Stereodynamics of Inversion and Rotation in Trialkylamines.[1] *N,N*-Diisopropyl Primary Alkylamines Studied by Dynamic NMR Spectroscopy and Molecular Mechanics Calculations

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From the temperature dependence of NMR spectra, two separate conformational processes can be distinguished and studied in *N,N*-diisopropylneopentylamine. A high-barrier inversion/rotation process involves eclipsing of t-butyl and isopropyl groups, while a rotation process with a lower barrier involves lesser eclipsing interactions. Molecular mechanics calculations help illustrate the ground state conformations involved. Barriers are smaller when the neopentyl group is replaced by less branched primary alkyl groups.

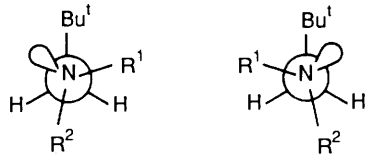
Inversion of nitrogen configuration in alkylamines always involves some rotation about carbon–nitrogen bonds to achieve the energy minimum in the new configuration, for otherwise a staggered Me–NR^1R^2 bond would become an eclipsed R^1R^2N–Me bond. Interconversion of rotational conformations[2] which may be separated by less than 120° of rotation or by as much as 360°, may often be facilitated by some flattening of nitrogen pyramidality or even complete inversion of nitrogen, for by such means three more-or-less simultaneous sets of eclipsing interactions can be avoided. However, if two large groups have to pass each other to interconvert rotational conformations, nitrogen inversion does not provide a magic way of avoiding this.

A reliable procedure is to consider any process being studied as an interconversion of enantiomeric, degenerate or, occasionally, different sets of structures where neither nitrogen inversion nor bond rotation alone is the process, but rather each is part of the mechanism of the process.

Some aspects of molecular structure or spectral behaviour may indicate that the high-energy point in the process has a near-to-planar nitrogen configuration, in which case the inversion/rotation process is inversion-dominated. If the high-energy point is one of rotational instability (*e.g.* eclipsing), the inversion/rotation process is rotation-dominated. While most commonly some intermediate combination of rotation and inversion will be involved, it is improbable that a molecule will favour a process that simultaneously maximises inversion and rotational destabilisation. Occasionally these may be of comparable importance consecutively.

Increasing steric congestion around a nitrogen atom leads to lower barriers to nitrogen inversion[3,4] but potentially to higher barriers to rotation. Much elegant recent dynamic NMR work[5] has probed such inversion-dominated processes in simple trialkylamines, *N,N*-dimethylethylamine[6] being the simplest, where rotation is likely to be less important. In some cases, however,[5,7] two processes, the second a discrete rotational interconversion, can be demonstrated.

In the search for rotation dominated processes, we have recently[8a] been studying neopentylamines t-butyl–CH_2–NR^1R^2, since whatever the mechanism, interconversion of enantiomeric structures **1** ⇌ **2** requires an R-group to eclipse a t-butyl group along an N–CH_2 bond. We herein report on *N,N*-diisopropylneopentylamine **3a** and other members of the series **3**. The usefulness of diisopropylamines in such studies has previously been shown,[8b,c] since different components of



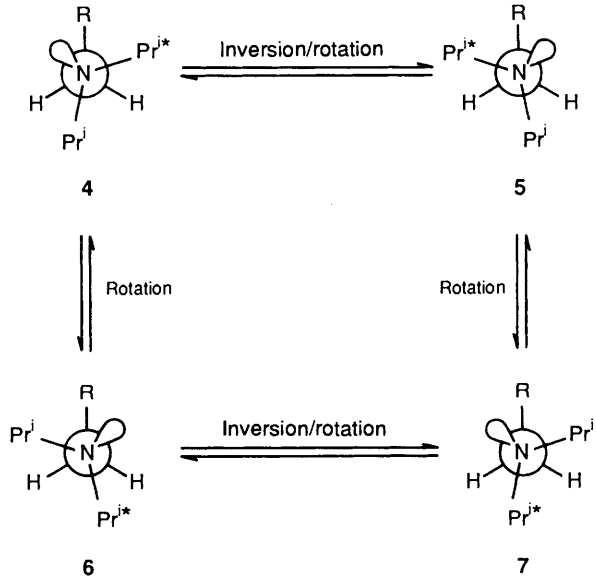
1 **2**

RCH_2–NPr^i_2

3

a R = Bu^t
b R = 1-adamantyl
c R = Pr^i
d R = Ph
e R = Me
f R = H

rotation and inversion make the two alkyl groups, and the two diastereotopic groups within one alkyl group, equivalent on the NMR timescale. Molecular mechanics calculations[9] provide



4 **5** **6** **7**

Scheme 1.

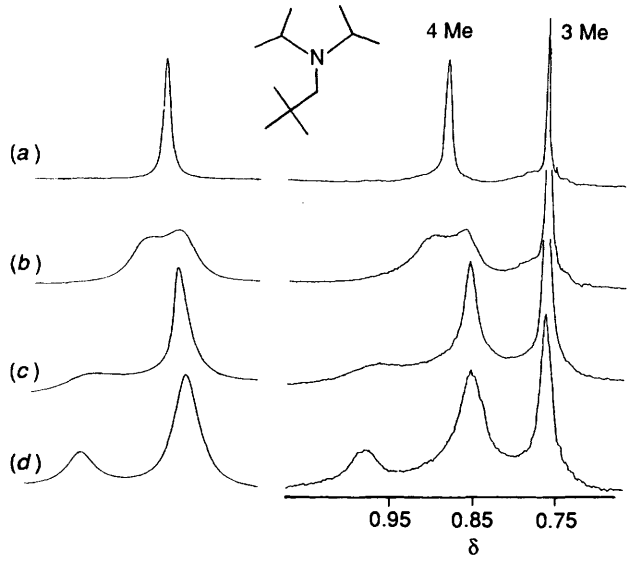


Fig. 1. Temperature dependence of the experimental (right hand side) ^{1}H NMR spectrum (300 MHz) of the methyl groups of $Pr^i_2NCH_2$–Bu^t obtained by decoupling the NCH signal. The lineshape had to be simulated (left hand side) by taking into account both the rate constants (reported in s^{-1}) for *N*-inversion (k_i) and *N*-Pr^i rotation (k_r). The k_r values match those obtained from the corresponding ^{13}C spectrum (see Fig. 2). From the ^{1}H spectrum two k_i values (22 and 30 s^{-1}) could also be determined (respectively at −101.5 and −98 °C). (*a*) −65 °C, $k_r \geqslant 5 \times 10^4$, $k_i \geqslant 2 \times 10^3$; (*b*) −98 °C, $k_r = 1250$, $k_i = 30$; (*c*) −120 °C, $k_r = 55$, $k_i = 0$; (*d*) −135 °C, $k_r = 0$, $k_i = 0$.

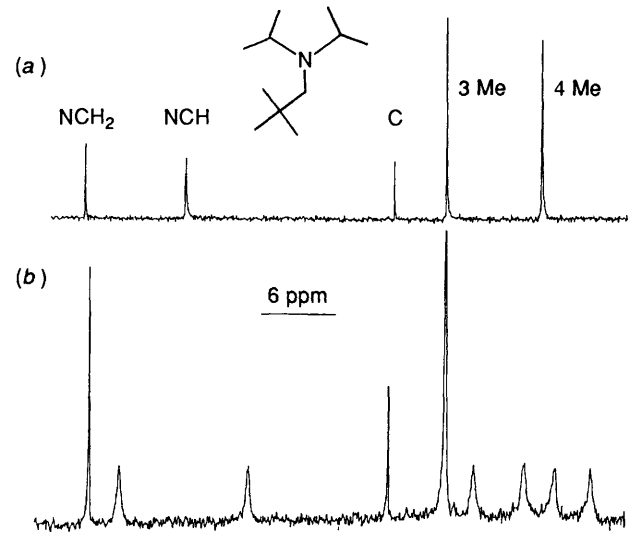


Fig. 2. ^{13}C NMR spectrum (75.5 MHz) of $Pr^i_2NCH_2$–Bu^t at (*a*) −30 and (*b*) −120 °C. The single line of the two NCH groups and that of the four methyl groups are split, respectively, into two and four lines of equal intensity. This indicates restriction of both *N*-inversion and *N*-Pr^i rotation. From the lineshape of the ^{13}C spectrum only the rate constant for the slower of the two processes (rotation) could be determined (see text).

information on stable conformations of these molecules as a basis for discussing such points of interest.

In a series of such molecules we may reasonably hope to distinguish two different interconversions of equivalent structures, see Scheme 1. While the dihedral angles shown are as suggested by our calculations, conformations about *N*-isopropyl bonds also need to be considered just as in alkyl diisopropylmethanes recently studied.[10]

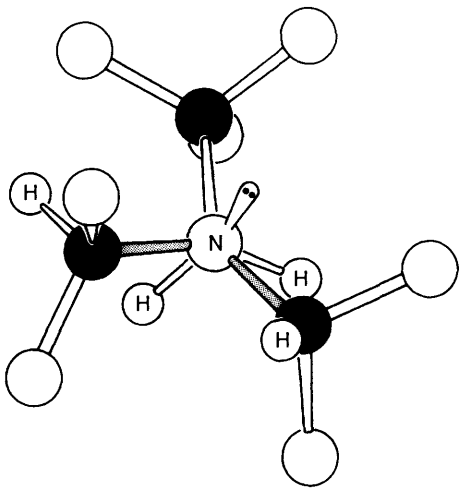


Fig. 3. Minimum energy conformation of **3a** viewed along the N–CH_2 bond, as calculated by molecular mechanics. (○) methyl groups; (●) tertiary or quaternary carbon atoms.

Results

N,N-*Diisopropylneopentylamine* **3a**.—Both the ^{1}H and ^{13}C NMR spectra of this compound are temperature dependent as described in Table 1 and shown in Figs. 1 and 2, and show that two processes, successively, become slow on the NMR timescale.

At room temperature, the proton NMR spectrum shows singlets for the t-butyl and methylene groups, and one doublet and one septet (J = 7.2 Hz) for the isopropyl groups. On cooling below about −50 °C the methyl doublet broadens, see Fig. 1, and splits at −96 °C to two broad signals, apparently of equal intensity, indicating a process with a barrier $\Delta G^{\ddagger}$ = 8.9 kcal mol^{-1} (1 kcal = 4.184 kJ) at −98 °C. On further cooling, further broadening, now of all but the t-butyl signal takes place. Eventually the signals split at temperatures around −115 °C, so that finally at −140 °C, the methylene protons appear as an AB quartet, the methine protons as two equal multiplets, and the isopropyl methyl protons as a complex signal, presumably four equal overlapping doublets. These changes indicate that a process with a barrier $\Delta G^{\ddagger}$ = 7.7 kcal mol^{-1} at −120 °C is taking place.

In the ^{13}C NMR spectrum, on cooling, corresponding behaviour is observed. Splitting of the isopropyl methyl signal due to the high barrier process has not occurred, however, before further broadening due to the second process obscures that change. Eventually, at −120 °C the two equal methine carbon signals, and four equal methyl carbon signals are seen for the isopropyl group, with no changes in the neopentyl group signal, see Fig. 2. Barriers calculated on the basis of these changes agree with those found from the ^{1}H NMR spectra.

Molecular mechanics calculations are reported in detail later, but in the case of **3a** suggest that the confirmation around the nitrogen centre is as in **8** (Fig. 3), and that Scheme 1 serves as a basis for discussion, where **4**, **6** and **7** are degenerate or enantiomeric forms of **5** ≡ **8**. Previous experience[8a,10] shows good agreement between known structures of amines and molecular mechanics calculations and some aspects of the above NMR changes support this.

The low-temperature limit NMR spectrum shows no signs of a second set of signals that could be attributed to molecules with different conformations for either the CH_2R group or the isopropyl group. From the structure and the nature of the spectral changes the higher barrier process is inversion/rotation **4** ⇌ **5** and **6** ⇌ **7**. On the NMR timescale at −100 °C, the isopropyl groups are still equivalent due to the rotation process

Table 1. NMR spectra of compounds **3a–d** at various temperatures.

Compound	Solvent	Observed nucleus (MHz)	T/°C	NCH_2	NCH	Me(Pr^i)	Group R
3a	CHF_2Cl	C-13 (75.5)	−35	57.95	50.15	21.85	q, 33.65 methyl 29.3
			−120	57.6	55.2, 44.95	26.85, 22.8, 20.4, 17.5	33.75 29.5
		H-1 (300)	−65	2.19	2.96	0.99	0.87
			−130	2.11, 2.04 J = 14 Hz	2.92, 2.75	0.98, 0.86, 0.86, 0.84	0.75
3b	CHF_2Cl– $CHFCl_2$	C-13 (100.6)	−75	60.2	51.0	22.4	q, 36.0, 'CH' 30.3, 'CH_2' 38.75, 43.2
			−135	59.5	55.8, 45.0	27.0, 23.0, 20.65, 17.7	35.3 29.5 37.95 42.3
		H-1 (400)	+20	2.05	2.88	0.92	'CH' 1.89, 'CH_2' 1.675, 1.605, 1.46 J = 11 Hz
			−140	1.99, 1.94 J = 14 Hz	2.92, 2.68	0.97, 0.83, 0.83, 0.82	1.86 1.59, 1.53, 1.435, 1.28 J = 11 Hz J = 11 Hz
3c	CHF_2Cl	C-13 (75.5)	+25	53.2	48.0	20.4	'CH' 27.5 'CH_3' 20.25
			−135	56.3	51.2	22.6, 22.6, 19.1, 19.1	31.0 22.0
	$CHFCl_2$– CHF_2Cl	H-1 (400)	+25	2.08	2.90	0.88	1.54 0.76
			−135	1.93	2.83	0.87, 0.80	1.48 0.72
3d		C-13	+25	48.49	49.92	21.19	127.50, 129.37, 145.04
		H-1	+25	3.65	3.03	1.05	7.12–1.45

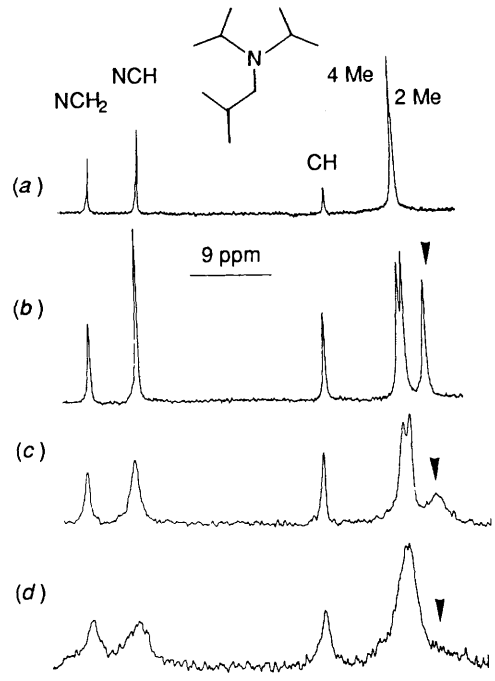


Fig. 4. ^{13}C NMR spectrum (75.5 MHz) of $Pr^i_2NCH_2$–Pr^i at (*a*) +25; (*b*) −128; (*c*) −155; (*d*) −165 °C. Below −120 °C the line of the two equivalent methyl groups is still a singlet whereas that of the four equivalent methyl groups is split into a 1:1 doublet, owing to the effect of a slow *N*-inversion. The upfield line of this doublet (indicated by an arrow) broadens considerably at −155 °C and disappears at −165 °C, having reached the coalescence region. The barrier for this second process (N–CH_2 rotation) has been estimated to be 4.7 ± 0.3 kcal mol^{-1} (see text).

4 ⇌ **6** and **5** ⇌ **7**, but geminal methyl groups are diastereotopic due to the asymmetry of substitution at slowly inverting nitrogen. However, they spend equal times *gauche* and *anti* to the lone pair, and this is reflected in the small relative chemical shift observed at intermediate temperatures for these methyl groups. The low barrier process is the rotation **4** ⇌ **6** or **5** ⇌ **7**, which makes the isopropyl groups and the methylene protons non-equivalent, as is observed in the NMR spectrum at −140 °C, where methyl group chemical shifts are much larger since methyl groups are either *gauche* or *anti* to the lone pair on the NMR timescale.

N,N-*Diisopropyl*-C-(1-*adamantyl*)*methylamine* **3b**.—The changes in the ^1H and ^{13}C NMR spectra of **3b** indicated in Table 1 are analogous to those for **3a**, except that the equivalent methylene protons of the adamantyl group become diastereotopic along with the N–CH_2 protons in a way now quite expected.[11] From this the barriers to inversion/rotation and rotation are as reported in Table 2.

N,N-*Diisopropylisobutylamine* **3c**.—This compound shows a doubling of the *N*-isopropyl methyl signal below about −95 °C in both the ^1H and ^{13}C NMR spectra, corresponding to inversion/rotation becoming slow on the NMR timescale, as for **3a**. In the ^{13}C NMR spectrum there is subsequent broadening of *N*-isopropyl and methine signals but even at the lowest temperature attainable, splitting corresponding to slow rotation was not quite achieved, see Fig. 4. These changes are described in detail in Table 1 and yield a barrier of 7.8 kcal mol^{-1} for inversion/rotation at −110 °C. Reasonable assumptions [12] as to chemical shift values and likely coalescence temperatures suggest that the barrier to the rotation process is 4.7 kcal mol^{-1} at −165 °C.

N,N-*Diisopropylbenzylamine* **3d**.—The ^1H and ^{13}C NMR spectra of this compound described in Table 1 do not change significantly with temperature, suggesting that the barrier to inversion/rotation and to any rotation process is less than about 5 kcal mol^{-1}.

N,N-*Diisopropylethylamine* **3e** *and* N,N-*Diisopropylmethylamine* **3f**.—The temperature dependence of the ^{13}C NMR spectrum of these compounds has been described elsewhere,[8b,c] and the results have been incorporated in Table 2. Inversion/rotation becomes slow on the NMR timescale with a barrier somewhat lower than that observed for **3a–c**, but there is no report of a second, rotation process becoming slow on the NMR timescale.

Table 2. Barriers to inversion/rotation and rotation in compounds **3** and **11**.

Compound	R	Nucleus (MHz)	Signal simulated	Barrier to inversion/rotation		Barrier to rotation		Mean
				ΔT/°C	$\Delta G^{\ddagger}$/kcal mol^{-1}	T/°C	$\Delta G^{\ddagger}$/kcal mol^{-1}	
3a	Bu^t	C-13 (75.5)	NCH			−107, −90	7.7	
		C-13 (75.5)	Me_4			−108, −97	7.65	
		H-1(300)	NCH_2			−120, −115	7.65	7.6
		H-1 (300)	Me_4	−101, −98	8.85	−120, −115	7.55	
3b	Adamantyl	C-13 (100.6)	NCH			−119, −104	7.2	
		H-1 (400)	NCH			−119	7.4	
		H-1 (400)	NCH_2			−120	7.1	7.3
		H-1 (400)	CH_{2Ad}			−120, −115	7.45	
		H-1 (400)	Me_4	−99	8.8	−129, −114	7.25	
3c	Pr^i	C-13 (75.5)	Me_4	−113, −101	7.95	−165	4.7	
		C-13 (50.3)	Me_4	−118, −110	7.65			
3d	Ph				<5.5			<5.5
3e	Me		*b*		6.8	*b,d*		
			c		6.5	*c,d*		
3f	H		*c*		6.0	*c,d*		
			c		6.0	*c,d*		
11	'RCH$_2$'[a]		*b*		<6.0	*b*		9.2

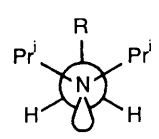
[a] 'RCH$_2$' = CH(CH$_2$CH$_3$)$_2$. [b] Ref. 8(*b*). [c] Ref. 8(*c*). [d] Not observed.

Table 3. Molecular mechanics calculations of conformational minima for compound **3a** (see Scheme 1, **5**)[a].

Conformation of isopropyl groups[b]		Conformational energy[c] /kcal mol^{-1}		Dihedral angle/°		
α	β	Absolute	Relative	Neopentyl group[d]	Isopropyl group α[e]	Isopropyl group β[e]
+*g*	+*g*	25.39	0.00	−22.3	73.0	80.2
+*g*	+*g*	25.71	0.32	−49.6	60.0	83.8
+*g*	−*g*	27.75	2.36	−17.2	78.1	−54.0
+*g*	−*g*	29.11	3.72	−50.1	49.9	−71.9
+*g*	*a*	26.53	1.14	−15.0	77.4	−173.1
−*g*	+*g*	30.30	4.91	−1.6	−82.8	57.1
−*g*	−*g*	30.37	4.98	−31.5	−62.2	−100.2
−*g*	*a*	26.80	1.41	+1.0	−55.4	−177.6
a	+*g*	26.80	1.41	−1.0	+177.6	+55.4
a	−*g*	33.06	7.67	−42.6	+165.1	−90.4
a	*a*	32.10	6.71	−7.7	−135.4	−177.0

[a] High enthalpy conformations of type **9** were not calculated. There exists a matching set of enantiomeric conformations where each dihedral angle has a sign opposite to that given here. [b] See **10** for conformation and absolute configuration. [c] The final steric energy of the MM282 program.[9] [d] The dihedral angle lone pair-N–C–t-butyl. [e] The dihedral angle lone pair–N–C–H.

Molecular Mechanics Calculations.—Such calculations have been simplified by considering only one conformation about the RCH$_2$–N bond, to obtain the set of conformations **5** with



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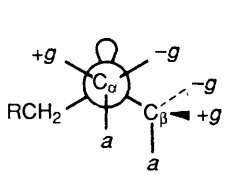

10

the −*gauche* arrangement of the lone pair-N–C–R dihedral angle. The entiomeric +*gauche* set **4** will show equal energies. The *anti* set of conformations **9** has the three alkyl groups *gauche* to each other and is expected to be of so high an energy as to be little-populated. The excess enthalpy of the most stable such *anti*-conformation for **3a** compared with the most stable *gauche*-conformation is calculated to be almost 7 kcal mol^{-1}.

Within the set **5** there are various combinations of conformations of the two isopropyl groups which have to be considered, as **10** suggests, using the obvious terms −*g*, +*g* and *a* to indicate the location of the methine proton with respect to the lone pair, in the isopropyl groups α and β respectively. Table 3 lists these conformations for **3a**, giving the dihedral angle about each carbon–nitrogen bond and the enthalpy as calculated using Allinger's MM282 program.[9] As is common with relatively highly branched compounds,[13] there are two different minima between eclipsed conformations, librated to either side of a perfectly staggered conformation to reduce long-range interactions. These minima need to be sought when

Table 4. Molecular mechanics calculations of conformational minima for compounds **3b** and **3c** (see **5**).[a]

Compound	Conformation of isopropyl groups[b]		Conformational energy[c]/kcal mol^{-1}		Dihedral angles/°			
					N-Isopropyl groups		RCH_2 group	
	α	β	Absolute	Relative	α[d]	β[d]	First[e]	Second[e]
3b	+*g*	+*g*	39.91	0.00	74.1	80.2	−22.1	
	+*g*	+*g*	40.33	0.42	58.1	82.2	−49.7	
	+*g*	*a*	40.89	0.98	77.6	−173.4	−14.7	
	+*g*	−*g*	42.17	2.26	77.1	−54.6	−15.1	
3c	+*g*	+*g*	20.52	0.00	59.2	44.4	−53.9	−63.0
	+*g*	+*g*	20.95	0.43	83.2	63.7	−52.2	−68.3
	−*g*	−*g*	22.54	2.02	−64.3	−92.2	−47.6	−62.8
	+*g*	*a*	22.71	2.19	72.6	−173.6	−59.4	−70.6

[a] Only conformations within 2.5 kcal mol^{-1} of the global minimum are shown. There exists a matching set of enantiomeric conformations where each dihedral angle has a sign opposite to that shown here. [b] See **10** for conformation and absolute configuration. [c] The final steric energy of the MM282 program.[9] [d] The dihedral angle lone pair-N–C–H. [e] First is the dihedral angle lone pair-N–CH_2–R, second is the dihedral angle N–C–C–H for **3c**.

determining significantly-populated conformations, and in Table 3 we include the two such librational isomers we have found, which are within 4 kcal mol^{-1} of the global minimum.

As one might expect,[10b] the most stable overall conformation for **3a** has an isopropyl hydrogen directed toward the t-butyl group, and the second isopropyl hydrogen directed towards the methyl groups of the first one, see Fig. 3. In the next most stable conformation the second isopropyl group has rotated *anti*, which again fits well with previous experience.[10b] The least stable conformations are ones in which the neopentyl group and isopropyl methyl groups are close, competing for the same space.

Calculations of the conformations of **3b** seem, not unexpectedly, to mimic those for **3a**. The three most stable conformations are reported in Table 4.

Calculations on the isobutyl compound **3c** were simplified as for **3a**, looking at only the set of conformations with the *C*-isopropyl group −*gauche* with respect to the lone pair. Calculations showed that of the three possible conformations about the Pr^i–CH_2N bond, the one with the H–C–C–N bond −*gauche* is the most stable, so the conformation was fixed thus in the set of conformations calculated. Table 4 shows the four most stable conformations, other librational and rotational conformations being at least 2.9 kcal mol^{-1} less stable than the global minimum.

Discussion

The conformational behaviour of **3a** can thus be discussed in terms of Scheme 1, although each structure may be modified by the presence of a small concentration of a second conformation exchanging rapidly on the NMR timescale as explained above. At room temperature, the interconversions of Scheme 1 all take place rapidly on the NMR timescale.

The process with a barrier of 8.9 kcal mol^{-1}, slow on the NMR timescale, at −98 °C is the inversion/rotation process (**4** ⇌ **5** or **6** ⇌ **7**), and as a result of the fixing of the nitrogen configuration, the two methyls of any isopropyl group become non-equivalent. Since the rotations **4** ⇌ **6** and **5** ⇌ **7** are still fast on the NMR timescale, methylene protons remain equivalent as do isopropyl groups. The latter rotations becoming slow on the NMR timescale induces the low temperature changes in the NMR spectrum of **3a** corresponding to a barrier of 7.7 kcal mol^{-1}.

Scheme 1 focuses on the nitrogen to neopentyl group bond and shows how the high energy inversion/rotation process is associated with eclipsing of the group R with an isopropyl group, whereas the low barrier process eclipses alkyl groups with hydrogen or a lone pair. If an alternative view is taken along a nitrogen to isopropyl group bond, only alkyl group/hydrogen eclipsing need take place during the high barrier process, whereas alkyl groups must eclipse each other during the low barrier process. Thus although both processes require some rotation about all bonds, the high barrier inversion/rotation process is most affected by rotation of the primary RCH_2 group, while the lower barrier rotation process reflects principally rotation of the isopropyl groups.

Table 2 shows that the low barrier rotation process is directly influenced by the size of the group R, as expected. That the inversion/rotation barrier shows a similar trend along the series shows the importance of the rotational contribution to that process.

The results for **3e** and **3f** are taken from an earlier report which also reported strikingly different behaviour for a diisopropylamine **11** with a 3-butyl group $(Et)_2CH$– as the third substituent. On changing from an amine with two secondary and one primary alkyl groups as substituent to one with three secondary alkyl groups, the relationship between enantiomeric and degenerate conformations changes, as do the processes which can be studied. The behaviour within our present set **3a–f** seems consistent and points to the need to continue exploring different sets of trialkylamines in a corresponding way.

Experimental

All the tertiary amines **3a–d** were prepared similarly by lithium aluminium hydride reduction of the corresponding amide as described below for **3a**.

N,N-*Diisopropylpivalamide*.—Diisopropylamine (13.7 g, 135 mmol) was mixed with pivaloyl chloride in an autoclave and the temperature was raised to 180 °C for 18 h. The crude product was extracted with ether and the extract was washed with water and dried. Removal of the ether yielded a crystalline material (10 g, 89%). NMR, δ_C($CDCl_3$, 25.16 MHz) 28.2 (Me_2C), 20.4 (Me_3C), 39.1 (C_q), 47.7 and 46.3 (both CH), and 176.0 (C=O); δ_H($CDCl_3$, 100 MHz) 3.75 (1 H, m, CH), 2.65 (1 H, CH), and 1.1–0.7 (br complex, 21 H, 3 × Me). Broad signals are due to rotation about the N–CO bond at an intermediate rate on the NMR timescale.

N,N-*Diisopropylneopentylamine* **3a**.—A solution of diisopropylpivalamide (5 g, 27 mmol), in dry tetrahydrofuran

(THF), was added to a suspension of lithium aluminium hydride (1 g, 27 mmol) in THF (25 cm^3), and the mixture was refluxed for 24 h under nitrogen gas. After cooling to 0 °C the reaction was completed by dropping the mixture into a saturated aqueous solution of ammonium chloride. The exothermic reaction was easily controlled and the resultant precipitate was extracted several times with ether. The ether extract was dried and the solvent was removed to give a liquid residue from which the amine **3a** was distilled under reduced pressure to yield 3 g, 65%. NMR spectra are described in Table 1. (Found: *m/z* 171.197 96. Calc. for $C_{11}H_{25}N$: *M*, 171.198 70). Compounds **3b** (Found: *m/z* 249.244 94. Calc. for $C_{17}H_{31}N$: *M*, 249.245 65) and **3c** (Found: *m/z* 157.183 06. Calc. for $C_{10}H_{23}N$: *M*, 157.183 04) were obtained similarly.

Dynamic NMR spectra were obtained using Bruker CXP300 and Varian VXR400 spectrometers, for *ca.* 0.05 mol dm^{-3} solutions in solvents recorded in Table 1. Barriers were calculated from rate constants determined by matching experimental and complete line-shape calculated spectra.

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