nine times as much an amount of 1:1 $CHCl_2F/CHClF_2$ by means of liquid nitrogen. The tubes were then sealed in vacuo and introduced into the precooled probe of the Bruker-AMX 400 MHz and DRX 500 MHz spectrometers operating at 100.6 and 125.7 MHz for ^{13}C. The low-temperature 2D EXSY spectra were run using a mixing time of 300 ms.

Dynamics calculations were run at 1000 K for 300 ps. After the low-energy conformers were identified, their energies were calculated from Allinger's MM3 program and HyperChem program using the MM+ method. An energy gradient tolerance of 0.001 kcal mol^{-1} A^{-1} was generally used. The one-bond energy profiles for compounds **1** and **2** resulted from grid scan search modules of the MM3 program.

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