Preference for Eclipsed Conformations in Acyclic Neopentyldialkylamines and the Stereodynamical Consequences: An NMR and Molecular Mechanics Investigation[1]

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Abstract: A dynamic NMR study of a number of acyclic *N,N*-dialkylneopentylamines, supported by molecular mechanics calculations, is reported. With simple alkyl groups, eclipsed conformations are encountered for the NCH_2-Bu^t bond, which has a high 1-fold rotational barrier. The N-inversion/rotation process for $Me_2NCH_2Bu^t$ was rendered detectable by desymmetrizing the molecule as $Me_2NCHDBu^t$. Here the decoalescence of separate ^{13}C signals for the diastereotopic NMe groups allowed the measurement of the corresponding free energy of activation ($\Delta G^{\ddagger} = 9.4$ kcal mol^{-1}). With significantly more branched alkyl groups, the $N-CH_2Bu^t$ bond adopts a conformation intermediate between staggered and eclipsed. Trineopentylamine and an analogue undergo a novel concerted back and forward 60° rotation through eclipsed conformations about the $N-CH_2Bu^t$ bonds, with a barrier which dynamic NMR indicates must be at least 8.3 kcal mol^{-1}.

Introduction

There has been much recent interest in molecules having a saturated bond which prefers to adopt an eclipsed conformation.[2−4] Particularly notable are simply substituted compounds such as *N*-neopentylpiperidine[4a] and *tert*-butoxycyclohexane,[3h] where the exocyclic $N-CH_2$ and C−O bonds, respectively, are eclipsed. This paper reports an investigation of the conformations of a number of *acyclic* neopentyldialkylamines $R^1R^2NCH_2Bu^t$ (**1**−**10**) and shows that, while eclipsing results from the interaction of substituents, the likelihood of eclipsed conformations does not necessarily increases with the increasing bulk of the substituents. It was early recognized that eclipsed bonds are generally to be associated with relatively high rotational barriers,[3e,4b] for these two features are a consequence of the same steric factors. However, if other conformations of the bond are not populated, the barrier is 1-fold and so cannot be measured by the usual dynamic NMR method. Neopentylamines $R^1R^2NCH_2Bu^t$ ($R^1 \neq R^2$) with an eclipsed $NCH_aH_bBu^t$ bond are not subject to this limitation since they exist in two equivalent arrangements (see structures I and IV in Scheme 1) in which protons H_a and H_b have different environments.

$R^1R^2NCH_2Bu^t$

1 R^1, R^2 = Me; **2** R^1 = Me, R^2 = Et; **3** R^1, R^2 = Et; **4** R^1, R^2 = Pr^i; **5** R^1 = Et, $R^2 = Bu^t$; **6** $R^1 = CH_2Ph$, $R^2 = Bu^t$; **7** R^1 = Me, $R^2 = CH_2Bu^t$; **8** $R^1 = CH_2Ph$, $R^2 = CH_2Bu^t$; **9** $R^1, R^2 = CH_2Bu^t$; **10** $R^1 = CH_2Bu^t$, R^2 = CH_2-(1-adamantyl)

Interconversion of these structures inevitably involves rotation about C−N bonds, since pure nitrogen inversion converts an eclipsed conformation (e.g., I) to an anti one (II), which requires 180° of rotation to bring about conversion to the equivalent stable confomation (IV). A high experimental barrier to the I−IV interconversion may indicate that the energy maximum occurs during rotation rather than nitrogen inversion, so the measured barrier corresponds, in practice, to this rotation.

In keeping with this high-barrier postulate, Forsyth and Johnson have reported[4b] that the nitrogen inversion/rotation process in *N,N*-diethylneopentylamine (**3**) has a barrier of 9.5 kcal mol^{-1}, significantly higher than in similar amines, for example *N,N*-diethylmethylamine[5a,b] (7.9 kcal mol^{-1}), indicating that the interconversion process is rotation-dominated. They also remarked that calculations for **3** suggest[4b] that different conformations about the *N*-ethyl bonds are of similar energy, a point which we will demonstrate here by direct experimental

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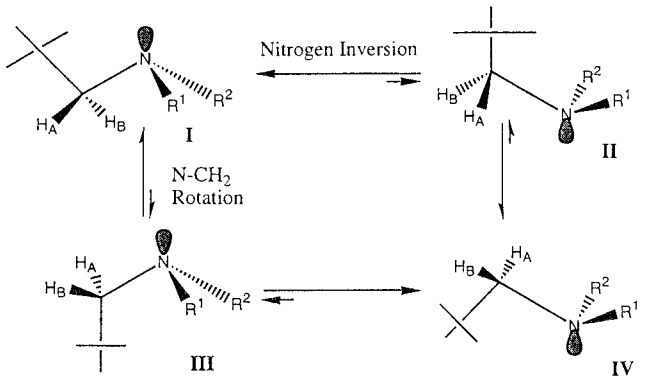
Scheme 1



measurements. An appropriate example of how much higher can become the barrier of a rotation-dominated process is that reported by Nelsen and Cunkle,[5c] who determined a $\Delta G^{\ddagger} = 12.0$ kcal mol^{-1} in a *N*-neopentyl-substituted azabicyclo derivative. Three additional studies of crowded acyclic neopentylamines are also worth noting.[6] In compounds **4**−**6,** it is calculated that the most stable conformation for the molecule has the nitrogen lone pair to neopentyl group bond about 20° from eclipsed, with nitrogen inversion/rotation barriers of 8.8, 8.2, and 9.2 kcal mol^{-1}, respectively,[6a−c] which are relatively large for such highly substituted amines. In the case of **6**, the conformation is confirmed by a crystal structure determination.[6c] For each of these molecules, other conformations of quite low relative energy, having the neopentyl group more or less perfectly eclipsed, are calculated to exist. In the case of **5**, a signal is seen in the NMR at −141 °C for this conformation, which is calculated to be over 20% populated at room temperature.[6b]

Dynamic NMR spectroscopy is suitable for studying unsymmetrical amines $R^1R^2NCH_aH_bBu^t$ ($R^1 \neq R^2$) since, when interconversion of forms I and IV of Scheme 1 is slow on the NMR time scale, protons H_A and H_B are diastereotopic and there may be also changes in the spectrum of groups R^1 and R^2, if they are suitable. When R^1 and R^2 are identical, there are no changes in the signals of the neopentyl group, but the interconversion may be studied from changes in the spectrum of the substituent R^1 if it comprises a prochiral group.

The evidence for eclipsing of the NCH_2-R bond is usually indirect. Molecular mechanics calculations (programs MMX[7] and MM3[8] have been used) suggest whether the bond is eclipsed, and in at least one case,[3i] this conclusion was confirmed by direct X-ray crystallographic evidence. Forsyth has suggested[4b] that, in $R_2NCH_2Bu^t$ derivatives, which have been desymmetrized by deuterium substitution (i.e., $R_2NCHDBu^t$), the temperature-dependent separation of the ^{13}C NMR signals for groups R_2 (which are enantiotopic in the absence of labeling) "is diagnostic of isotopic perturbation of a degenarate equilibrium". On this basis he concluded[4a,b] that in compounds such as 4-*tert*-butyl-*N*-benzyl-d_1-piperidine or $Me_2NCHD(CH_2)_3Me$ a substantial amount of gauche N−CHD bond conformation had to be present. On the contrary, the 4-*tert*-butyl-*N*-neopentyl-d_1-piperidine is likely to adopt essentially a single (eclipsed) conformation[4a] since the ^{13}C shift separation of its carbons C2 and C6 appeared to be independent of temperature.

We here discuss dialkylneopentylamines **1**−**10**, compounds **7**−**10** having two or more neopentyl groups. The results for **4**−**6** have been taken from the literature.[6]

Table 1. Calculated Conformations (Torsion Angles) for Dialkylneopentylamines $R^1R^2NCH_2Bu^t$ (**1**−**10**) as Obtained by MM3 Calculations[a]

compd	R^1	R^2	neopentyl group lp-N−CH_2−Bu^t	group R^1 lp-N−C−X	group R^2 lp-N−C−X	relative energy
1	Me	Me	13	56	62	0.00
			44	54	58	0.68
2	Et	Me	13	48	64	0.00
			17	−47	64	0.01
			8	178	64	0.65
			43	52	65	1.18
3	Et	Et	19	42	64	0.00
			8	179	53	0.36
			44	176	−42	1.65
4	Pr^i	Pr^i	22	73	80	
5	Et	Bu^t	26	22	176	0.00
			9	175	175	0.67
6	CH_2Ph	Bu^t	24	33	176	
7	CH_2Bu^t	Me	23	37	61	0.00
			6	49	74	0.02
			2	169	66	1.68
8	CH_2Bu^t	CH_2Ph	27	32	47	0.00
			24	35	167	2.79
9	CH_2Bu^t	CH_2Bu^t	31	32	32	
10	CH_2Bu^t	CH_2Ad	31	32	31	

[a] The relative energies are given in kcal mol^{-1}.

Results and Discussion

Calculations of Conformations and Their Energies. Table 1 shows selected information on the MM3-calculated minimum energy conformations of compounds **1**−**10**. For each of these compounds, all conformational minima having more than 2.5 kcal mol^{-1} excess relative energy have been excluded. For convenience the torsion angle between the lone pair and the group X (when R is of the form CH_2X) is shown unless otherwise stated. Except for **7**, conformations with the *tert*-butyl of a neopentyl group anti to the lone pair are always at least 4 kcal mol^{-1} higher in energy so will not be further discussed. It is important however that this justifies our talking of nitrogen inversion/rotation as a single process. In other systems,[3j] nitrogen inversion and bond rotation in neopentyl compounds can be distinguished clearly and given separate barriers.

NMR Observations. (a) *N,N*-Dimethylneopentylamine (1). MM3 calculations (Table 1) indicate that along the NCH_2 bond there is a significant predominance of the eclipsed conformation over the gauche-staggered one. MMX suggests a less marked preference, eclipsed being more stable by only 0.2 kcal mol^{-1} compared with 0.68 kcal mol^{-1} (MM3). Experimental support for an eclipsed form might come from a barrier for the N-inversion/rotation process close to or higher than 9 kcal mol^{-1}. This suggests that the interconversion is rotation dominated, a feature associated with an eclipsed ground state conformation (Scheme 1). Because of its symmetry, compound **1** is unsuitable for dynamic NMR study, so we used Forsyth's stratagem of isotopic desymmetrization[4] of **1** as $Me_2NCHDBu^t$ (**1**-d_1). Here the *N*-methyl groups become diastereotopic when the N-inversion/rotation is slow on the NMR time scale. Furthermore, as explained in the Introduction, their observed chemical shift separation, by being dependent on (or independent of) the temperature, shows whether a significant amount of the two gauche conformers (i.e., **1B**,**C** of Scheme 2) is present (or not) in the equilibrium.

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(7) MMX forcefield as in PC MODEL, Serena Software, Bloomington, IN. See also: Gajewski, J. J.; Gilbert, K. K.; McKelvey, J. *Advances in Molecular Modelling*; JAI Press: Greenwich, CT, 1992; Vol. 2.

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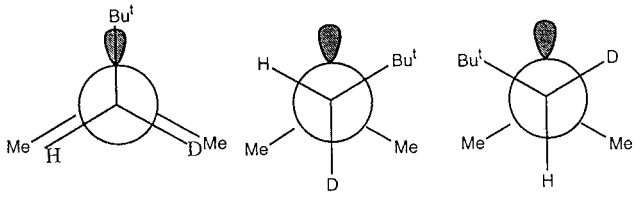
Scheme 2



In a $CCl_2F_2/CHF_2Cl/CD_2Cl_2$ solution, the NMe signal of **1**-d_1, which appears as a single line (^{13}C, 75.5 MHz) at ambient temperature, broadens below −80 °C, decoalesces at about −104 °C and splits (at −110 °C) into a doublet, with a chemical shift separation (0.029 ± 0.001 ppm) which remains *constant* down to −130 °C. Nitrogen inversion/rotation is now slow on the NMR time scale, and the methyl groups are diastereotopic due to the chirality, created by the deuterium labeling, of the *tert*-butyl bonded carbon atom (intrinsic isotope effect).[4] A complete line-shape fit of the signal leads to a free energy of activation ($\Delta G^{\ddagger}$) of 9.4 ± 0.2 kcal mol^{-1}, corresponding to the interconversion of I and IV in Scheme 1.

It seems therefore appropriate to conclude that the quite high (9.4 kcal mol^{-1}) interconversion barrier, as well as the temperature-independent shift separation of the two NMe lines is indicative of a single, eclipsed conformer (**1A** in Scheme 2). This agrees with MM3 calculations mentioned above which correspond to a population of almost 90% eclipsed (at −110 °C). Furthermore, the observed chemical shift difference of 0.029 ppm agrees exactly with that found in the corresponding deuterated *N*-neopentylpiperidine derivative which is eclipsed at the N−CHD bond. This suggests that there is no conformational equilibrium contributing to the difference in chemical shifts but, in both cases, merely an intrinsic isotope-induced asymmetry.

It should also be reported that the ^{13}C *tert*-butyl methyl signal in both **1**-d_1 and in the unlabeled **1** broadens below −140 °C and eventually splits (−155 °C at 75.5 MHz) into a 1:2 doublet (Figure 1), whereas the other signals of the spectrum are not affected. Such a feature is clearly the consequence of a restricted H_2C-CMe_3 bond rotation, which yields a staggered rotamer where two equivalent methyl groups of the *tert*-butyl moiety are gauche to the dimethylamino group and the third one is anti. The corresponding interconversion barrier ($\Delta G^{\ddagger}$ = 5.9 ± 0.15 kcal mol^{-1}) fits the expectation for this type of rotational process.

Quite surprisingly, in an acetone-d_6/CCl_2F_2 solution of **1**-d_1, the separation of the two ^{13}C NMe signals (detected below −100 °C at 100.6 MHz) *increases* remarkably on further lowering the temperature (i.e., 0.045, 0.062, 0.078, and 0.090 ppm at −105, −110, −115, and −120 °C, respectively), whereas the interconversion barrier was unaffected by the change of the solvent. As mentioned above, such a change in relative shifts indicates a temperature-dependenent equilibrium, the most obvious possibility being one involving eclipsed and gauche conformations. This implies that in the highly polar acetone solution there is now a significant population of the asymmetric (thus probably more polar) gauche conformer in contrast to the situation encountered in a solvent of lower polarity such a $CCl_2F_2/CHF_2Cl/CD_2Cl_2$. Indeed MM3 (and even more so MMX) calculations yield an energy difference between the two conformers which is relatively small (Table 1), so it is not implausible that there be a noticeable change of their relative proportions in solvents of quite different polarity. Any significant equilibrium, however, might be responsible for the temperature dependence of chemical shifts.[9]

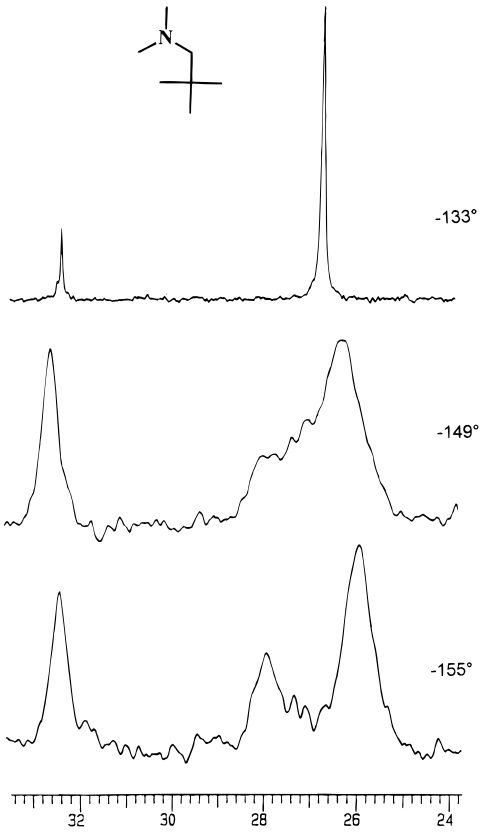


Figure 1. ^{13}C NMR spectrum (75.5 MHz) of the *tert*-butyl group of $Me_2NCH_2Bu^t$ (**1**) as function of temperature, showing the splitting of the methyl signals due to the restricted CH_2-CMe_3 rotation.

Table 2. Low-Temperature ^{1}H NMR (300 MHz) Selected Parameters for $Bu^tCH_2NR^1R^2$ (**2, 3,** and **7**−**10**) and Free Energies of Activation ($\Delta G^{\ddagger}$ in kcal mol^{-1}) for the Observed Dynamic Processes

compd	R^1	R^2	$\Delta G^{\ddagger}$	group	δ (ppm)	J (Hz)	T (°C)
2[a]	Et	Me	8.75	N*CH*$_2$Me	2.41		−60
					2.27; 2.37	−11.5	−130
			8.95	N*CH*$_2$Bu^t	2.06		−60
					1.83; 2.18	−14.0	−130
3[b]	Et	Et	9.7	N*CH*$_2$Me	2.45		−60
					2.35; 2.45	−12.8	−110
7[a]	CH_2Bu^t	Me	8.45	N*CH*$_2$Bu^t	2.28		−80
					2.08; 2.22	−12.8	−125
8[c]	CH_2Ph	CH_2Bu^t	8.40	N*CH*$_2$Bu^t	2.30		−75
					2.13; 2.50	−13.5	−120
9[d]	CH_2Bu^t	CH_2Bu^t	8.4	N*CH*$_2$Bu^t	2.20		−70
					2.09; 2.30	−13.5	−125
10[a,e]	CH_2Bu^t	CH_2Ad	8.3	N*CH*$_2$Bu^t	2.15		−40
					1.97; 2.16	−13.0	−125
					1.99; 2.15	−13.0	−125
			8.3	N*CH*$_2$Ad	2.07		−40
					1.91; 2.06	−13.6	−125

[a] In CHF_2Cl/C_6D_6. [b] In CF_2Cl_2/acetone-d_6. [c] In CHF_2Cl/CD_2Cl_2. [d] In CHF_2Cl/CD_3OD. [e] At 600 MHz.

(b) *N,N*-Diethylneopentylamine (3). This compound is considered before *N*-ethyl-*N*-methylneopentylamine (**2**) since knowledge of the conformations of the former helps an understanding of the latter. Both the ^{1}H and ^{13}C NMR spectra of **3** are temperature dependent, and some of the changes of ^{1}H spectra have been reported previously by Forsyth.[4c] Thus, the protons of the ethyl groups become diastereotopic at low temperatures (see Table 2), showing that the nitrogen inversion/

Table 3. Low-Temperature ^{13}C NMR (75.5 MHz) Selected Shifts (ppm) for $Bu^tCH_2NR^1R^2$ (**2, 3,** and **10**) and Free Energies of Activation ($\Delta G^{\ddagger}$ in kcal mol^{-1}) for the Observed Dynamic Processes

compd	R^1	R^2	$\Delta G^{\ddagger}$	*T*, °C	NCH_2*Me*	N*C*H_2Me	C(Bu^t)	N*C*H_2Bu^t
2[a]	Et	Me	6.6	-80	13.3			
				−145	14.1; 20.4			
3[b]	Et	Et	6.0	−130	11.5	49.8		64.5
				−151	4.5; 13.2	48.3; 51.4		61.2; 65.1
10[c]	CH_2Bu^t	CH_2Ad	8.6	−80			32.3	71.9
				−120			33.3; 33.5	71.2; 71.9

[a] In CF_2Cl_2/CD_3OD. [b] In CHF_2Cl/C_6D_6. [c] In CHF_2Cl/CD_2Cl_2.

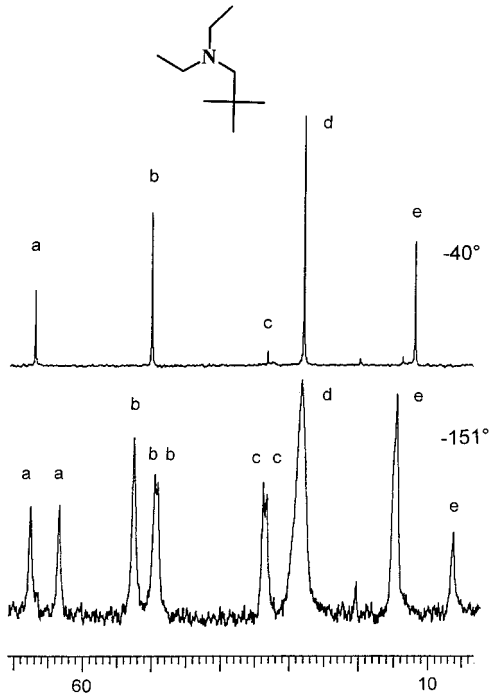


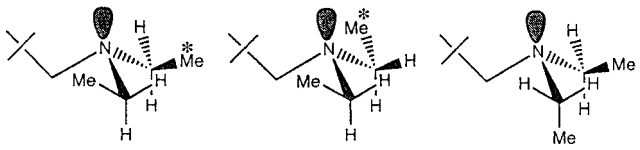
Figure 2. ^{13}C NMR spectrum (100.6 MHz) of $Et_2NCH_2Bu^t$ (**3**) at −40 °C (above) showing a single line, respectively, for the NCH_2 carbon of the neopentyl group (line a), for the two NCH_2 carbons of the ethyl group (line b), for the quaternary carbon (line c), for the three *tert*-butyl methyl carbons (line d), and for the two methyl carbons of the ethyl group (line 2). Underneath is displayed the spectrum at −151 °C, showing the splitting of the lines a, b, c, and e due to restricted N−Et rotation.

rotation process, interconverting structures I and IV in Scheme 1, has become slow on the NMR time scale. We measured for the corresponding barrier a value of 9.7 kcal mol^{-1}, which is essentially equal (within the ± 0.2 kcal mol^{-1} error) to that of 9.5 kcal mol^{-1} previously reported[4c] for the same molecule and to that we measured for the labeled derivatives **1**-d_1.

These changes have no equivalent in the ^{13}C NMR since no two carbon atoms have become diastereotopic; however, at lower temperatures, further changes, not previously observed, take place in the ^{13}C NMR (see Table 3 and Figure 2). The signals of the methylene and quaternary carbon of the neopentyl group split to a doublet of apparently 1:1 relative intensity, while the signal of the *tert*-butyl methyls shows only broadening. The ethyl group signals split to give a 3:1 doublet for the methyl groups and three peaks, with an apparent 2:1:1 relative intensity, for the methylene groups. Corresponding changes were observed in the ^1H NMR but are very complex.

(9) As an alternative explanation, it could be assumed that acetone exerts a temperature-dependent solvent effect upon one of the two diastereotopic NMe signals of the eclipsed form which differs from that exerted on the other signal. Such "ad hoc" hypothesis might explain the experimental observation without having to contemplate a change in the proportion of the eclipsed and gauche conformers. Such an explanation, however, would contradict the considerations reported in ref 4 and, anyway, seems quite unlikely to us.

Scheme 3



The doubling of the signals for the lone neopentyl group (lines a and c of Figure 2) indicates that two different sets of conformations, fortuitously of about equal population, are present. The very low temperature range at which these conformers become detectable strongly suggests that they result from restricted rotation of the N ethyl groups. Indeed both MM3 and MMX calculations (see Table 1, first two entries for **3**) suggest that two such forms, differing by the arrangement at the two ethyl moieties, have quite similar energies (the computed difference being respectively 0.36 and 0.1 kcal mol^{-1}). The same calculations suggest that the neopentyl group eclipses the N lone pair in both cases.

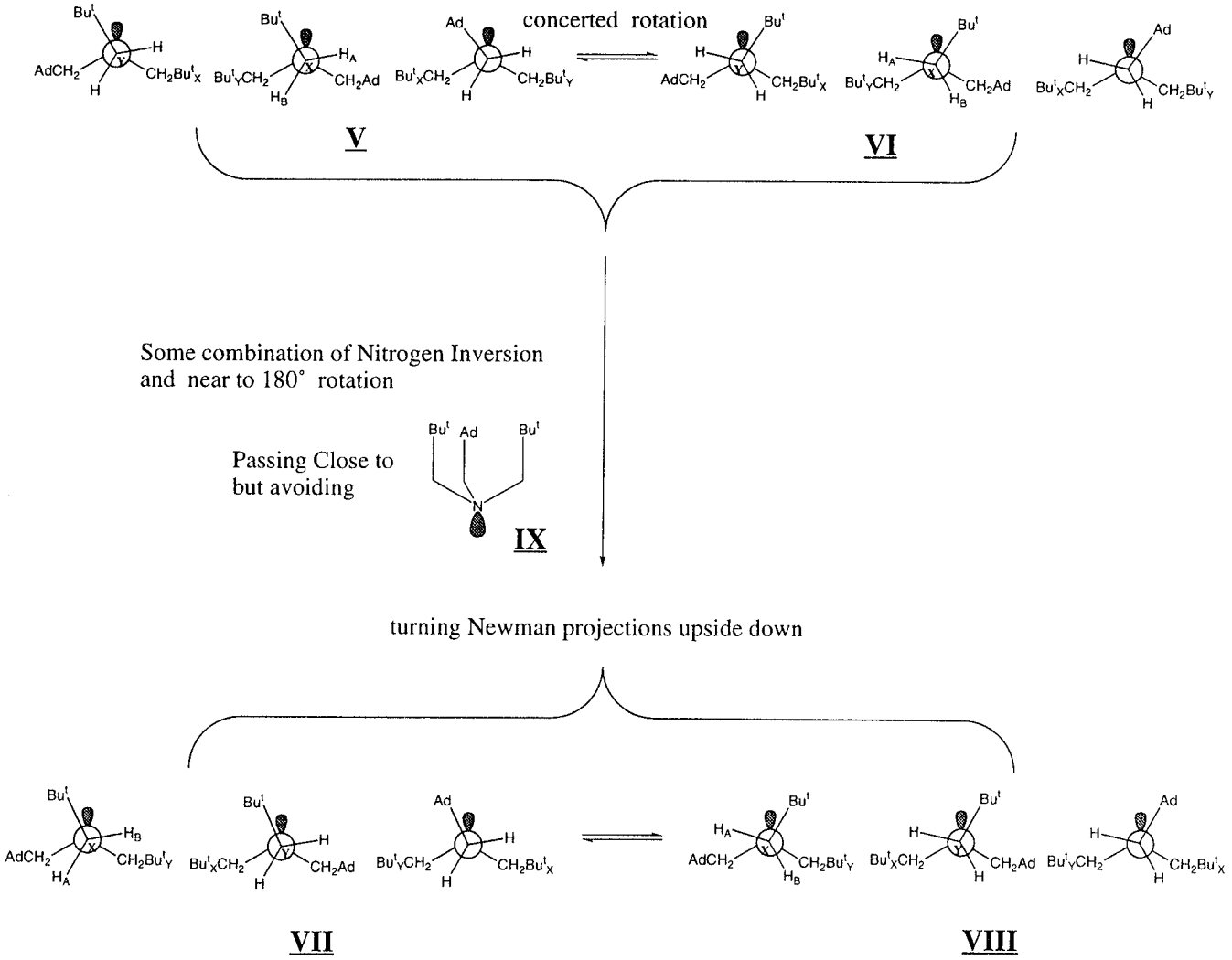
The three signals (lines b of Figure 2) observed for the NCH_2 ethyl carbons at −151 °C, and the 3:1 intensity ratio observed for the two signals of the methyl ethyl carbons (lines e of Figure 2), indicate that in one of the two exchanging sets the two ethyl groups are different, whereas in the other they are equivalent. Since neither of the two most stable computed structures of **3** has a symmetry which would account for two equivalent ethyl groups, the observed equivalence must be the result of a fast (in the NMR time scale) dynamic exchange. The stereodynamics of such a process can be understood on the basis of Scheme 3.

Structure **3A** corresponds to the first entry for **3** in Table 1, calculated to be most stable, and has both the methyl groups of the ethyl moiety in a gauche relationship to the nitrogen lone pair. The methyl (starred) of one of the two ethyl groups can rotate past the nitrogen lone pair in a low-energy process leading to the symmetrical conformer **3B** (where the two ethyl groups are equivalent).

The energy of **3B** is computed to be more thant 2 kcal mol^{-1} higher than **3A**, so that this conformer is not appreciably populated (thus not observed experimentally). From **3B**, however, an analogous rotation of the methyl of the *other* ethyl group (unstarred) leads equally easily to the enantiomeric conformer (**3A′**, not shown) of **3A**. The rapidly interconverting conformational set comprising **3A**, **3B,** and **3A′** thus yields only one set of signals for the two ethyl groups even at the lowest temperatures.

The second kind of conformational minimum **3C (**or its enantiomer **3C′**) corresponds to the second entry for **3** in Table 1 and has one methyl group anti to the lone pair while the other is gauche. Contrary to the previous case, a low barrier rotation of a methyl group past a lone pair *is not* a means of interconverting **3C** and **3C′** so a single molecule in conformation **3C** (or **3C′**) gives *two* ethyl signals, one each for the anti and

Scheme 4



gauche ethyl groups. The interconversion of **3C** (and **3C′**) into the first conformational set (**3A, 3B, 3A′**) involves a methyl group rotating past an ethyl or neopentyl group, and it is such rotation processes which are slow on the NMR time scale at −151 °C. A complete line shape analysis yielded the corresponding barrier, i.e., $\Delta G^{\ddagger} = 6.0 \pm 0.2$ kcal mol^{-1}.

(c) *N*-Ethyl-*N*-methylneopentylamine (2). Two dynamic processes appear in the NMR of this compound. The first is visible only in the ^{1}H NMR spectra (300 MHz) of the CH_2-N groups, where the two protons of the CH_2Bu^t and of the CH_2-Me groups become diastereotopic, below −80 and −100 °C, respectively. These changes, summarized in Table 2, correspond to nitrogen inversion/rotation becoming slow on the NMR time scale with barriers (derived again by total line-shape analysis) equal to 8.95 and 8.75 kcal mol^{-1}, respectively, yielding an average value of 8.85 ± 0.15 kcal mol^{-1}.

Below about −120 °C, further changes are seen in the ^{13}C spectra (75.5 MHz). Different degrees of broadening, followed by sharpening on further cooling, are observed for a number of the signals, behavior typical of a dynamic NMR process between two conformers of very different intensity.[10] The effect is most evident for the methyl signal of the ethyl group, which reaches its maximum broadening at −129 °C. A separate minor signal could not be observed, however, when the line sharpened again at the lowest attainable temperature (−145 °C), which suggests an intensity for this second conformer lower than about 5%. It seems reasonable to conclude, by comparison with **3**, that an ethyl-group rotation process is taking place, and the method of Anet and Basus[11] allowed us to determine a free energy of activation of 6.6 ± 0.3 kcal/mol for the $N-CH_2$ bond rotation.

Calculations suggest (see Table 1) that the neopentyl group is always eclipsed but that the three staggered conformations for the ethyl group are of similar energy. The first two of these, where the methyl of the ethyl group is gauche to the lone pair, interconvert by that methyl group rotating past the lone pair in a low-barrier process. The process producing the observed line broadening (at −129 °C) is plausibly the interconversion of the gauche pair of conformations with the anti conformation, in which the methyl of the ethyl group rotates past a methyl or a neopentyl group. Within the experimental errors the barrier measured for **2** (6.6 kcal mol^{-1}) is of a size comparable to that found for ethyl group rotation in **3** (6.0 kcal mol^{-1}).

(d) Trineopentylamine (9) and *N*-[(1-Adamantyl)methyl]-dineopentylamine (10) are calculated to have similar conformational behaviors, with one conformer (and its enantiomer) being more stable than all others. The preferred conformation is calculated (Table 1) to be the one in which each tertiary alkyl group is gauche to the lone pair in the same sense with a torsion angle just over 30°, almost exactly halfway between staggered and eclipsed.

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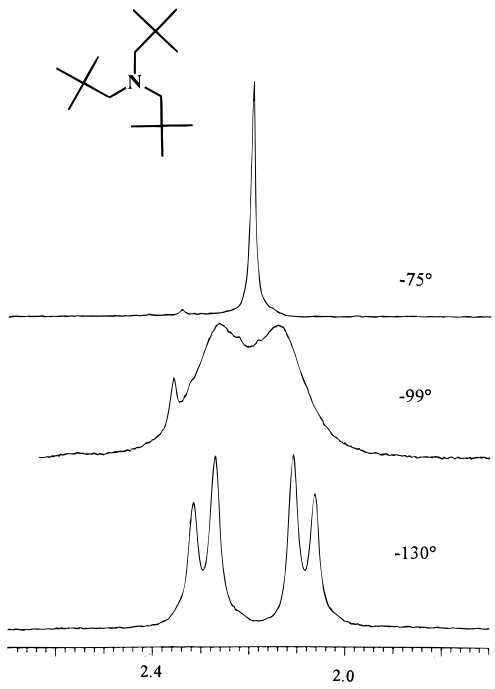

Figure 3. ^{1}H signal (300 MHz) of the methylene hydrogens of trineopentylamine (**9**) as function of temperature.

Structure V in Scheme 4 represents this conformation for **10** (R = 1-adamantyl) with each N−CH_2 bond rotated anticlockwise from eclipsed by 32°. This is accompanied by anticlockwise rotation of 11° about each CH_2−C_{quat} bond away from its normal staggered conformation and rotation of about 2° in a similar sense for each Me−C_{quat} bond.

In the enantiomeric conformation VI, all of these rotations are in a clockwise sense. Minimum energy conformations have thus been reached by rotation of all bonds, concertedly in the same sense, away from the ideal, taking this to mean the eclipsed conformation reported earlier for simpler molecules, for the N−CH_2 bonds.

As for NMR evidence, considering the more symmetrical compound **9** first, the ^{13}C NMR spectrum shows no changes down to −150 °C, while in the ^{1}H NMR (Figure 3), the singlet for the methylene group broadens and splits to a symmetric AB-spectrum below −95 °C, with a barrier of 8.4 kcal mol^{-1} for the dynamic process responsible. In contrast, the CH_2 signals of triethylamine[5a] and tribenzylamine,[5b] which have the same 3-fold symmetry formally, were found to split into more complex, asymmetric groups of lines.

Additional information was afforded by the less symmetric close analogue **10**, in which the adamantyl moiety, although a different substituent, has steric requirements similar to those of the *tert*-butyl group. In the ^{13}C NMR at −120 °C (Figure 4 and Table 3), the signals of the neopentyl groups are split into equal doublets, except for the methyl carbon signal which is, however, broadened. There is no significant change in the adamantyl carbon signals compared with room temperature.

The low temperature appearance of the ^{1}H signals of the three N−CH_2 groups could be clearly interpreted only at much higher field (600 MHz). Down to −75 °C, this region appears as two singlets of relative intensity 4:2, but splits into three AB-type quartets of equal intensity at −125 °C (Figure 5 and Table 2). From the spectral parameters and the temperature of maximum broadening of these quartets, the barrier at the coalescence temperature was evaluated as 8.3 kcal mol^{-1}, which is not different, within the experimental error, from that (8.6 kcal mol^{-1}, as in Table 3) determined by ^{13}C NMR.

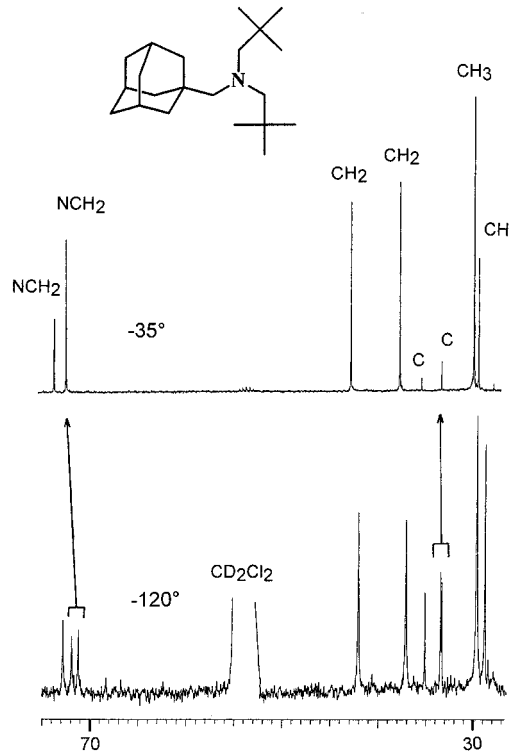

Figure 4. ^{13}C NMR spectrum (75.5 MHz) of **10** at −35 °C (top) and −120 °C (bottom). At the latter temperature, the line of the neopentyl NCH_2 carbons and that of the quaternary *tert*-butyl carbons are split.

There are two sets of processes that can interconvert enantiomeric conformations, and in Scheme 4, which shows Newman projections along CH_2−N bonds, some protons and carbons are labeled A, B, X, and Y to indicate their fate when this happens. The first process is a rotation of about 60° by each CH_2R group which interconverts conformers V and VI. According to the calculations, there is no conformational minimum with one CH_2R group rotated in the sense opposite to the other two, so this suggests that the three groups must rotate together in a single process in which each N−CH_2 bond is eclipsed in turn.

The second enantiomerization route is formally inversion of the nitrogen atom plus rotation of about 180° about N−CH_2 bonds leading to structures VII and VIII, which correspond to V and VI but with groups X and Y interchanged. If N−CH_2 bond rotation and N-inversion occur independently of each other, a very unstable intermediate structure like IX would be involved. It is more likely that as nitrogen inversion progresses some degree of rotation of one or more of the CH_2R groups takes place, so that interconversion takes place with a smaller barrier by not involving IX.

Consideration of Scheme 4 shows that for the more symmetrical compound **9**, neither the slowing of 60° rotation *alone* nor the slowing of nitrogen inversion/rotation *alone* produces a change in the spectrum. H_A becomes different from H_B only when *both* processes are slow on the NMR time scale, and even then, groups X and Y remain equivalent. Thus, of the two enantiomerization processes for **9**, one has a barrier of 8.4 kcal mol^{-1} while the other has a barrier greater than this, but how much greater cannot be determined, nor is there any indication which barrier is which.

Considering the less symmetrical compound **10** in the light of Scheme 4, slowing of 60° rotation on the NMR time scale does not make H_A different from H_B, nor group X different from group Y. Slowing of nitrogen inversion/rotation *alone* does make H_A different from H_B but does not make X and Y different. Differentiation of X and Y requires both processes

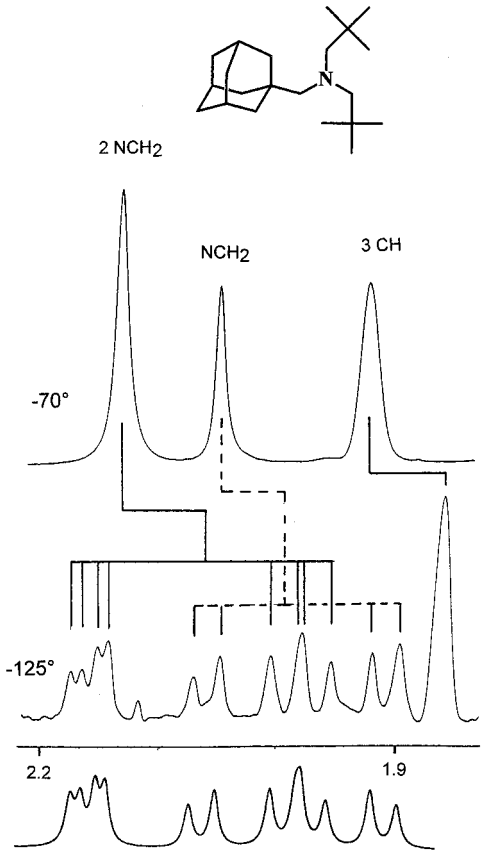

Figure 5. (top) Selected region of the ^{1}H spectrum (600 MHz) of **10** at −70 °C, displaying two signals for the two types of NCH_2 hydrogens (bonded to *tert*-butyl and to adamantyl groups, respectively) with a 4:2 intensity ratio, and a third signal for the three equivalent adamantyl CH hydrogens. (middle) At −125 °C, the signal of the pair of *tert*-butyl bonded NCH_2 hydrogens splits into two distinct AB spectra and, simultaneously, also the signal of the adamantyl bonded NCH_2 hydrogens splits into an AB spectrum (the adamantyl CH signal is unaffected). (bottom) Computer simulation of the three AB patterns obtained with the parameters of Table 2.

to be slow. Since, in the dynamic NMR experiment, A becoming different from B and X becoming different from Y are associated with barriers which are the same within experimental error, the barrier to 60° rotation must be at least as high as that for nitrogen inversion/rotation.

It is difficult to suggest what barrier should be expected for a concerted 60° rotation about N−CH_2 bonds. The nitrogen inversion/rotation process involves a *tert*-butyl or adamantyl group rotating past a neopentyl or adamantylmethyl group, so it is plausible that the barrier is greater not only than the 8.4 kcal mol^{-1} experimental value but also than the 9.4 kcal mol^{-1} value found for compounds **1**−**3**, yet a cooperative movement of all three groups may keep the barrier low.

Therefore, if this is the motion responsible for the barrier we measured, the concerted 60°-rotation process must have at least this value, and the present results do not preclude its being significantly larger. On the other hand, if the measured barrier reflects the 60°-concerted rotation process, then the nitrogen inversion/rotation must have a barrier larger than 8.3−8.6 kcal mol^{-1}. The latter posssibility seems even more likely than the former since that process involves *tert*-butyl or adamantyl groups rotating past bulky CH_2R groups (R being, in turn, as large as a *tert*-butyl or adamantyl groups). Indeed, in N-inversion/rotation processes where the rotational contribution is quite high, the barriers can be as large as 9.5 kcal mol^{-1} (as for instance in **2** or **3**[4b]), which means 1 kcal mol^{-1} larger than the barrier we measured in **9** and **10**.

(e) *N,N*-Dineopentylmethylamine (7) and *N,N*-Dineopentylbenzylamine (8). As the temperature is lowered in both of these compounds, the methylene protons of the neopentyl groups broaden and split to give an AB-quartet (see Table 2) in a way that is quite typical of nitrogen inversion/rotation becoming slow on the NMR time scale. This corresponds in both cases to a barrier of 8.4 kcal mol^{-1}. At lower temperatures, down to −135 °C, in both cases no further changes are observed in the spectra, in particular the benzylmethylene protons signal remains a singlet, and no changes are seen in the ^{13}C NMR.

Molecular mechanics calculations are once again helpful in understanding the conformational possibilities. For **7,** two closely related types of minima of very similar energy, interconverting readily with each other, are the most stable. In the slightly more stable, the conformation is reminiscent of the trineopentylamine conformation discussed above, with the *tert*-butyl rotated away from eclipsing by 23° and 36° in the same sense, so that there are two enantiomeric versions of this structure. Almost as stable is the pair of enantiomeric conformations with *tert*-butyl groups rotated away from eclipsing in opposite directions, i.e., toward the methyl group substituent, one by only 6° (thus eclipsed) and the other by 49° (thus nearly staggered). Interconversion of these four conformations is presumably always fast on the NMR time scale since it is calculated to require an energy as low as 0.9 kcal mol^{-1}.

The additional phenyl substituent of compound **8** compared with **7** makes it more like **9** superficially, and the conformation like V of Scheme 4 is calculated to be the most stable, see Table 1. There is much less crowding than in **9** since the phenyl group rotates to present a face toward the two adjacent *tert*-butyl groups. The rotation process of about 60° appears to be much easier for **8** than **9** and to follow a stepwise mechanism, since it is calculated that for **8** conformational minima exist with one group skewed in the opposite sense from the other two.

For **7** and **8**, interlocking of alkyl groups in the ground state is much less important than in **9** and **10** and in a different way in **6**.[6c] The high barriers associated with eclipsed neopentyl groups in compounds **1**−**3** are not found, so **7** and **8** are closest in behavior to compounds **4** and **5.**

Conclusions

Eclipsing is expected for a trialkylamine $R^1R^2NCH_2R^3$ when R^3, sterically compressed by R^1 and R^2, prefers to distance itself as much as possible from these groups and ends up eclipsing the nitrogen lone pair. Forsyth showed that for neopentylamines, i.e., where R^3 is as big as a *tert*-butyl group, eclipsing is found even when R^1 and R^2 are quite small, as in *N*-neopentylpiperidine and diethylneopentylamine (**3**). Eclipsing has now been demonstrated in even simpler compouds **1** and **2,** and the relatively high *tert*-butyl rotation barrier in **1** suggests that the eclipsed ground state of that molecule is not particularly strained. In **3**, substantial barriers have been found for rotation about the *N*-ethyl bond when it involves a methyl group rotating past another alkyl group. The results reported for **7**−**10,** when considered together with earlier results for **4**−**6**, show that, with additional steric crowding, eclipsing of the neopentyl group is no longer the favored outcome, although sometimes the eclipsed conformation is quite close in energy to the most stable (it is even 20% populated in **5**). When R^1 and R^2 do little more than compress the *tert*-butyl group laterally, as in **1**−**3**, eclipsing is favored, but when these two groups are branched enough to make significant steric demands on each other, eclipsing of the neopentyl group is not the outcome. It is reasonable to be mindful that eclipsing of bonds other than C−N may become less likely in a similar way as the degree of substitution increases.

Scheme 5

12A **12B**

The concerted back and forward 60° rotation of neopentyl groups found in **9** and **10** is a striking process reminiscent somewhat of some of the stereodynamics of triarylmethanes. The high-energy point in the interconversion is presumably close to a conformation with all N−CH_2 bonds eclipsed although there may be some mutual accommodation by neopentyl groups that avoids this highly symmetrical arrangement. The ground state conformation is thus calculated to be only 32° away from the rotational transition states, yet the rotational barrier is at least 8.3 kcal mol^{-1} , reflecting no doubt a quite complex process. As described above, every C−C and C−N bond in **9** is skewed away from the ideal in the same sense, that is coherently. This is a standard way of accommodating great steric strain in symmetrical molecules, best exemplified by tri-*tert*-butylmethane.[13] There, concerted libration (e.g., **12A** ⇌ **12B**) between conformations coherently skewed in the opposite sense about all C−C bonds has a barrier of 9.2 kcal mol^{-1}: this, formally, is the barrier passing through a perfectly staggered conformation.[13b]

In the cases of both tri-*tert*-butylmethane (**12**) and compounds **9** and **10**, some degree of rotation has to take place about all bonds in the molecule (outside the adamantyl group of **10**), and until this is half completed, each of these rotations reduces the coherence of the distortions that have produced the stable ground state. Herein lies the explanation of the high barrier observed.

Experimental Section

***N,N*-Dimethylneopentylamine (1).** In a flask containing 4.5 mL (0.120 mol) of formic acid was dropped 5.0 mL (0.043 mol) of neopentilamine, keeping the temperature below 10 °C as the reaction is very exotermic. A 9.0 mL (0.130 mol) volume of formic aldehyde (40% in water) was added dropwise and the mixture refluxed for 3 h.[14] When the reaction was completed, the mixture was cooled at room temperature and HCl (37%) was dropped until a strong acid pH was obtained. The mixture was concentrated at reduced pressure, and the residual liquid was trated with NaOH (30%) to reach a strongly basic pH. The mixture was extracted with ether (3 × 20 mL), dried, and concentrated at ambient pressure. The rough product was distilled to yield 3.2 g of colorless liquid: bp 96 °C (760 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.79 (s, 9H, C*Me*$_3$), 1.94 (s, 2H, N*CH*$_2$), 2.18 (s, 6H, N*Me*); ^{13}C NMR ($CDCl_3$) δ 28.1 (C*Me*$_3$), 32.75 (quat, *C*Me$_3$), 48.82 (N*Me*), 72.26 (N*CH*$_2$).

***N,N*-Dimethylneopentylamine-1-*d*$_1$ (1-*d*$_1$).** To a solution (kept under N_2) containing 4 mL (0.037 mol) of 2,2-dimethylacetaldehyde and 5 g (0.16 mol) of dimethylamine in 20 mL of dry benzene was added dropwise 2 mL (0.0185 mol) of $TiCl_4$ in 5 mL of benzene. The mixture was sitirred for 3 h until the IR aldehyde band (1729 cm^{-1}, in benzene) was replaced by that of the imine (1673 cm^{-1}). The precipitate was filtered off under nitrogen, whereas the solution was slowly added to a mixture of 1.6 g (0.038 mol) of $LiAlD_4$ in 20 mL of dry ether. After being stirred overnight at room temperature, the reaction was completed. A saturated acqueous NH_4Cl solution (20 mL) was slowly added, and after stirring for 0.5 h, the organic layer was separated, dried, and saturated with dry HCl to yield 4 g of the white chloridrate of the deuterate secondary amine. The amine, separated by treating the salt with 5 mL of 10 M KOH, was refluxed 3 h with 8 mL of formic acid and 4.8 mL of formic aldehyde (40% in water). The rough product obtained after the work up was distilled to yield 2 g of a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 9H, C*Me*$_3$), 1.98 (t, J = 9.7 Hz, 1H, N*CH*D), 2.25 (s, 6H, N*Me*); ^{13}C NMR ($CDCl_3$) δ 28.0 (C*Me*$_3$), 32.60 (*C*Me$_3$), 48.76 (N*Me*), 65.78 (N*CH*$_2$).

Amines **2**−**10** were synthesized with a general procedure[6a−c] starting from neopentylamine (Aldrich) that was reacted with the appropriate acyl chloride. The amide was reduced with $LiAlH_4$ and the secondary amine reacted again with the appropriate acyl chloride. The resulting secondary amide was reduced with $LiAlH_4$ to give the desired tertiary amine. The compounds were identified as follows.

***N*-Ethyl-*N*-methylneopentylamine (2):** ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 9H, C*Me*$_3$), 1.02 (t, 3H, CH_2*CH*$_3$), 2.07 (s, 2H, N*CH*$_2$), 2.28 (s, 3H, N*Me*), 2.45 (q, 2H, *CH*$_2$$CH_3$); ^{13}C NMR ($CDCl_3$) δ 12.81 (CH_2*CH*$_3$), 28.13 (C*Me*$_3$), 32.75 (*C*Me$_3$), 45.28 (N*Me*), 54.26 (*CH*$_2$$CH_3$), 69.62 (N*CH*$_2$).

***N,N*-Diethylneopentylamine (3):** ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 9H, C*Me*$_3$), 0.88 (t, 3H, CH_2*CH*$_3$), 2.05 (s, 2H, N*CH*$_2$), 2.45 (q, 2H, N*CH*$_2$-CH3); ^{13}C NMR ($CDCl_3$) δ 12.43 (CH_2*CH*$_3$), 28.26 (C*Me*$_3$), 32.70 (*C*Me$_3$), 49.58 (N*CH*$_2$$CH_3$), 66.58 (N*CH*$_2$).

***N,N*-Dineopentmethylamine (7):** ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 18H, C*Me*$_3$), 2.20 (s, 4H, N*CH*$_2$), 2.32 (s,3H, N*Me*);^{13}C NMR (CHF_2Cl/C_6D_6) δ 28.9 (C*Me*$_3$), 33.4 (*C*Me$_3$), 48.1 (N*Me*), 74.6 (N*CH*$_2$).

***N,N*-Dineopentylbenzylamine (8):** ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 18H, C*Me*$_3$), 2.23 (s, 4H, N*CH*$_2$Bu^t), 3.56 (s, 2H, N*CH*$_2$Ph), 7.13−7.37 (m, 5H, *Ar*); ^{13}C NMR ($CDCl_3$) δ 29.31 (C*Me*$_3$), 33.08 (*C*Me$_3$), 63.26 (N*CH*$_2$Ph), 69.27 (N*CH*$_2$Bu^t), 126.53 (CH, Ar), 127.86 (CH, Ar), 129.24 (CH, Ar), 140.98 (C, Ar).

***N,N,N*-Trineopentylamine (9):** ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 9H, C*Me*$_3$), 2.40 (s, 2H, *CH*$_2$); ^{13}C NMR ($CDCl_3$) δ 29.67 (C*Me*$_3$), 32.79 (*C*Me$_3$), 71.44 (N*CH*$_2$).

***N*-(1-Adamantylmethyl)-*N,N*-dineopentylamine (10):** ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 18H, C*Me*$_3$), 1.615 (d, 6H, *CH*$_2$, Adm),1.64 (AB doublet J = 12 Hz, 3H, *CH*$_2$, Adm), 1.69 (AB doublet J = 12 Hz, 3H, *CH*$_2$, Adm), 1.97 (m broad, 3H, *CH*, Adm), 2.09 (s, 2H, N*CH*$_2$Adm), 2.19 (s, 4H, N*CH*$_2$Bu^t); ^{13}C NMR ($CDCl_3$) δ 28.82 (CH, Adm), 29.82 (C*Me*$_3$), 32.88 (*C*Me$_3$), 35.02 (C, Adm), 37.37 (*CH*$_2$, Adm), 42,43 (*CH*$_2$, Adm), 71.86 (N*CH*$_2$Bu^t), 73.01 (N*CH*$_2$Adm).

NMR Measurements. The variable-temperature NMR spectra were recorded at 300 or 600 MHz (^{1}H) and at 75.5 or 100.6 MHz (^{13}C). The simulation of the line shape was performed by a computer program based on the Bloch equations, and the best fit was visually judged by superimposing the plotted and experimental traces.

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