Eclipsed Conformation of the Exocyclic N−CH_2 Bond in *N*-Neopentylpiperidines and the Stereodynamic Consequences As Studied by Dynamic NMR Spectroscopy and Molecular Mechanics Calculations

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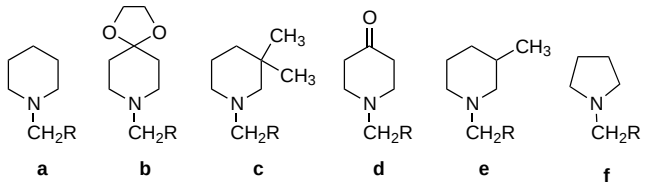
Received November 5, 1997

The dynamic stereochemistry of a range of *N*-neopentylpiperidines **1** with an eclipsed N−CH_2-*t*-Bu bond is compared with that of the corresponding range of *N*-ethylpiperidines **2** with a gauche N−CH_2Me bond. By using dynamic NMR spectroscopy, the relative importance of ring inversion, exocyclic bond rotation, and nitrogen inversion are elucidated and barriers are reported and discussed. Minor populations of the neopentyl-axial-eclipsed conformation are detected directly and identified with the help of molecular mechanics calculations. The corresponding *N*-alkylpyrrolidines are also reported.

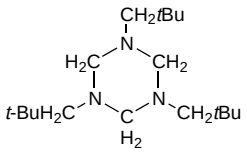
Introduction

There has been much recent interest in molecules that contain saturated bonds that prefer to adopt an eclipsed conformation.[1−3] Particularly striking is the demonstration that the exocyclic N−C bond in *N*-neopentylpiperidine[3] and analogues[2i,j] and the exocyclic C−O bond in *tert*-butoxycyclohexane[2h] are eclipsed.

Such eclipsing has possible consequences for the interconversion of molecular conformations,[2f,3b] so we have synthesized and investigated a set of compounds chosen to show a range of stereodynamic behavior, *N*-neopentylpiperidine and some of its derivatives **1a**−**e**, the equivalent *N*-ethylpiperidines **2a**−**e** as noneclipsed comparisons, and the two *N*-alkylpyrrolidines **1f** and **2f**.



1, R = tert-butyl **2**, R = methyl



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Scheme 1 shows the ground-state chair conformation **I** of *N*-neopentylpiperidine **1a**, which is known to have the substituent equatorial and the exocyclic N−CH_2-*t*-Bu bond eclipsed.[3a] There is an equivalent form **V** reached from **I** by three processes, namely ring inversion, nitrogen inversion, and N−CH_2 bond rotation, which, putatively, can take place in any sequence, some more likely than others. Scheme 1 is thus a conformational cube that encompasses these possibilities and shows the intermediate structures **II**−**IV** and **VI**−**VIII**, which may be involved and may or may not be significantly populated. Dynamic NMR is suitable for studying the overall interconversion of **I** and its equivalent form **V**, for geminal protons on the ring are diastereotopic when interconversion of these structures is slow on the NMR time scale and this is in fact observed at suitably low temperatures.

Thus, if ring inversion first becomes slow on the NMR time scale, **I** and less stable structures **II**, **IV**, and **VII** on the left-hand side are distinct from **V** (and **III**, **VI**, and **VIII**) on the right-hand side of the cube. If it is nitrogen inversion that first becomes slow, structure **I** and others on the top face become distinct from structure **V** and others on the bottom face of the cube. If it is

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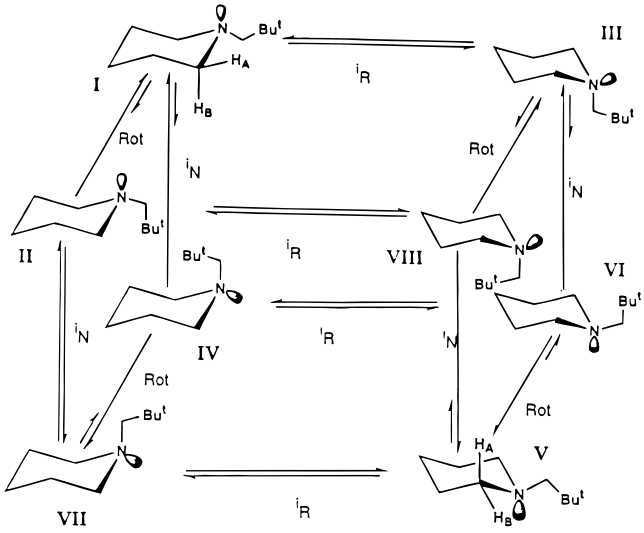
S0022-3263(97)02034-3 CCC: $15.00
Published on Web 04/30/1998

Scheme 1



N−CH_2 bond rotation that first becomes slow, structure **I** on the rear face becomes distinct from structure **V** on the front face. Geminal protons becoming diastereotopic thus does not indicate which of the three processes has become slow on the NMR time scale. The answer may emerge from other evidence and turns out to be different for different *N*-alkylpiperidines studied. If forms such as **II**, **III**, and **IV** are of sufficiently low relative energy to be significantly populated, a second set of dynamic NMR changes due to slowing of a second of these processes on the NMR time scale may be observed at even lower temperatures, resulting in two sets of NMR signals of different intensity.

We will show examples with separate sets of spectra for a minor conformation, but in another case, when the minor population is less than about 2%, the slowing of the interconversion will appear only as a broadening of signals, followed by their narrowing once again as the temperature is progressively lowered, the expected minor signal being too weak to be discerned from noise.[4] Finally, when there is no explicit or implicit NMR evidence for them, other minor conformations will be described only from molecular mechanics calculations of their structure and energy.

The eclipsing of the N−CH_2 bond has been demonstrated[3] for **1a** and for *N*,*N*′,*N*″-trineopentyltriazane, **3**,[2i] but there is no simple NMR method for deciding whether further analogues **1b**−**f** are also eclipsed, although of course the bond environment is very similar. MM3[5,6] and MMX[7] molecular mechanics calculations have reliably predicted the eclipsing found[2i,3] for **1a** and **3** and so are used to predict the structure and energy of the various plausible stable conformations in the series of compounds **1** and **2**.

Results

Molecular Mechanics Calculations. Table 1 lists relevant details of MM3 calculations of N−CH_2 bond conformational minima, eclipsed, anti, or gauche for the compounds **1a**−**f** and **2a**−**f**, in both CH_2R-equatorial and CH_2R-axial conformations. Some axial/equatorial energy differences were also determined by MMX calculations,[7] and values are shown in parentheses. For neopentylpiperidines **1a**−**e**, the equatorial-neopentyl conformations **I** and **V** with the *tert*-butyl group eclipsing the lone pair are the most stable, with the axial eclipsed conformations **III** and **VII** the next most likely. No minima are found with a gauche arrangement, and the anti-equatorial conformations **II** and **VI** are about 3.6 kcal/mol higher in energy. Conformations such as **IV** and **VIII** and nonchair conformations were calculated to be of so high relative energy that they are not considered further nor reported in Table 1.

Table 1. MM3-Calculated Relative[a] Enthalpies E_{Rel}[b] and Exocyclic Bond Conformational Minima[c] for *N*-Neopentyl- and *N*-Ethylpiperidine and Pyrrolidine Derivatives 1 and 2 (Selected MMX Results Are Shown in Parentheses)

	equatorial minima								
	eclipsed		gauche		anti		axial min		measured
	E_{Rel}	ϕ	E_{Rel}	ϕ	E_{Rel}	ϕ	E_{Rel}	ϕ	E_{Rel}
1a	0.00	2			3.60	171	2.12 (2.24)	9	**1.04**
1b	0.00	13			3.53	172	2.13 (2.57)	16	**0.78**
1c	0.00	16			3.67	171	4.05 (4.44)	14	
1d	0.00	17			3.68	172	1.98 (2.51)	9	**0.03**
1e	0.00	12			3.56	172	1.15[d] (1.24)	1	
							2.10[e] (2.31)	9	**1.35**
1f	0.00	0			3.13	166			
2a			0.00	51	0.76	179	2.25	53	*f*
2b			0.00	53	0.77	179	2.29	53	*f*
2c			0.00	51	0.79	179	5.04	−42	*f*
2d			0.00	52	0.77	180	1.95	51	*f*
2e			0.00	51	0.77	179	1.40[d]	50	*f*
							2.30[e]	50	*f*
2f			0.00	54	1.48	179			

[a] The MM3 final steric energy (kcal/mol) of the most stable conformation is as follows **1a**, 21.92; **1b**, 22.88; **1c**, 25.41; **1d**, 22.08; **1e**, 36.65; **1f**, 31.55; **2a**, 14.82; **2c**, 18.44; **2d**, 14.99; **2e**, 29.51; **2f**, 23.85. [b] kcal/mol. [c] ϕ is the lp−N−C−*t*−Bu torsion angle in compounds **1**, the lp−N−C-Me torsion angle in compounds **2**. [d] Methyl axial, ϕ for the equatorial CH_2R group. [e] *N*-CH_2R group axial. [f] Separate sets of signals for different kinds of conformations were not observed for compounds *2*.

The most stable conformations for neopentylpyrrolidine **1f** are calculated to be gauche, where the lone-pair N−CH_2−*t*-Bu torsion angles are 22°. There is a barrier of 0.31 kcal/mol to rotation to the eclipsed conformation, which is only 0.24 kcal/mol less stable. The different geometry around the nitrogen center in the five-membered ring reduces the compression that leads to eclipsing in neopentylpiperidines and acyclic neopentylamines, and there is a broad potential well with two gauche and one eclipsed minima.

For the *N*-ethylpiperidines **2**, the conventional conformations with a staggered equatorial *N*-ethyl group are most stable, and the staggered axial conformation is usually at least 2 kcal/mol less stable: in fact, it is relatively more improbable than the axial neopentyl group conformation in the series **1**. Nitrogen inversion in this series **2** is accompanied by about 60° of N−CH_2 bond rotation to reach a new staggered conformation, so for **2** the cube of Scheme 1 should be modified to reflect this point. Barriers to rotation about equatorial N−CH_2R bonds were calculated and are similar *within* each series **1** and **2**, since changes in substitution are remote from this bond. For the N−CH_2Me bond in equatorial confor-

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(6) Allinger, N. L.; Rahman, M.; Lii, J.-H. *J. Am. Chem. Soc.* **1990**, *112*, 8293.

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Table 2. Dynamic NMR Barriers ($\Delta G^{\ddagger}$, kcal/mol) to Conformational Processes, Ring Inversion, R.I., Nitrogen Inversion, N.I., or Bond Rotation, Rot.

compd	barrier (T (°C))	process	compd	barrier (T (°C))	process
1a	10.6 (−40)	R.I.	**2a**	11.50 (−15)	R.I.
	7.56 (−)	N.I.			
1b	10.96 (−40)	R.I.	**2b**	11.42 (−20)	R.I.
	8.25 (−80)	N.I.			
1c	11.8 (−35)	R.I.	**2c**	11.4 (−45)	R.I.
1d	9.3 (−75)	Rot.	**2d**	7.60 (−100)	N.I.
	6.5 (−120)	R.I.			
1e	9.6 (−40)	R.I.	**2e**	no equilibrium	
	8.0 (−80)	N.I.			
1f	8.1 (−90)	Rot.	**2f**	8.0 (−95)	N.I.

mations of **2a**−**f**, bond rotation takes place in steps of 120° with a small barrier of ∼2.5 kcal/mol for a methyl group rotating from +gauche past the lone pair to −gauche and of about 5 kcal/mol for rotation from gauche to anti past the N−CH_2 bond of the ring. This agrees well with experimental measurements[8,9] of such *N*-ethyl rotational barriers.

In contrast for the N−CH_2-*t*-Bu bond in compounds **1a**−**e**, barriers of about 10 kcal/mol are calculated for 180° rotation from the eclipsed conformation **I** to the anti-conformation **II**. It has been pointed out previously[2f,3b] that eclipsed bonds often have high rotational barriers. The interaction of the *tert*-butyl group with the equatorial hydrogen atoms at C2 and C6 (e.g., H_A in **I**) causes both eclipsing *and* a relatively high barrier to rotation since, in contrast to simple staggered bonds, rotation involves the increase in this repulsion over 120° of bond rotation until maximium interaction is reached near the point where the *tert*-butyl group eclipses the C−C bond of the ring. As an *experimental* point of reference, it is notable that in eclipsed *N*,*N*-diethylneopentylamine[2j,3b] the rotational barrier is 9.4−9.5 kcal/mol. For neopentylpyrrolidine **1f** with a broad potential energy minimum described above, the calculated barrier for 180° is distinctly lower at 8.5 kcal/mol.

Dynamic NMR Spectra. The ^{1}H and ^{13}C NMR spectra of the compounds studied are temperature dependent, showing splitting of signals as the temperature is lowered. A full-line shape matching of experimental and calculated spectra yields barriers $\Delta G^{\ddagger}$ for the process responsible; see Table 2. Some of the spectral changes are clearer than others and will be described in some detail below. Tables 3 and 4 in the Experimental Section describe ^{1}H and ^{13}C spectra for each compound at various significant temperatures. Results for the conformationally biased 3-methyl-substituted compounds **1e** and **2e** will be discussed after those for the other compounds.

It is useful to begin by reporting the results for *N*-neopentylpyrrolidine **1f** and *N*-ethylpyrrolidine **2f**. There are no changes in the ^{13}C NMR spectrum, and in the ^{1}H NMR spectrum only geminal protons of the five-membered ring become nonequivalent at low temperature, yielding barriers of about 8.0 kcal/mol in each case. The only plausible process in molecule **2f** is nitrogen inversion, and it is reasonable to expect that barriers of a similar size will be obtained for nitrogen inversion in other members of the series **2**.

For neopentylamines of which the compounds of series **1** are examples, there is no clear indication what barriers to pure nitrogen inversion should be, since, from a ground-state **A** this single process takes a neopentyl group from an eclipsed conformation to an anti one, which is unpopulated, so the process cannot be observed in a dynamic NMR experiment. Rotation of the neopentyl group through 180°, however, may then lead on to a stable populated conformation **B**. The overall interconversion **A** ⇆ **B** may be studied by dynamic NMR, yielding a barrier, but experience suggests that it is due to the second, rotation process. Thus, it is known that ground-state strain lowers barriers to nitrogen inversion, so the strain that leads to eclipsed conformations for neopentylamines may also lead to pure nitrogen inversion barriers significantly lower in the series **1** than that of 8.0 kcal/mol found for **2f**. We have suggested that in *N*,*N*′,*N*″-trineopentyl-1,3,5-triazane a barrier of 6.4 kcal/mol measured is to be associated with nitrogen inversion, although a hindered neopentyl group rotation process that should be detectable was not located.

The barrier of 8.1 kcal/mol measured for interconversion of two equivalent conformations of neopentylpyyrrolidine **1f** thus seems rather high to be attributed to nitrogen inversion, but in good agreement with that of 8.5 kcal/mol calculated for neopentyl group rotation. We thus assign this barrier to such a rotation, noting that calculations for the equivalent barrier in neopentylpiperidines that we will now discuss are about 1.5 kcal/mol higher.

The ^{1}H spectrum of each of **1a**−**c** shows broadening of signals from the protons on the ring below about −20 °C and eventually splitting into equal multiplets below about −40 °C (see, for instance, the spectra of **1c** in Figure 1). There are no corresponding changes in the ^{13}C spectra except for doubling of the geminal dimethyl singlet for **1c** and of the methylenedioxy singlet in **1b**. Very similar behavior is observed for the corresponding *N*-ethyl compounds **2a**−**c**. In each case, interconversion of structures such as **I** and **V** has become slow, so atoms or groups attached to ring carbon atoms are either axial or equatorial on the NMR time scale at −40 °C. Barriers are in the range 10.6−11.8 kcal/mol (see Table 2), close in size to that of 11.8 kcal/mol observed for ring inversion of *N*-methylpiperidine,[10] so it is reasonable to conclude that the slowing of ring inversion is responsible for these changes.

The piperidones **1d** and **2d** display analogous spectral changes but at considerably lower temperatures. Ring inversion is expected to have a much lower barrier than in the piperidine derivatives since the piperidone ring is flattened around the carbonyl group. A comparison of ring-inversion barriers for cyclohexanone[11] and cyclohexane[12] (4.0 and 10.3 kcal/mol, respectively) dramatically illustrates this effect. In fact, broadening appears in the proton NMR as the temperature is lowered below about −50 °C for **1d** and below about −70 °C for **2d** with eventual splitting of the signals for geminal protons as before. Once more, the intercoversion of structures such as **I** and **V** of Scheme 1 has become slow on the NMR time scale with barriers of 9.3 and 7.6 kcal/mol, respec-

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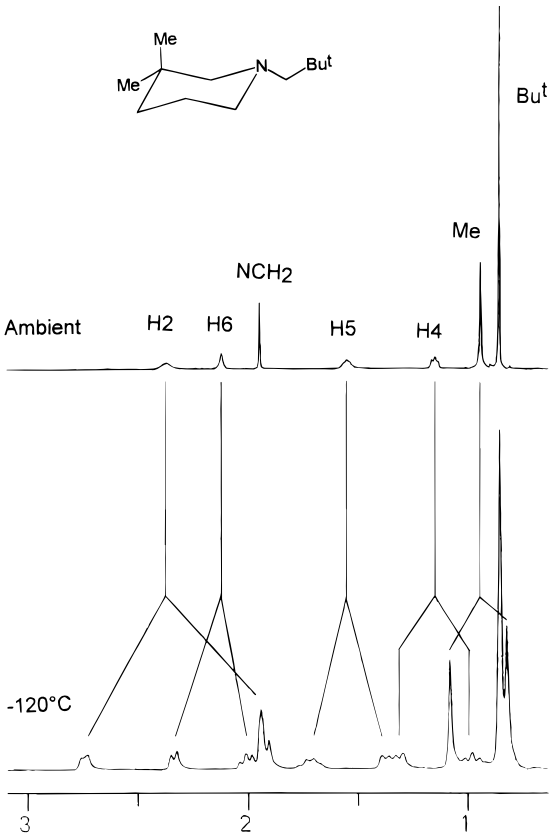


Figure 1. Proton NMR spectra of 3,3-dimethyl-*N*-neopentylpiperidine **1c** at ambient temperature (top) and at −120° when geminal groups on the ring and the geminal neopentyl protons are nonequivalent on the NMR time scale.

tively, significantly different from each other when set alongside the similar barriers of **1f** and **2f** and from the ring inversions found for **1a**−**c** and **2a**−**c**.

The barrier of 7.6 kcal/mol measured for *N*-ethylpiperidone **2d** is of the size found for what is certainly nitrogen inversion of **2f**, and the same process in *N*-methyl-4-piperidone[13] has a barrier of 8.6 kcal/mol, so the barrier measured for **2d** is assigned to nitrogen inversion. The barrier of 9.3 kcal/mol for *N*-neopentylpiperidone **1d** is significantly larger than that of **2d** and much greater than expected for either ring inversion or nitrogen inversion, as discussed above. It agrees satisfactorily with the calculated and experimental barriers mentioned above for rotation about the *N*-neopentyl bond so is assigned to this rotation.

A second dynamic NMR process is seen in the spectra of **1a**,**b**,**d**,**e**, but not of **1c** and **1f** nor for any of the compounds **2a**−**f**. This second process involves the appearance of two sets of signals as summarized in Tables 2 and 3 in the Experimental Section. Changes are much clearer in the ^{13}C spectra, which in each case broaden below about −80 °C and then sharpen, appearing at about −120 °C as a major and a minor set of signals. Figure 2 shows the spectrum for **1a** with 3% of the minor structure, which is thus 1.04 kcal/mol less stable at −120 °C. For **1b**, there is 8% of the minor structure, which is thus 0.72 kcal/mol less stable at −120 °C. Barriers to this second process determined from the

(13) Lehn, J. M.; Wagner, J. *J. Chem. Soc., Chem. Commun.* **1970**, 414.

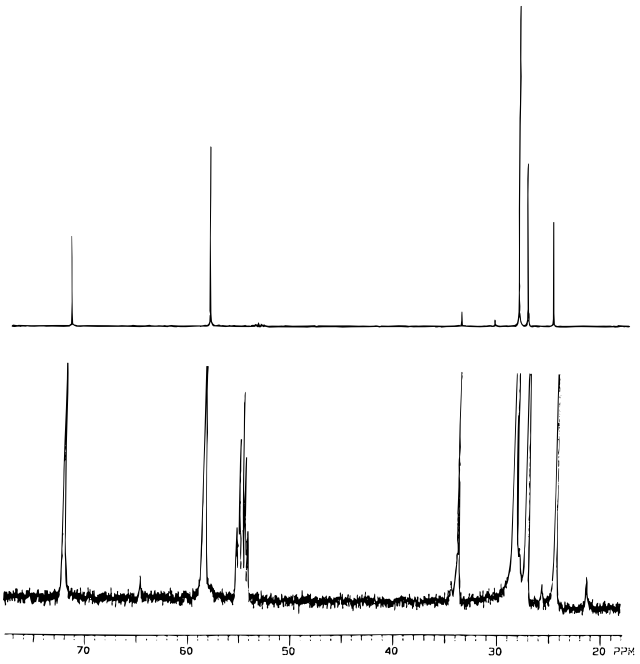


Figure 2. Carbon-13 NMR spectra of *N*-neopentylpiperidine **1a** at ambient (top), and at low temperature, when two sets of signals are seen for equatorial (97%) and axial (3%) neopentyl chair conformations. CD_2Cl_2 solvent appears at δ 54.0.

maximum signal broadening by the method of Anet and Basus[4] are 7.6 and 8.2 kcal/mol, respectively.

The MM3-calculated energies (see Table 1) suggest that the second set of signals comes from the conformation **III** (≡ **VII**) with the neopentyl group axial-eclipsed (see Scheme 1). The failure to observe a second conformational process for **1c** fits well with "neopentyl axial" as the second conformation of **1a** and **1e**, for the axial methyl group at ring position 3 in **1c** disfavors such a conformation. The agreement between the calculated axial/equatorial energy difference (about 2 kcal/mol) and that measured experimentally (about 1 kcal/mol) is only moderately good. Interconversions of **I** and **VII** and of **V** and **III** thus have also become slow on the NMR time scale in these compounds at −120 °C. This happens when either nitrogen inversion or N−CH_2 bond rotation is slow, but the assignment of barriers to one or other process, rotation or nitrogen inversion, needs careful consideration.

The barriers of 7.6−8.3 kcal/mol for **1a**,**b**,**e** determined using the approximation of Anet and Basus[4] are significantly lower than that of 9.3 kcal/mol certainly assigned to neopentyl group rotation in **1d**, yet the immediate environment of the neopentyl group is identical in all four cases. On the other hand, there is no reason nitrogen inversion should have barriers in the range 7.6−8.3 kcal/mol. The best interpretation is that these barriers represent hindered rotation but that their magnitude is somewhat uncertain. We note immediately below for compound **1d** that the population of equatorial and axial conformations is very temperature dependent. This, and the assumptions of the Anet and Basus approximation,[4] may be responsible for the 7.6−9.3 kcal/mol range for neopentyl group rotation barriers that we report.

The second set of changes in the spectrum of the piperidone **1d** occur at about 20 °C lower in temperature, where the ^{13}C NMR show two sets of spectra at −145 °C

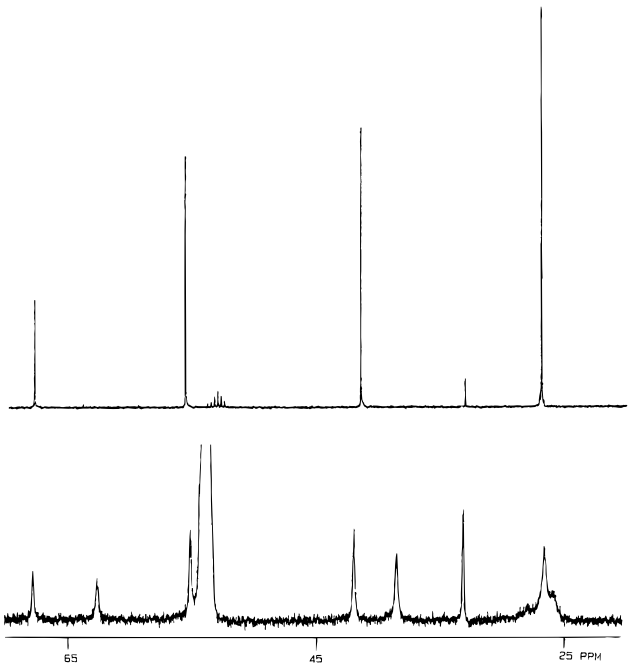


Figure 3. Upfield region of carbon-13 NMR spectra for *N*-neopentyl-4-piperidone **1d** at ambient temperature (top) and at −145°, showing two sets of signals of almost equal intensity for equatorial- and axial-neopentyl chair conformations. Similar doubling is seen for the carbonyl carbon. Slow rotation of the *tert*-butyl group affects the signal at δ 27.0. Chemical shifts suggest that one of these two conformations substantially predominates at room temperature.

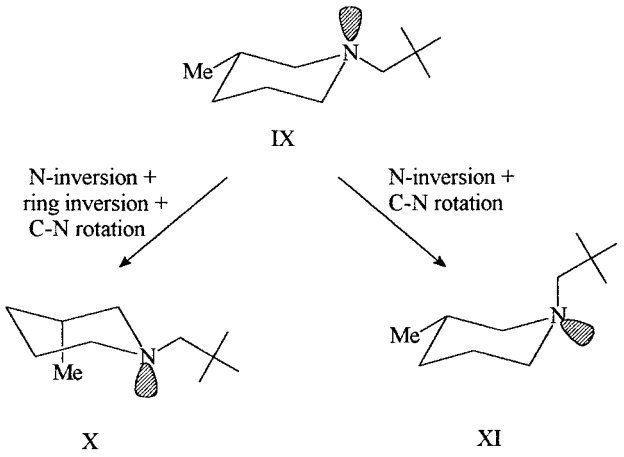
of relative intensity 53:47 (see Figure 3). This suggests two kinds of conformation for **1d** differing in energy by only 0.03 kcal/mol at that temperature and interconverting slowly, with a barrier calculated to be 6.5 kcal/mol.

This experimental energy difference of 0.03 kcal/mol for **1d** is so small that it would be unwise to rely on calculations for deciding which is the major conformation, although they admit no doubt that the two conformations in question are equatorial eclipsed and axial eclipsed. Since the signal of a carbon atom antiperiplanar to a lone pair appears upfield from that of a gauche carbon atom,[14] the relative upfield shift of the minor signal for carbons 3 and 5 of the ring fits with the minor conformation being the one with an axial eclipsed neopentyl group. Calculations suggest that this conformation is less stable than the eclipsed equatorial by 1.98 (MM3) or 2.51 (MMX) kcal/mol, much larger than experimental values, representing even poorer agreement with experiment for **1d** than was reported above for **1a** and **1b**.

Here, inspection of Scheme 1 suggests that these changes cannot be due to slowing down of nitrogen inversion because the populated conformations, eclipsed-equatorial and eclipsed-axial, can still interconvert by ring inversion. The anti-conformations **II**, **IV**, **VI**, and **VIII** are calculated to be so high in energy as to be unpopulated. This implies that the second process slowing down in **1d**, to produce two sets of signals, is ring inversion (e.g., **I**−**III**), with a barrier of 6.5 kcal/mol at −120 °C. This barrier is significantly higher than in cyclohexanone, but the *N*-methylpiperidine ring inversion

(14) Eliel, E. L.; Pietrusiewicz, K. M. *Top. ^{13}C NMR Spectrosc.* **1979**, *3*, 171.

Scheme 2



barrier[10] is itself 1.5 kcal/mol higher than that of cyclohexane.[12]

A further interesting point can be derived from the ^{13}C chemical shifts in Table 4 (see also Figure 3). Signals are referenced to internal CD_2Cl_2, and all show small upfield shifts as the temperature is lowered. The quaternary *tert*-butyl carbon signal, which does not split, illustrates this point being at δ 34.0 at room temperature and δ 33.0 at −145 °C. Correcting for this small intrinsic temperature dedpendence of shifts, the averaged signals at room temperature [^{13}C(3,5), 42.2, ^{13}C(2,6), 56.8, and $^{13}CH_2$-*t*-Bu, 69.4] correspond closely to those for the major conformational isomer signal at low temperature. The compound apppears to have a normal marked preference for the equatorial conformation at room temperature, contrasting with the observed 53:47 conformation ratio at −145 °C and thus reinforcing the oddity of the latter result.

The analogous *N*-ethyl compounds **2a**−**d** show only a single dynamic process in the NMR in which geminal groups on the ring become nonequivalent on the NMR time scale (see Table 2). Arguments as used above for the series **1** suggest that for **2a**−**c** ring inversion is the process involved, whereas for compound **2d**, discussed above, the process is nitrogen inversion. The magnitudes of the barriers fit well with these assignments. The absence of a very low temperature set of spectral changes for **2a**−**d** probably means that the ethyl-axial conformation of **2** is unpopulated since by calculation it is relatively less stable than the neopentyl-axial conformation of **1**. This agrees with the high axial/equatorial energy difference of 2.7 kcal/mol reported for *N*-methylpiperidine.[15]

For the 3-methylpiperidines **1e** and **2e**, the conformational cube is distorted. For **1e**, the equatorial,equatorial conformation **IX** is calculated to be the most stable, with the 3-methyl-axial conformation **X** and the neopentyl-axial conformation **XI** being 1.15 and 2.10 kcal/mol less stable, respectively; see Scheme 2, noting that a set of enantiomeric drawings is required for the enantiomer of **1e**. In the proton-decoupled ^{13}C NMR spectrum of **1e** as the temperature is lowered, there is a broadening of some

(15) (a) Delpuech, J.-J. In *Cyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takeuchi, Y., Eds.; VCH: New York, 1992; Chapter 6. (b) Crowley, P. J.; Robinson, M. J, T.; Ward, M. G. *J. Chem. Soc. Chem. Commun.* **1974**, 825. (c) Crowley, P. J.; Robinson, M. J. T.; Ward, M. G. *Tetrahedron* **1977**, *33*, 915. (d) Appleton, D. C.; McKenna, J.; McKenna, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 292.

signals with a maximum breadth at about −45 °C and then a sharpening. On further cooling, before a minor set of signals can be detected, there is a new broadening of a different set of signals with a maximum at about −85 °C and then sharpening of signals until, at −105 °C, two sets of signals (relative intensity 98:2) are seen for some carbon positions (see Table 4).

Two processes become slow as the temperature is lowered but only one minor set of signals of 2% relative intensity is observed. Results from other neopentyl piperidines suggest that the first process to slow is ring inversion, so the minor conformation whose signals should then emerge is **X**, the only low-energy conformation with the methyl group axial. The interconversion of **IX** and **XI** is the second process becoming slow, and as before, this is seen when either neopentyl group rotation or nitrogen inversion becomes slow. The barriers to these two processes are determined by the Anet and Basus method[4] to be about 9.6 and 8.0 kcal/mol, respectively, at the temperature of maximum broadening.

^{1}H NMR shows a less well-defined set of changes, but in spectra taken at −100 °C minor signals are seen adjacent to the major signals of some groups, and in particular, there is a minor isomer doublet for the methyl group at δ 0.83: when compared with the downfield ^{13}C sideband of the *tert*-butyl signal of the major isomer this allows a direct estimate of population of the minor isomer (about 2.0%). The fact that the minor methyl doublet signal is downfield from the major does *not* correspond to a methyl axial location and so favors **XI** as the second populated conformation. The coupling constants in these two equatorial methyl doublets are markedly different, namely 7.2 Hz in the major and 5.6 Hz in the minor conformation.

The assignment of structure **XI** to the 2% conformation agrees with the observations for other neopentylpiperidines and is further confirmed by the relative upfield shift of the minor C3 signal, suggesting that C3 is antiperiplanar to a nitrogen lone pair.[14] Although calculations suggest that structure **X**, not **XI**, is the more stable, they have been shown to underestimate the population of axial-*N*-neopentyl conformations in other compounds of the series **1**. The absence of a second minor spectrum that we would assign to structure **X** probably reflects the experimental difficulty in detecting populations less than about 1% and, possibly, a temperature-dependent population. Derivative **2e** does not display any line broadening attributable to conformational processes, thus suggesting that essentially only a single conformation is populated.

Discussion

The series of barriers measured for the compounds **1a**−**f**, and **2a**−**f** are shown together in Table 2 along with assignment to the processes involved. The pyrrolidine **2f** provides a good model for nitrogen inversion.

In the *N*-ethylpiperidines **2**, calculations agree that only equatorial *staggered* conformations deserve consideration. Only one dynamic NMR process is ever observed experimentally for each compound and is assigned on the basis of barrier size to ring inversion (**2a**−**c**) or nitrogen inversion (**2d**,**f**), so little further discussion of the assignments of these is needed.

Following the calculations and previous results,[2i,3] there is no doubt that in all the *N*-neopentylpiperidines the most stable conformation is the equatorial eclipsed one shown in the conformational cube of Scheme 1 as structures **I** and **V** and that the next most stable, except for **1c**, is the axial eclipsed one **III** and **VII**.

The results for **1a**−**c** with barriers over 10 kcal/mol undoubtedly represent ring inversion, and the changes in the NMR spectrum of the 3-methyl compound **1e** are assigned to ring inversion as well, since for reasons already explained the somewhat low barrier of 9.6 kcal/mol is only an estimate.

The only clearly identified barrier to rotation about the piperidine nitrogen−neopentyl bond is that of 9.3 kcal/mol for the *N*-neopentylpiperidone **1d**. This is justified as it is markedly higher than nitrogen inversion barriers in similar compounds and the expected ring inversion barrier. When nitrogen inversion subsequently becomes slow, there should be no effect on the spectrum since the two populated structures can interconvert by ring inversion. Thus, no barrier of about 8 kcal/mol should be or is in fact observed. The 6.5 kcal/mol barrier is then assigned to ring inversion becoming slow.

Calculations suggest, however, that the barrier to rotation is about 10 kcal/mol in all neopentylpiperidines. In the NMR of **1a** and **1b**, as the temperature is lowered, after ring inversion is slow, a second process might be expected at intermediate temperatures where interconversion of structures **I** and **III** is slow due to hindered rotation. We believe that in **1a** and **1b** (and also perhaps in **1e**), with very small amounts of the minor conformation, the overlap of the dynamic changes in the spectrum with temperature and the uncertainties of the Anet and Basus approximation make detection of the minor isomer difficult until both processes are slow. The clear demonstration of bond rotation in **1d** emerges since it appears in the NMR as geminal protons becoming nonequivalent.

It is interesting to consider the suite of changes experienced by a molecule of type **1**. Both rotation and nitrogen inversion lead to anti conformations **II** and **IV** at least 3.6 kcal/mol higher in energy than eclipsed by calculation, so further very rapid changes are expected. Molecules are likely either to return to the original conformation by reversal of the first process or to move on to give the axial eclipsed conformation by nitrogen inversion or rotation, respectively. Overall, this two-step passage through an unstable intermediate not significantly populated is a single process as far as changes in the NMR are concerned.

Chair−chair interconversion of the six-membered rings of type **1** also involves unstable intermediate twist conformations, so whatever is the first process taking place in Scheme 1, there is a significant likelihood that the reverse process take place. This means that the rate of crossing the first barrier may be significantly higher than indicated by dynamic NMR measurements, so the barriers reported in Table 2 should be reduced by up to 0.3 kcal/mol. In other words, a transmission coefficient less than 1 in value should be used in converting a rate of site exchange derived from the NMR into a potential barrier.

Combination of two of the processes into a single process, different from two processes taking place one after the other, may occur in some symmetrical staggered amines.[16] Since it is likely to *combine* the greater part

(16) Bushweller, C. H.; Anderson, W. G. *Tetrahedron Lett.* **1972**, 129 and references therein.

Table 3. ^{1}H Chemical Shifts (400 MHz) of Compounds 1A−1f and 2A−2f at Various Temperatures (ppm from Me_4Si in $CCl_2D_2/CHF_2Cl/CHClF_2$)

		observed signals					
compd	*T* (°C)	NCH_2-*t*-Bu	C(CH_3)$_3$	C$H_{2(2,6)}$	C$H_{2(3,5)}$	C$H_{2(4)}$	
1a	+25	1.89	0.76	2.34	1.42	1.28	
	−130	1.88	0.74	2.67	1.41	1.55	
				2.01			0.98
1b	+25	2.08	0.89	2.61	1.68		3.82 [OCH_2]
	−120	2.06	0.87	2.69	1.68		3.80
				2.39	1.51		
1c	+25	1.85	0.75	2.14	1.45	1.04	0.84 [C(CH_3)$_2$]
				2.27			
	−120	1.83	0.72	1.92	1.27	1.19	0.72
				2.25	1.65	0.89	0.99
				2.47			
				2.65			
1d	+25	2.11	0.82	2.28	2.75		
	−120	2.09	0.80	2.40	2.91		
				2.22	2.61		
1e	−30	1.98	0.89	2.73	(1.50−1.83)		0.82 [$^-$HCCH_3]
	−120	1.97	0.80	2.72	(1.41−1.75)		0.75 (98%)
							1.06 (2%)
1f	+25	2.30	0.89	2.64	1.78		
	−120	2.25	0.89	3.01	1.72		
				2.98			

		observed signals					
compd	*T* (°C)	NCH_2CH$_3$	CH_3	C$H_{2(2,6)}$	C$H_{2(3,5)}$	C$H_{2(4)}$	
2a	+25	2.22	0.93	2.24	1.46	1.33	
	−120	2.21	0.91	2.84	1.40	1.06	
				1.54	1.38	1.63	
2b	+25	2.45	1.10	2.52	1.75		3.94 [OCH_2]
	−120	2.30	1.09	2.81	1.75		3.85
				1.94	1.60		
2c	+25	2.20	0.93	2.21	1.49	1.13	0.84[C(CH_3)$_2$]
				1.91			
	−120	2.22	0.91	2.75	1.47	1.39	0.82
				2.41		0.91	0.71
				1.55			
				1.24			
2d	+25	2.42	1.03	2.32	2.62		
	−120	2.45	1.08	2.40	3.06		
				2.02	2.16		
2e	−60	2.29	1.10	2.86	(1.5−1.7)		0.78 [HCCH_3]
2f	+25	2.48	0.98	2.40	1.65		
	−120	2.28	0.98	2.88	1.60		
				1.68			

of the activation energy for each process, such a combination is improbable in the present molecules. This does not preclude one process, say nitrogen inversion flattening, taking place to some small extent so as to reduce somewhat the activation energy of another, say bond rotation. This could be represented by joining vertexes of the cube of Scheme 1 by lines curved inward rather than straight. A combined process is more plausible when the intermediate minimum is of high relative energy, existing as a shallow depression on the potential surface.

Experimental Section

Tables 3 and 4 show details of NMR spectra at a range of temperatures. Molecular mechanics calculations using Allinger's MM3 program[5,6] yield torsion angles between the *tert*-butyl (or methyl) group and the N−C2 and N−C6 bonds. The torsion angle with the lone pair is derived from these by assuming that the lone pair is located on the external bisector of the C2−N−C6 angle in the projection.

General Synthetic Method. All *N*-neopentyl- and *N*-ethyl compounds, with the exception of the piperidones **1d** and **2d**, were prepared from the corresponding piperidine or pyrrolidine by acylation followed by lithium aluminum hydride reduction as described in detail below. Piperidones were prepared from the correponding ethylenedioxy ketal **1b** or **2b** by acid-catalyzed hydrolysis. Pyrrolidine and piperidine and its 3-methyl, its 3,3-dimethyl, and its 4-ethylenedioxy derivatives were commercially available (Aldrich).

Preparation of Acylated Amines. Pyrrolidine, or the appropriately substituted piperidine (95 mmol), and pyridine (7.7 mL, 95 mmol) were dissolved in chloroform (75 mL), and the solution was cooled to 0 °C, acyl chloride (95 mmol) was added dropwise. After 18 h of reflux, a white precipitate had formed. The reaction mixture was allowed to cool to room temperature, and 50 mL of water was added. The reaction mixture was extracted with ether (3 × 50 mL), and the ether extracts were dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the product, typically produced in about 85% yield, was used directly for the reduction step.

Reduction of Acylated Heterocycles. The product from the acylation reaction was added under nitrogen to a suspension of lithium aluminum hydride (4.7 g, 122 mmol) in diethyl ether (150 mL) cooled to 0 °C. After 18 h of stirring, 20 mL water was added dropwise until effervescence subsided. The organic layer was extracted with ether (3 × 50 mL), and the ether extracts were dried and concentrated as before to yield the crude products **1** or **2**, which were purified by distillation under reduced pressure.

Table 4. ^{13}C Chemical Shifts (100.6 MHz) of Compounds 1a−f and 2a−f at Various Temperatures (ppm from Me_4Si in $CCl_2D_2/CHF_2Cl/CHClF_2$)

		observed signals						
compd	*T* (°C)	NCH_2-*t*-Bu	$C(CH_3)_3$	$C(CH_3)_3$	$C_{(2,6)}$	$C_{(3,5)}$	$C_{(4)}$	
1a	+25	72.0	34.1	28.2	58.2	27.4	25.0	
97%	−120	70.5	32.1	27.0	57.0	25.5	22.8	
3%	−120	63.0	33.0	*a*	53.4	19.9	24.1	
1b	+20	69.5	32.4	27.1	53.9	35.1	107	64.0 [OCH_2]
92%	−120	72.0	33.2	26.8	56.0	35.5	106.5	66.8, 66.6
8%	−120	65.2	33.4	*c*	53.0	29.6	*c*	*c*
1c	+25	71.5	34.5	28.7	58.6	24.5	38.4	28.0[$C(CH_3)_2$]
					70.3	32.9		
	−80	71.0	34.2	28.1	58.6	24.2	38.2	32.4
					70.1	32.4		
1d	+25	69.4	34.0	28.0	56.8	42.2	212.0	25.0
53%	−145	67.8	33.0[b]	27.5	55.2	42.0	213.8	
47%	−145	62.5	33.0[b]	27.0	53.1	38.5	213.3	
1e	−10	70.8	33.3	26.3	65.5	26.3	33.0	193 [$HCCH_3$]
					57.1	32.0		
98%	−100	70.8	33.2	26.4	65.4	26.4	32.5	19.7
					56.9	31.9		
2%	−100			19.1		29.1		
1f	+25	69.0	32.0	28.2	56.7	23.0		
	−120	69.2	32.1	8.53	56.8	23.0		

		observed signals						
compd	*T* (°C)	NCH_2CH_3	CH_3	$C_{(2,6)}$	$C_{(3,5)}$	$C_{(4)}$		
2a	+25	53.8	12.5	55.0	27.0	25.5		
	−130	52.8	12.0	53.7	25.2	24.0		
2b	+25	52.8	12.9	52.0	35.9	108.2	64.5	
	−120	51.9	12.4	50.9	34.4	107.2	64.4	64.2
2c	+25	53.8	12.8	66.9 55.5	38.7	31.8	23.5	[$C(CH_3)_2$]
					28.2			
	−120	52.7	12.0	64.5	36.8	30.5	22.1	
				55.0	30.1			
2d	+25	52.0	13.0	53.4	41.9	210.5		
	−120	51.8	13.0	53.8	41.5	212.0		
2e	−30	53.8	12.4		62.9	32.3	34.0	20.2 [$HCCH_3$]
					54.6	26.5		
2f	+25	50.1	13.2	53.5	23.0			
	−120	50.0	14.0	54.0	23.0			

[a] Signala for the *tert*-butyl methyl group of the minor isomer could not be distinguished and are presumably overlapped by the major isomer signal. [b] The ^{13}C NMR at −140 °C. This signal is unusually broad at the lowest temperature observed in a manner quite in keeping with rotation about the *t*-Bu−CH_2N bond becoming slow on the NMR time scale. [c] Signals for *t*-BuMe group, C_4 and $^1C_{(3,4)}$ for the minor isomer could not be distinguished and are presumably overlapped by the major isomer signal.

Hydrolysis of Piperidone Ketals. The corresponding ketal (5 g) was added to a mixture of 5% HCl solution (60 mL) and acetone (10 mL) and refluxed for 12 h. After cooling, 1 M sodium hydroxide solution was added until the reaction mixture was basic. Extraction with diethyl ether and workup as above led to a crude product that was purified by column chromatography on silica using 20:1 pentane/ethyl acetate as eluant.

***N*-Neopentylpiperidine (1a):** bp 70−72 °C/0.6 mmHg. Anal. Calcd for $C_{10}H_{21}N$: C, 77.41; H, 13.55; N, 9.03. Found: C, 77.04; H, 13.94; N, 8.93.

4-(Ethylenedioxy)-*N*-neopentylpiperidine (1b): mp 45 °C. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.61; H, 10.84; N, 6.61. Found: C, 67.56; H, 11.03; N, 6.56.

3,3-Dimethyl-*N*-neopentylpiperidine (1c): bp 88−90 °C/0.45 mmHg. Anal. Calcd for $C_{12}H_{25}N$: C, 78.68; H, 13.70; N, 7.61. Found: C, 78.23; H. 14.17; N, 7.50.

***N*-Neopentyl-4-piperidone (1d):** bp 97−99 °C/24 mmHg. Anal. Calcd for $C_{10}H_{19}NO$: C, 71.01; H, 11.24; N, 8.28. Found: C, 70.59; H, 11.52; N, 8.10.

3-Methyl-*N*-neopentylpiperidine (1e): bp 80−82 °C/26 mmHg. Anal. Calcd for $C_{11}H_{22}N$: C, 78.50; H, 13.18; N, 8.82. Found: C, 78.47; H, 13.25; N, 8.40.

***N*-Neopentylpyrrolidine (1f):** bp 108−110 °C. Anal. Calcd for $C_9H_{19}N$: C, 76.60; H, 13.48; N, 9.92. Found: C, 76.55; H, 13.27; N, 9.68.

N-Ethylpiperidine (**2a**) and *N*-ethylpiperidone (**2d**) are known compounds.[17,18]

4-(Ethylenedioxy)-*N*-ethylpiperidine (2b): bp 90−92 °C/0.3 mmHg. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.18; H, 9.88; N, 8.19. Found: C, 62.52; H, 10.24; N, 8.21.

3,3-Dimethyl-*N*-ethylpiperidine (2c): bp 80−82 °C. Anal. Calcd for $C_9H_{19}N$: C, 76.61; H, 13.52; N, 9.87. Found: C, 76.25; H, 13.89; N, 9.82.

3-Methyl-*N*-ethylpiperidine (2e): bp 139−140 °C/760 mmHg. Anal. Calcd for $C_8H_{16}N$: C, 76.13; H, 12.78; N, 11.10. Found: C, 76.28; H, 12.70; N, 11.20.

***N*-Ethylpyrrolidine (2f):** bp 100−102 °C. Anal. Calcd for $C_6H_{13}N$: C, 73.40; H, 12.78; N, 13.82. Found: C, 72.72; H, 13.13; N, 14.14.

Acknowledgment. We are grateful to a reviewer for helpful comments.

JO9720344

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